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Pathophysiology and Pharmacotherapy of Cardiovascular Disease

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Preface

With the advance of modern civilization, the historical causes of death in human populations such as war, drought, famine and the spread of microbes have been replaced by a new wave of global killers: 'non-communicable diseases (NCDs)'. According to the World Health Organization report, NCDs kill 38 million people each year, with cardiovascular diseases (CVDs) accounting for most NCD deaths (17.5 million deaths, or 46.2 % of NCD deaths). Urbanization, industrialization, globalization and a larger ageing population have amplified the role of NCDs in global mortality and morbidity. NCDs affect both men and women, devastating both rich and poor nations alike, although more people in poor nations are more likely to die as they lack access to lifesaving medicines. In the past, we tussled against nature to combat communicable diseases; now, it is a battle against the lifestyles, dietary habits and indulgences of human nature to combat these NCDs, of which one important battlefront is to prevent, delay and effectively treat CVDs and promote global cardiovascular health.

While we are acquainted with a lot of information about CVDs and relevant treatment strategies, we still need to know more about current advances in CVD patterns, pathophysiology, diagnosis and pharmacotherapy. In addition, there is a constant stream of newly approved medicines entering the pharmaceutical drug market necessitating periodical updates in drug information to meet the rational use of drugs. We have attempted to collate here the knowledge of experts in different aspects of CVDs. This effort has been an innovative collaboration of global clinicians and scientists with the goal of advancing our thinking and testing new approaches to combat CVDs. Keeping these principles in mind, our authors have narrated the basic understanding of physiology and pathophysiology of the cardiovascular system, its regulation, and its excessive indulgence or over-activation causing an imbalance in the neural and hormonal systems to release harmful factors/chemicals changing the integrity of the cells, tissues and organs to precipitate disease(s). Applying the findings from these studies, treatment algorithms were generated by the authors, giving detailed descriptions of complex cellular mechanisms of drug action for the CVDs described in each chapter.

The book has eight major sections comprising 62 chapters. The emphasis is clinical, covering all key areas such as heart failure, cardiac hypertrophy and cardiomyopathy, coronary heart disease, atherosclerosis and hyperlipidemia, hypertension, cardiac arrhythmias, valvular heart diseases and cardiovascular conditions of childhood and pregnancy. Emerging areas of cardiovascular therapies such as cell and gene therapy, microRNA therapeutics, biomarkers, devices and mechanical approaches to control diseases are presented in addition to classic pharmacologic and therapeutic approaches. The editors are greatly indebted to all authors and co-authors for the expert write-up of their respective chapters in a field that is dynamic and ever growing.

Our objective is to provide meaningful guidance in understanding and treating CVDs. This book is not just a database of therapeutics for CVDs. This book is particularly intended for pharmaceutical, biomedical and health science professionals. We have tried our level best to make the subject contents interesting and thought provoking. This book offers an opportunity for readers to keep abreast of recent advances in the practice of cardiovascular medicine. We sincerely welcome comments and suggestions from readers.

We are grateful to Dr. Amitabh Prakash, Editor of *Clinical Pharmacokinetics* and the *American Journal of Cardiovascular Drugs* for having initiated the project and for his timely advice in the preparation of the book. We are also pleased to acknowledge the indispensable role played by Ms. Lorna Venter-Lewis, Ms. Ursula Gramm, Mr. Gurunadham Prasad and Mr. PremLal Prejith of Springer in the preparation of this book.

The opinions expressed in the book are those of the respective chapter authors and do not necessarily represent those of the editors and their employers.

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Part I
Heart Failure

Chapter 1
Heart Failure, Introduction

Tina Shah, Nicholas Palaskas, and Biykem Bozkurt

Abstract Heart failure (HF) is a growing worldwide epidemic that results in significant morbidity and mortality in the aging population. HF is an important contributor to both the burden and cost of national healthcare expenditures, with more older Americans hospitalized for HF than for any other medical condition. Over the last two decades, there has been considerable progress in the treatment of HF with angiotensin-converting-enzyme (ACE) inhibitors, aldosterone antagonists, beta-receptor blockers, and resynchronization therapy. Nevertheless, HF is still associated with a poor prognosis. Approximately half of the people who develop HF die within 5 years of diagnosis. The search for better treatments for HF is one of the major challenges in cardiology. Greater understanding of the molecular dynamics and humoral perturbation will lead to newer HF treatment. In this chapter, different etiologies of HF, a systematic approach to the evaluation of a patient with HF, current strategies for the treatment, and emerging therapies in this field are discussed.

Keywords Heart failure • Emerging therapies • Guideline-directed medical treatment • Stages of heart failure • Devices in HF

1.1 Introduction

Heart failure (HF) is an important healthcare issue because of its high prevalence, mortality, morbidity, and cost of care. It is estimated that more than eight million Americans will have HF by 2030 [1]. HF incidence increases with age, rising from

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approximately 20 per 1,000 individuals 65–69 years of age to >80 per 1,000 individuals among those >85 years of age [2]. Because of aging of the population, the increase in HF will be greatest for older Americans. Approximately half of people who develop HF die within 5 years of diagnosis [3]. One in nine deaths includes HF as contributing cause [3]. Total costs, including indirect costs for HF, are expected to increase from $31 billion in 2012 to $70 billion in 2030 [1].

Ischemic heart disease, hypertension, and valvular heart disease are the most common causes of HF. Less common causes include diabetes; genetic cardiomyopathies and muscular dystrophies; autoimmune and collagen vascular diseases; toxic cardiomyopathies, including alcohol or illicit drugs such cocaine; chemotherapy-induced cardiomyopathies (e.g., Adriamycin); myocarditis and viral cardiomyopathy; postpartum cardiomyopathy; tachycardia-mediated HF; infiltrative disorders, such as sarcoidosis, hemochromatosis, and amyloidosis; high-output states; and stress-induced (takotsubo) cardiomyopathy.

1.2 Classifications of HF

Commonly used classifications of HF include classifications according to the stages of HF disease progression; symptoms and functional capacity of patients; etiology of HF; and left ventricular (LV) function and structure.

1.2.1 HF Defined According to Left Ventricular Systolic Function

HF with reduced left ventricular ejection fraction (HFrEF) The definition of HFrEF has varied but usually implies EF less than 40–50 %. In the 2013 ACCF/AHA guideline for the management of HF, HFrEF is defined as the clinical diagnosis of HF and LVEF ≤40 %. Patients with EF >40 and less than 50 % are recognized as borderline or intermediate group, with their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF with preserved EF (HFpEF).

HF with preserved left ventricular ejection fraction (HFpEF) Approximately half of the HF patients enrolled in the clinical trials or hospitalized HF patients in acute HF registries have HFpEF. Currently there are no specific treatment strategies for HFpEF other than treatment of underlying risk factors and comorbidities, such as hypertension, diabetes, obesity, coronary artery disease, and atrial fibrillation, which are quite common in patients with HFpEF.

1.2.2 HF Defined According to Etiology and LV Structural and Hemodynamic Changes

In clinical practice, the etiology of HF has often been placed into two categories: ischemic and nonischemic cardiomyopathy. In general practice and clinical research trials, the term ischemic cardiomyopathy usually refers to cardiomyopathy due to ischemic heart disease. Though this approach may be practical, it fails to recognize that the term "nonischemic cardiomyopathy" may include cardiomyopathies due to volume or pressure overload, such as hypertension or valvular heart disease.

Classifications of cardiomyopathies (see Chap. 16) mixing anatomic designations (i.e., hypertrophic and dilated) with functional ones taking hemodynamic properties into consideration such as restrictive cardiomyopathies can be quite challenging and have failed to satisfy purposes of all users. Confusion may arise because the same disease could appear in two categories (i.e., hypertrophic and restrictive); there could be heterogeneity of clinical expression in different phenotypes and change from one category to another during their natural clinical course; e.g., amyloid and other infiltrative conditions may progress from a restrictive cardiomyopathy state to a dilated form. The most recent MOGE(S) classification (morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease, and the functional status (S) of the disease) provides the flexibility of such potential transitions between morphofunctional types, involvement of different cardiac structures and organs, progression of symptomatology and functional status, and addition of different etiologies such as genetic defects that may be discovered through the lifetime of a patient or affected families [4].

1.3 Stages of HF According to Risk and Symptoms

The ACCF/AHA stages of HF emphasize the development and progression of disease and can be used to describe individuals and populations:

Stage A is defined as patients at high risk for HF but without structural heart disease or symptoms of HF.

Stage B is defined as patients with structural heart disease but without signs or symptoms of HF.

Stage C is for patients with structural heart disease with prior or current symptoms of HF.

Stage D is patients with refractory HF requiring specialized interventions [5] (Fig. 1.1).

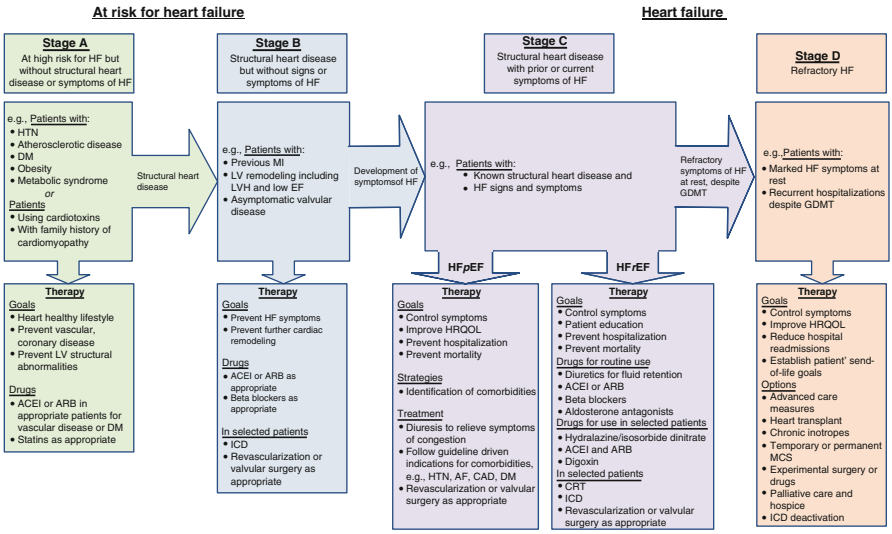

Fig. 1.1 ACCF/AHA stages of HF according to risk and symptoms (Reproduced with permission from *JACC* [5])

NYHA classes focus on exercise capacity and symptoms of HF (see Chap. 9):

NYHA class I patients with no limitation of physical activity and ordinary physical activity does not cause symptoms of HF

NYHA class II slight limitation of physical activity, comfortable at rest, but ordinary physical activity results in symptoms of HF

NYHA class III marked limitation of physical activity, with patient being comfortable at rest, but less than ordinary activity causes symptoms of HF

NYHA class IV patients who are unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest

1.4 Evaluation of a HF Patient

Evaluation of a HF patient includes a thorough history and physical examination, ascertainment of symptoms, functional capacity, and volume status including ascertainment of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and lower extremity edema. Etiology, comorbidities, and contributing factors for HF should be addressed including presence of diabetes; hypertension; smoking; prior cardiac disease; family history of cardiac disease, HF, or cardiomyopathy; history of heart murmur, congenital heart disease, and rheumatic fever; sleep disturbances; thyroid disease history; exposure to infectious etiology; exposure to cardiotoxins; and past or current use of alcohol and illicit drugs.

Pertinent physical examination includes heart rate and rhythm; blood pressure; measurements of weight, height, and body mass index; overall volume status;

Table 1.1 Initial diagnostic work-up of a HF patient

Detailed history	Detailed history for causes of HF, review of comorbidities, medications, social history, drug or substance use, cardiotoxin or infectious exposure, pregnancy. In patients with idiopathic DCM, a 3-generational family history should be obtained to aid in establishing the diagnosis of familial DCM
Initial diagnostic work-up	Complete blood count with differential
	Metabolic panel: serum electrolytes including glucose, calcium, magnesium, BUN, creatinine, HbA1c
	Urinalysis
	Thyroid function tests
	Liver function tests
	Chest radiography
	Echocardiography
	12-Lead electrocardiography
	Measurement of BNP or NT-proBNP to support clinical judgment for the diagnosis of acutely decompensated HF, especially in the setting of uncertainty for the diagnosis
	Screening for or HIV, hemochromatosis, rheumatologic diseases, amyloidosis, or pheochromocytoma in patients at risk or with clinical suspicion
Other testing that may be considered according to initial clinical assessment and further indications	Cardiac MRI to assess for myocardial infiltrative processes
	Cardiac catheterization for coronary or hemodynamic assessment
	Invasive hemodynamic monitoring with a pulmonary artery catheter to guide therapy in patients who have respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment
	Ischemia and viability assessment in patients with ischemic heart disease
	Endomyocardial biopsy in patients presenting with HF when a specific diagnosis is suspected that would influence therapy
	Cardiopulmonary exercise testing to assess for functional capacity and or consideration for cardiac transplantation

jugular venous distension; carotid upstroke and presence/absence of bruits; lung examination for rales or effusions; cardiac examination for systolic or diastolic murmurs; displaced PMI (point of maximum impulse); presence of left ventricular heave; intensity of the second heart sound (S2); presence of third or fourth heart sound (S3 or S4); liver size; presence of ascites; presence of renal bruits; presence of abdominal aortic aneurysm; peripheral edema; peripheral pulses; checking whether the extremities are cold and clammy.

Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone [5]. Screening for hemochromatosis, human immunodeficiency virus (HIV), pheochromocytoma, amyloidosis, or rheumatologic diseases reasonable in selected patients, particularly if there is clinical suspicion for testing [5] (Table 1.1).

Initial cardiac evaluation includes a baseline electrocardiogram (ECG); chest X-ray; and a 2-dimensional echocardiogram with Doppler should be performed to

assess ventricular function, size, wall thickness, wall motion, and valve function [5] (Table 1.1). Cardiac magnetic resonance imaging is reasonable when assessing myocardial infiltrative processes or scar burden. Biomarkers, especially natriuretic peptides, are useful to support clinical decision making regarding the diagnosis of HF and establish prognosis both in chronic ambulatory or acutely decompensated/hospitalized HF patients [5]. Natriuretic peptide-guided HF therapy can be useful to achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured outpatient HF disease management program, while the usefulness of serial measurement of BNP or NT-proBNP to reduce hospitalization or mortality in patients with HF or the usefulness of BNP- or NT-proBNP-guided therapy for acutely decompensated HF is not well established. Cardiac troponins and other evolving biomarkers can be helpful with prognosis and risk stratification of HF patients (see Chaps. 10, 11, and 12).

1.5 Current Management Strategies in HF

1.5.1 Guideline-Directed Medical Therapy (GDMT)

The 2013 ACCF/AHA guideline for the management of HF provides a comprehensive guide to evaluation and management of HF patients [5]. Guideline-directed medical therapy (GDMT), which represents the optimal medical therapy recommended with a class I indication in patients with systolic HF, includes ACE inhibitors (ACE-I), angiotensin receptor blockers (ARBs) when ACE-I intolerant, β-blockers (specifically, bisoprolol, carvedilol, and extended-release metoprolol), and, in select patients, aldosterone receptor antagonists, hydralazine-nitrates, and diuretics as the mainstay of pharmacological therapy for HFrEF (Fig. 1.2) (see Chaps. 8, 36, 38, and 40). It should be noted that indications for aldosterone antagonists for symptomatic HFrEF patients include mild to moderate HF (NYHA class II) patients with a history of a prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels. Additionally existing indications include NYHA class III and IV HF patients with severe HF [5] but with safeguards of creatinine $\leq$2.5 mg/dL in men or $\leq$2.0 mg/dL in women and potassium $\leq$5.0 mEq/L along with the necessity for careful monitoring of potassium, renal function, and diuretic dosing at initiation follow-up in patients treated with aldosterone antagonists. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is considered potentially harmful and is not recommended [5]. The combination of hydralazine and isosorbide dinitrate is recommended in African-American patients with NYHA class III–IV HFrEF and is considered potentially useful in patients who are ACE inhibitor or ARB intolerant. Digoxin similarly is potentially beneficial in patients with HFrEF to decrease hospitalizations for HF (remains a class IIa recommendation) [5].

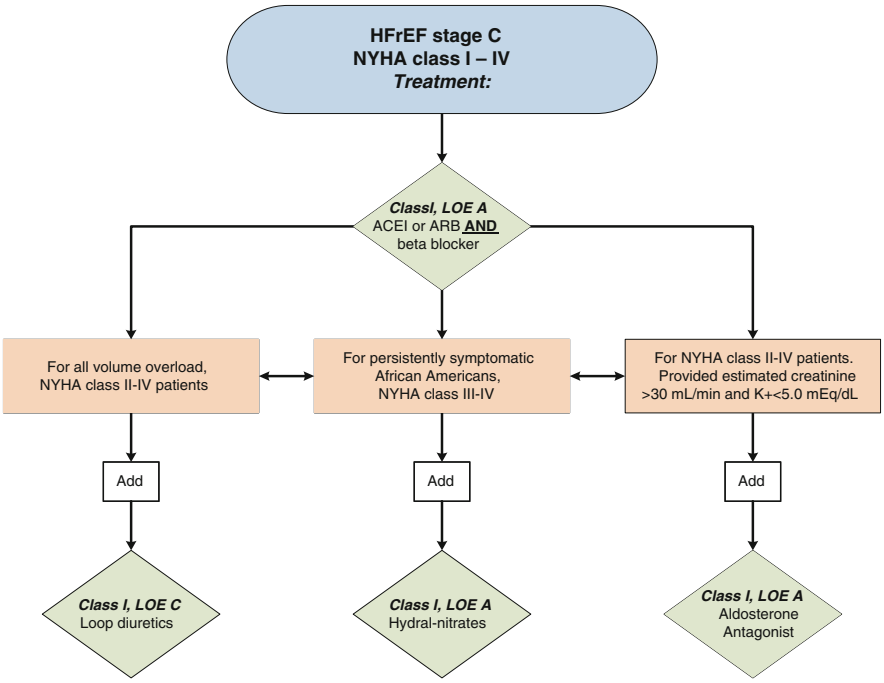

Fig. 1.2 Evidence-based, guideline-directed medical therapy in symptomatic stage C (NYHA class I–IV) HF patients with reduced ejection fraction (HFrEF) (Reproduced with permission from *JACC* [5])

1.5.2 Device Therapy

Implantable cardioverter defibrillator (ICD) is recommended for primary prevention of sudden cardiac death in selected patients with LVEF ≤35 % and NYHA class II or III symptoms, who have reasonable expectation of meaningful survival for more than 1 year [5] (Chap. 8).

Cardiac resynchronization therapy (CRT) is recommended in patients who have LVEF ≤35 %, sinus rhythm, left bundle branch block (LBBB) with a QRS duration of ≥150 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT. CRT can be useful in patients with LBBB but QRS duration of only 120–149 ms or those with non-LBBB pattern and QRS ≥150 ms. Of note, for patients with non-LBBB and QRS 120–149 ms, the CRT indication is not expanded beyond patients with NYHA class III/ambulatory class IV; and in patients with non-LBBB and QRS <150 ms and with NYHA class I or II symptoms, CRT or ICD is not indicated in patients in whom cardiac or noncardiac comorbidity and/or frailty limit survival with good functional capacity to less than 1 year [5].

Mechanical circulatory support (MCS) can be considered in select advanced HF patients in whom definitive management such as cardiac transplantation is planned

(i.e., as a "bridge to transplant"); or cardiac recovery is anticipated (i.e., as a "bridge to recovery"), or as "destination therapy." Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices, is considered reasonable as a "bridge to recovery" or a "bridge to decision" for carefully selected patients with acute, profound hemodynamic compromise. These considerations are in line with the current patient care spectrum, reflecting a higher and broader use of these devices in different clinical scenarios [5].

1.5.3 Acute Decompensated HF

In acute decompensated hospitalized HF patients, intravenous loop diuretics such as furosemide, torsemide, and bumetanide remain as first-line therapy. When diuresis is inadequate, it to be reasonable to intensify the diuretic regimen using either higher doses of intravenous loop diuretics or adding a second (e.g., thiazide) diuretic. In the absence of hypotension, intravenous vasodilators such as nitroglycerin, nitroprusside, or nesiritide may be considered as an adjunct to diuretic therapy for relief of dyspnea in patients admitted with acutely decompensated HF [5].

1.6 Emerging Therapies in HF

Some of the emerging therapies in HF are reviewed below, and strategies such as gene therapy and microRNA therapeutic are also discussed at length in Chap. 14 and 15.

1.6.1 Cardiac Inotropes

Currently used inotropic agents have failed to show benefit beyond short-term hemodynamic improvements in patients with HF [6]. These include cardiac glycosides, β-adrenoceptor agonists, phosphodiesterase (PDE) inhibitors, and calcium sensitizers. Heightened energy utilization and the coupling of contractility, chronotropy, and calcium represent significant limitations to their use. Not only do they induce maladaptive remodeling by increasing metabolic demands on the heart, they are also pro-arrhythmic. Increased arrhythmias associated with their use increase mortality and morbidity in patients with decompensated HF. Two novel therapies attempting to dissociate inotropy and arrhythmogenicity are cardiac myosin activators such as omecamtiv mecarbil and istaroxime.

Cardiac myosin activators (CMA) are drugs that directly target the force-generating cardiac enzyme and myocardial myosin ATPase, accelerating its activity in order to enhance contractility. They increase cardiac myosin ATPase, enhancing the release of inorganic phosphate, which strengthens binding between myosin and actin, leading to shortening of the cardiac sarcomere. CMAs increase the efficiency

with which ATP is utilized without increasing ATP consumption by increasing the number and duration of actin-myosin crossbridges for each ATP molecule consumed. This prolongs systole but not the rate at which force is developed. This is unlike conventional inotropic agents that generally increase ATP consumption and increase the velocity of contraction and rate of force generation but may shorten the duration of systole. Importantly, CMAs do not possess phosphodiesterase activity, do not increase diastolic calcium concentrations, and can increase cardiac performance in patients receiving beta-blockers. In the phase II Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute HF (ATOMIC-AHF) study, omecamtiv mecarbil did not achieve its primary efficacy endpoint in reducing dyspnea in patients with acute HF. However, a cohort which received the highest dose of the drug showed greater dyspnea relief compared with placebo. *C*hronic *O*ral *S*tudy of *M*yosin Activation to *I*ncrease *C*ontractility in *HF* (COSMIC-HF) is a double-blind, randomized, placebo-controlled, multicenter, dose escalation study designed to assess the pharmacokinetics and tolerability of three oral modified-release formulations of omecamtiv mecarbil in patients with chronic HF and left ventricular systolic dysfunction. Calcium dynamics play a prominent role in cardiac function, and its abnormalities contribute to several cardiac diseases including HF, which is discussed at length in Chap. 4.

Istaroxime, an inhibitor of Na^+/K^+-ATPase and an activator of sarcoplasmic reticulum calcium pump (SERCA), is a new luso-inotropic compound that stimulates cardiac contractility and relaxation in healthy and failing hearts in animal models and in patients with acute HF syndrome. The HORIZON-HF trial evaluated the hemodynamic, echocardiographic, and neurohormonal effects of intravenous istaroxime in 120 patients hospitalized with HF and reduced ejection fraction. In this randomized, double-blind, placebo-controlled, dose-escalating study, three doses of istaroxime or a placebo were given as intravenous infusions over 6 h to patients with a history of HF and a pulmonary capillary wedge pressure (PCWP) over 20 mmHg [7]. A reduction in PCWP was the primary endpoint, which was attained in all three dose groups during the entire observation period of 6 h. There was an increase in systolic blood pressure and a transient increase in cardiac index with the highest dose and a decrease in heart rate and diastolic and systolic volume, without a change in ejection fraction. Echocardiographic indicators of diastolic function also showed improvement. The limitation of this study is related to the fact that patients included presented with milder forms of acute HF, not requiring inotropic interventions.

Research involving gene therapy approaches to increase sarcoplasmic reticulum calcium pump activity and is also ongoing (Chap. 15).

1.6.2 Neurohormonal Modulation

The renin-angiotensin aldosterone system (RAAS) represents a long established therapeutic target in cardiovascular disease, and multiple inhibitors of the pathway have been shown to improve outcomes in chronic HF. However, the inhibition of downstream pathway activity can produce a compensatory rise in plasma renin

activity that can competitively overcome RAAS blockade. Hence, aliskiren, a direct renin inhibitor, was studied in the Aliskiren Trial on Acute HF Outcomes (ASTRONAUT) [8]. This international, double-blind study enrolled stable patients hospitalized for HF and followed them after discharge. Patients were randomized to receive either aliskiren, starting at 150 mg and increasing to 300 mg, or placebo, in addition to other standard HF therapies. After 6 months, patients in both groups had a similar likelihood of cardiovascular death or rehospitalization for HF. Despite a significant and sustained reduction in natriuretic peptide level, aliskiren did not reduce mortality or rehospitalization rates. It is possible that a beneficial effect on HF progression, as suggested by this long-term improvement in natriuretic peptide level, was offset by potential negative drug-associated effects, such as hyperkalemia, hypotension, and worsening renal function, particularly in patients with diabetes mellitus (Chap. 36).

More recently, the results of the PARADIGM-HF trial were presented at the European Society of Cardiology meeting where the angiotensin receptor neprilysin inhibitor LCZ696 was superior to enalapril in reducing the risk of death and of hospitalization for HF [9]. Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling. Combined inhibition of the renin-angiotensin system and neprilysin had effects that were superior to those of either approach alone in experimental studies, but in clinical trials, the combined inhibition of ACE and neprilysin was associated with serious angioedema. LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, was designed to minimize the risk of serious angioedema.

1.6.3 Autonomic Nervous System Modulation in HF

The pathophysiology of HF is characterized by neurohormonal activation and autonomic imbalance with increase in sympathetic activity and withdrawal of vagal activity. In the failing human heart, increased sympathetic outflow from the central nervous system in HF affects several key organs, including the heart, the kidney, and the peripheral vasculature. In the acute setting, catecholamine-induced augmentation of ventricular contractility and heart rate helps maintain cardiac output. Increased sympathetic activity also leads to systemic vasoconstriction and enhanced venous tone, both of which initially contribute to maintenance of blood pressure. Both norepinephrine and angiotensin II stimulate proximal tubular sodium reabsorption, which contributes to sodium retention and volume expansion characteristic of HF. The heart responds to the increase in venous return with an elevation in end-diastolic volume that results in a rise in stroke volume via the *Frank–Starling* mechanism. However, chronic sympathetic stimulation causes detrimental effects on the heart like interstitial growth and remodeling that increase myocardial mass

and may lead to further enlargement of the left ventricular chamber [10]. The elevated sympathetic nervous system (SNS) outflow and norepinephrine in chronic HF lead to chronically elevated stimulation of the cardiac β-adrenergic receptor system. In an attempt to defend the heart against excessive catecholaminergic toxicity, the body responds by downregulating β1-adrenergic receptors and causes G-protein-coupled receptor kinases (GRK2)-mediated cardiac β1-adrenergic receptor and β2-adrenergic receptor desensitization. This results in a reduction in cardiac β-adrenergic receptor density and responsiveness and resulting in cardiac inotropic reserve depletion. The pathophysiology of HF is discussed in detail in Chap. 3.

1.6.4 Novel Sympathetic Nervous System Modulation Drugs

Clinical trials clearly demonstrate a strong association between increased heart rate increased mortality and morbidity in patients with a wide spectrum of cardiac diseases including CAD and HF. Heart rate reduction has in part been shown to contribute to the beneficial effects of beta-blockers in HF (Chap. 5). Post hoc analysis of the CIBIS II trial showed that baseline heart rate and heart rate change on beta-blocker, bisoprolol, are significantly related to prognosis in HF [11]. The lowest baseline heart rate and the greatest heart rate change were associated with best survival and reduction of hospital admissions. Heart rate is currently not the determining factor when uptitrating β-blockers in HF. In the major guidelines, the emphasis has been on trying to achieve the target doses used in the major clinical trials. In these trials, β-blocker dose was not determined by heart rate effects, but by a prespecified "target" dose or limiting symptoms. The use of beta-blockers in patients with HF is limited by hypotension and symptoms which precludes upward titration of the dose to the "target dose."

Ivabradine, a novel medication, is a selective inhibitor of the hyperpolarization-activated cyclic-nucleotide-gated *funny* current (I_f) involved in pacemaking generation and responsiveness of the sinoatrial node, which results in heart rate reduction with no other apparent direct cardiovascular effects. The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) investigated the effect of heart rate reduction using the selective sinus node inhibitor ivabradine on outcomes in HF. A total of 6,558 patients with HF, a left ventricular ejection fraction ≤35 %, and a sinus heart rate of ≥70 beats per minute were randomly assigned to ivabradine or placebo and followed for a median of 23 months [12]. The primary endpoint was a composite of cardiovascular death or hospital admission for worsening HF. Patients in the ivabradine group experienced the primary endpoint less frequently than those in the placebo group (24 vs. 29 %) largely due to reduced hospitalizations for HF (HR 0.74, 95 % CI 0.66–0.83) and reduced deaths due to HF (HR 0.74, 95 % CI, 0.58–0.94). Patients in the ivabradine group with an achieved heart rate less than 60 bpm at 28 days had fewer primary endpoint events than those with higher heart rates. Based on the results of the SHIFT, the European Society of Cardiology (ESC) guidelines in 2012 recommended that ivabradine should be considered to reduce the

risk of heart failure hospitalizations in patients in sinus rhythm (SR), LVEF ≤35 %, an HR ≥70 bpm, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of β-blocker, ACE-I, and an aldosterone receptor antagonist (class of recommendation/level of evidence: IIa/B). Also it may be considered to reduce the risk of HF hospitalization in patients in SR with an EF ≤35 % and an HR ≥70 bpm, who are unable to tolerate a β-blocker (COR/level of evidence: IIb-C). However, a limitation of the SHIFT is that only 23 % of patients were receiving target doses of beta-blockers. Patients receiving 50 % or more of target β-blocker doses at baseline had no significant benefit from ivabradine for the primary endpoint. Also the mechanism of benefit of ivabradine is not completely clear. HR reduction might be part of the benefit, but ivabradine also has other effects, e.g., on calcium handling which might affect ventricular remodeling and contribute to the beneficial effect of the drug. From the available data, ivabradine might reduce heart failure hospitalizations when added to contemporary heart failure therapies. It remains unknown whether ivabradine can improve outcomes in addition to optimally managed heart failure therapies or its benefits relative to other therapies, especially β-blockers. The results from SHIFT provide the basis for additional trials to test these important and clinically relevant questions.

1.6.4.1 Vagal Nerve Stimulation

Reduced vagal activity is associated with increased mortality in patients with HF, and many investigators have shown that restoration of autonomic regulatory function by vagal nerve stimulation improves survival in animal models of HF [13]. A multicenter, open-label phase II safety and feasibility study was reported with the use of right cervical vagal nerve stimulation synchronized to the cardiac cycle (Cardiofit System, BioControl Medical, Yehud, Israel), which showed that chronic vagal nerve stimulation may be safe and tolerable and may improve quality of life and LV function [14]. This was followed by a feasibility study, the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study [15], which used the Cyberonics vagal nerve stimulation therapy system and provides additional information on the role of autonomic regulation therapy in patients with LV dysfunction and chronic symptomatic HF. In this study, subjects were randomized to thoracic subcutaneous vagal nerve stimulation (VNS) therapy system implantation for either right or left cervical VNS. Following titration, VNS was then delivered for 6 months at an amplitude of 2.0 (±0.6) mA and a constant frequency of 10 Hz.

The study showed significant improvement (mean 4.5 %) from baseline in left ventricular ejection fraction (LVEF) among all patients, with no statistically significant differences between left- and right-sided VNS. There was also a mean improvement of 56 m in the 6-minute walk test, but this improvement was significantly less with left- compared to right-sided VNS. There was a similar rate of device-related adverse events in both groups, including transient mild dysphonia (voice alteration), cough, and oropharyngeal pain, which resolved during the study. These results are promising and need to be confirmed in a larger, controlled trial (Chap. 6).

1.7 Advances in Devices in HF

In the last 15–20 years, the treatment of HF has expanded with the addition of implantable devices to the standard pharmacotherapy. Devices continue to evolve and change with each new generation that is produced. With their changes in design, function, and the addition of cardiac monitoring abilities, the devices are beginning to be studied at earlier stages of HF emphasizing the importance of consideration of device therapy as one would consider pharmacotherapy in their patients (Chap. 8).

Despite the benefits of CRT, about 25–30 % of HF patients with proper indications for CRT are nonresponders and do not have clinical benefit or echocardiographic evidence of improvement in ventricular dyssynchrony. This is mostly due to ineffective placement of the left ventricular lead [16]. In an attempt to improve left ventricular pacing, CRT devices were made with quadripolar left ventricular leads as opposed to the standard bipolar left ventricular lead. This allows for more pacing options proximally along the left ventricular lead in order to tailor therapy for the individual patient. There has been some echocardiographic evidence of improved ventricular synchrony, but no studies have compared bipolar to quadripolar CRT devices for clinical benefit [17]. The technical difficulties of placing endovascular leads in the coronary sinus were also thought to contribute to suboptimal lead placement; therefore, epicardial leads have been developed. Despite this, no clinical benefit has been demonstrated with epicardial leads as opposed to endovascular [18]. Also being developed are leadless CRT devices in which endocardial electrodes are placed and a wireless transmitter is implanted subcutaneously [19]. The wireless transmitter sends ultrasound signals to the endocardial electrodes which then electrically pace. Eliminating the need for leads allows one to place the pacing electrode almost anywhere in the heart, and it is not dependent on the anatomy of the coronary sinus. Another emerging area of improvement for nonresponders is automatic optimization of atrioventricular (AV) and interventricular (VV) delay by the device itself. The RESPOND-CRT trial is evaluating for safety and clinical benefit of a device that automatically reprograms the AV and VV delay weekly according to vibration sensing of the right atrial lead that is a surrogate for contractility [20].

Additional cardiac monitoring abilities of implantable devices include impedance measurements to assess for increasing volume overload. Right ventricular lead impedance monitoring was unable to show clinical benefit due to the high rate of false positives, but early evaluation of using the left ventricular lead in CRT devices has shown greater specificity, thus decreasing the amount of false positives [21, 22]. The clinical benefit is yet to be established, but some recent studies have shown that telemonitoring of cardiac parameters by intracardiac devices results in decreases in composite outcomes of death, hospitalizations, and change in NYHA class [23]. Further trials are needed to evaluate the clinical effectiveness or use of these newer CRT devices with monitoring capabilities.

Clinical trials demonstrating benefit of ICDs were performed with single-chamber ICDs. Dual-chamber ICDs help in the identification of atrial rhythms, but there is controversy over whether the increased cost justifies the identification. Also it is controversial, and studies conflict on the ability of dual-chamber ICDs to reduce

unnecessary shocks by their identification of atrial rhythms. In the ICD subset of the MADIT-CRT trial, unnecessary shocks were not significantly different in single-chamber versus dual-chamber devices [24]. As with CRT, trials have evaluated the clinical effectiveness of ICDs that have the ability to perform HF parameter monitoring. Impedance testing to look for pulmonary fluid overload has shown decreases in hospitalizations by identifying worsening volume overload sooner [25]. Going even farther than impedance testing was the HOMEOSTASIS trial which was the first to test a septal anchoring device with ICDs that directly measures left atrial pressure [26]. This measurement combined with a physician-directed patient self-management program resulted in decreased hospitalizations and mortality. Newer methods of placing ICDs subcutaneously, as opposed to endovascular, have not changed outcomes but allow for better options in select patients, such as those with history of device infection and end-stage renal disease patients needing venous dialysis access [27].

Patients who continue to have worsening hemodynamics and HF despite pharmacologic and implantable device therapy mentioned above are considered for transplant and ventricular assist devices. The growing population of advanced HF patients and limited availability of donor hearts creates an increasing number of patients with left ventricular assist devices (LVADs). LVADs were initially intended for bridge to transplant, but with continued use and development of smaller, more durable devices are being increasingly used as "destination therapy" [28]. LVADs are also being used as "bridge to recovery" and are able to be explanted in patient's that recover enough heart function to be managed solely by pharmacologic agents [29]. First-generation LVADs (Novacor and HeartMate XVE) worked by pulsatile flow, but second-generation (HeartMate II and Jarvik 2000) and third-generation (HeartMate HVAD) LVADs have moved to continuous flow pumps that allow for smaller pumps with higher flow rates [30]. Most models consist of an inflow tract that draws blood out of the left ventricle into the pump which then sends blood to the outflow tract typically attaching to the aorta. The second-generation pumps have to sit in the abdominal cavity due to their size, but some of the emerging smaller third-generation pumps reside within the pericardium. LVADs allow for ventricular unloading which is thought be a significant contributor to reverse remodeling that allows for either bridge to recovery or bridge to candidacy for transplant by improving hemodynamics and perfusion of other affected organs [30–32]. The major complications associated with current LVADs include infection, stroke, and gastrointestinal bleeding.

Emerging therapies include percutaneously placed ventricular assist devices which include the Impella LP2.5, TandemHeart, and Reitan catheter pump [33]. The advantages of these pumps are that they can be placed quickly in the catheter lab for patients with acute cardiogenic shock and removed easily once the acute event is over. The disadvantage is that they should not stay in place for long periods of time for patients who do not recover. These percutaneous LVADs are increasingly being used for patients with HF but not acutely decompensated undergoing high-risk percutaneous coronary intervention (PCI). The Impella is a catheter-based system that uses an impeller-driven continuous flow pump which delivers blood from

the left ventricle to the aorta with up to 2.5 L/min of cardiac output. The TandemHeart is a left atrial to femoral artery bypass system that uses a continuous flow centrifugal pump to deliver up to 5.0 L/min of cardiac output. The Reitan catheter pump is placed in the proximal descending aorta and uses a propeller pump to create a gradient in the aorta thereby decreasing afterload.

Still being studied in ongoing trials are micropumps that are percutaneous ventricular assist devices designed to be placed in patients with NYHA class IIIb or IV HF [34, 35]. They are meant for patients to be able to wear in the ambulatory setting just as the first-, second-, and third-generation LVADs mentioned above, but they do not produce as much cardiac output with peak flow around 2.5–3.0 L/min. The micropumps are inserted underneath the skin much like an ICD generator and then have inflow catheter that is transseptal to draw blood from the left atrium. The outflow catheter then delivers blood to the subclavian. The clinical benefit with micropumps is being evaluated with further trials.

1.8 Exercise in HF

A number of studies have demonstrated the need of small amounts of exercise for patients with HF. This is being discussed at length in Chap. 9.

1.9 Care Coordination, Transitions of Care, and Shared Decision Making

Clinicians must maintain vigilance about psychosocial, behavioral, and socioeconomic issues that patients with HF and their caregivers face, including access to care, risk of depression, and healthcare disparities. Every patient with HF should have a clear, detailed, and evidence-based plan of care that ensures the achievement of GDMT goals, effective management of comorbid conditions, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with guidelines [5]. This plan of care should be updated regularly and made readily available to all members of each patient's healthcare team.

Effective systems of care coordination with special attention to care transitions should be deployed for every patient with chronic HF that facilitate and ensure effective care that is designed to achieve GDMT and prevent hospitalization. This may include communication between primary care physicians, hospitalists, HF specialists, family, patient, nurses, nurse practitioners, clinical pharmacists, and physician assistants.

Improved communication between clinicians and nurses, medication reconciliation, carefully planned transitions between care settings, and consistent documentation are examples of patient safety standards that should be ensured for all patients with HF [5].

Palliative and supportive care is effective for patients with symptomatic advanced HF to improve quality of life [5]. The HF team should help patients and their families explore treatment options and prognosis, with emphasis on patient's goals and preferences, especially for advanced HF patients who require frequent hospitalizations and who remain refractory despite advanced therapies. Along with above strategies, patients with HF should receive specific education to facilitate HF self-care and shared decision making [5].

1.10 Concluding Remarks

HF is a very prevalent medical condition with significant mortality and morbidity. In the last two decades, our understanding of etiology, definition, classification, diagnosis, and treatment of heart failure has significantly evolved, but HF still remains as the leading cause of hospitalizations among elderly patients and approximately half of the people who develop HF will die within 5 years of diagnosis. Development of patient centric care delivery models, new medical and device therapies, and enhancement of care coordination will likely improve clinical outcomes and patient quality of life.

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Chapter 2
Cardiac Prevention Guidelines

John W. McEvoy, Roger S. Blumenthal, and Erin D. Michos

Abstract In this chapter, we summarize a number of recently released guideline documents for the prevention of cardiovascular disease. Specifically, guidelines for the assessment of cardiovascular risk, the treatment of high cholesterol, the treatment of obesity, optimizing diet and healthy lifestyle habits, and the treatment of hypertension are discussed. Particular focus is given to new developments in these guidelines, pharmacologic considerations related to the guidelines, as well as positive and negative attributes of the recommendations. A thorough understanding of these recent guidelines, including their strengths and weaknesses, is critical in order to deliver the most up-to-date evidence-based cardiovascular care.

Keywords Guidelines • Preventive cardiology • Cardiac risk • Hypercholesterolemia • Hypertension • Obesity

2.1 Introduction

The year 2013 was memorable and extremely productive from a cardiac guideline perspective. In particular, four US guideline documents were released just prior to the American Heart Association Scientific Sessions conference in November 2013. These guidelines were met with fevered anticipation due to delays in their release that were, in part, due to a decision by the National Institutes of Health to withdraw from guideline development, requiring that these documents be released through professional groups (the American Heart Association [AHA] and the American College of Cardiology [ACC]). However, despite the long incubation period, these groundbreaking documents will shape the delivery of cardiovascular prevention care in the USA, and throughout the world, for years to come.

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The documents consisted of:

1. 2013 AHA/ACC Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults by Stone et al. [1]
2. 2013 AHA/ACC Guidelines on the Assessment of Cardiovascular Risk by Goff et al. [2]
3. 2013 AHA/ACC Guidelines on Lifestyle Management to Reduce Cardiovascular Risk by Eckel et al. [3]
4. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults by Jensen et al. [4]

These official guidelines were closely followed by updated hypertension treatment recommendations from the panel appointed to the Eighth Joint National Committee [5]. The overarching theme of the new guidelines was to maximize the number of recommendations that are based on high-quality evidence from randomized controlled trials. This focus was motivated by recommendations from the Institute of Medicine (IOM) in 2011 regarding guideline development. Indeed, these new 2013 cardiac guidelines were all based on a framework of evidence synthesis, ethical standards, and dissemination that was proposed by the IOM. As part of this framework, a systematic review of the medical literature was performed for each guideline by an independent group, separate from the guideline writing group. Only studies that were of sufficient quality were then forwarded to the guideline writers for inclusion in their recommendations. In addition, the guideline writers, particularly for the risk assessment document, were committed to delivering more generalizable recommendations, applicable to a wider demographic in the population. In this chapter, we will detail the major recommendations contained in each of these new guideline documents and also discuss strengths, weaknesses, and controversies. Where relevant, we will also briefly discuss how recent US guidelines differ from other major international documents.

2.2 Interpretation of Guideline Recommendations

The guideline recommendations have two components:

1. Level of evidence (nature of the clinical evidence – ranging from recommendations based on multiple randomized studies or meta-analysis to recommendations based on expert option)
2. Class of recommendation (based on the strength of the effect, ranging from strong benefit [should be performed] to potential harm [should not])

These guidelines are meant to inform clinical management and are not a replacement for clinical judgment. It is generally recommended that the ultimate decision

about care of a particular patient must be made by both the healthcare provider and patient. As a result, situations might arise in which deviations from these guidelines may be appropriate.

2.3 Risk Prediction Guidelines

As an understanding of the risk prediction guidelines is important for the application of the cholesterol treatment guidelines, we will start with these recommendations first. A major development, and strength, of these risk prediction guidelines was the derivation of a new Pooled Cohort Risk Equation. The guideline panel was concerned that prior risk calculators, notably the Framingham risk score (FRS), were derived from relatively homogenous populations of mostly white participants. Thus, the new equation was drawn from four large, racially and geographically diverse, modern NHLBI-sponsored cohort studies. These were the Cardiovascular Health Study, the Atherosclerosis Risk in Communities (ARIC) study, the Framingham original and offspring cohorts, and the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Important features of this new equation are:

1. Separate formulas applied to men and women and to non-Hispanic whites and non-Hispanic blacks (aged 40–79 years of age).
2. The outcome predicted by this equation was expanded to predict all atherosclerotic cardiovascular disease (ASCVD) events, recognizing the importance of stroke in an aging population.

To review, ASCVD events are comprised of nonfatal myocardial infarction, coronary heart disease (CHD) death, or fatal or nonfatal stroke, over a 10-year period, among people free from ASCVD at the beginning of the period. Primarily because of geographical variations in practice patterns, coronary revascularization, angina pectoris, and heart failure were not included in the global ASCVD end point. In addition, and somewhat surprisingly, the risk factors entered into the new equation are essentially unchanged from before (age, total and HDL cholesterol, systolic blood pressure (BP) [including treated or untreated status], diabetes, and current smoking status). Thus, despite the many years that had passed since the derivation of the FRS, no novel risk factors have been included in this new risk equation. One of the reasons for this is that the cohorts used to derive this new risk equation were somewhat dated (by design they required over 10 years of follow-up) and many did not collect novel risk markers such as coronary artery calcium (CAC).

In addition to deriving a new risk equation for use in cardiac prevention, the new risk prediction guidelines also address two further "critical questions." The first was "What is the evidence regarding reclassification when high-sensitivity C-reactive protein (hs-CRP), apolipoprotein B (ApoB), glomerular filtration rate (GFR),

microalbuminuria, family history, cardiorespiratory fitness, ankle-brachial index (ABI), carotid intima-media thickness (CIMT), or CAC score are considered in addition to the variables that are in the traditional risk scores?" The second question was "Are models constructed to assess the long-term (≥15 years or lifetime) risk for a first ASCVD event in adults effective in assessing variation in long-term risk among adults at low and/or intermediate short-term risk, whether analyzed separately or combined?"

Based on their review of the evidence, and after considering the above "critical questions," the guideline writers recommended that the new equation (10-year ASCVD risk) be applied every 4–6 years to non-Hispanic blacks and non-Hispanic whites, 40–79 years of age, who do not have known ASCVD (persons in primary prevention). This equation may be considered for other ethnicities, although with caution. For persons aged 20–79, it is reasonable to assess traditional ASCVD risk factors every 4–6 years, and if there are any abnormalities, then assessment of 30-year or lifetime risk may be considered (specifically for those aged 20–59 years at low 10-year risk). Lifetime risk can be used to enhance the risk discussion with the patient and to modify risk factors.

In addition, in cases where a provider feels the risk-based treatment decision is uncertain (after discussing the treatment possibilities with the patient), additional testing with hs-CRP, CAC, or ABI is reasonable to guide reclassification. Upward reclassification of risk is advised for persons who have a family history of premature CVD (male first-degree relative <45 years and females <55 years), hs-CRP ≥2 mg/L, CAC ≥300 Agatston units (or 75th percentile for age, sex, and ethnicity), or ABI <0.9. However, the nature of how such reclassification should be performed was not detailed specifically in this document. In addition, there was also no specific mention of possible "down-titration" of risk, such as for those with CAC scores of 0. Importantly, routine use of CIMT (without assessment of the presence of carotid plaque) was recommended against in these new guidelines.

Major strengths of these guidelines include:

1. The thorough evidence-based approach
2. The use of rigorously evaluated historical cohorts that accrued when statin therapy was not widespread and, thus, facilitates closer approximations to the natural history of ASCVD (making predictions more valid estimations of pretreatment risk and also easier to align with evidence from randomized controlled trials)
3. The derivation of a new equation that incorporates stroke (an increasingly important end point in modern aging populations) as part of the predicted end point
4. Gender- and race-specific equations [6]

However, the new risk equation was not without controversy, and major concerns regarding overestimation of risk [7] initially threatened to overshadow the many positive attributes of this guideline. However, while it is clear that the new

equation is not perfect and that discrimination for events is typically no better than for older risk equations (such as FRS) [8], it has been demonstrated that the new equation is reasonably well calibrated to modern populations (particularly in those to whom the equations are most important, such as persons aged 40–75 years, without diabetes, not taking statins, and with LDL-C levels of 70–189 mg/dl) [9]. Notably, the risk assessment guidelines caution against applying this algorithm to groups that are neither white nor black. This may result in overestimation of ASCVD risk in groups such as Chinese/East Asian Americans and underestimation in American-Indians and Americans of South Asian descent. Indeed, one notable absence from the pooled cohorts was the Multi-Ethnic Study of Atherosclerosis (MESA), which unfortunately had not reached 10 years of follow-up time at the time the 2013 risk models were being developed. This is disappointing because by design MESA is the most ethnically diverse of the NHLBI-funded cohorts.

Other concerns relate to the failure to include family history of premature CHD in the equation (although this variable is suggested as a potential option for up-titration of risk), the use of all-cause stroke rather than vascular stroke in the combined outcome (atherosclerotic stroke such as from carotid disease is more likely to be statin responsive than embolic stroke from atrial fibrillation or lacunar stroke from hypertensive disease), and limited guidance on how to incorporate novel markers of risk such as CAC scoring into the risk discussion [6]. Despite these reservations, it has become increasingly clear that these new equations are a step in the right direction and provide a solid platform for improving future iterations.

2.4 Cholesterol Treatment Guidelines

Of all the recent guideline updates, perhaps the most important, and controversial, one was the cholesterol treatment guideline. This guideline will drive future statin utilization in the USA and, thus, may have the biggest impact on ASCVD events. In many respects, this new cholesterol treatment guideline represents a sea change in our collective thinking about the use of statins in primary prevention and also a paradigm shift in how treatment decisions are made in primary prevention settings. Once again, the primary focus was on high-quality randomized trial evidence. Therefore, it is likely that the validity of these recommendations is the strongest of any cholesterol treatment guideline to date. However, because observational evidence was deemed unsuitable for inclusion in these recommendations, some unexpected "collateral damage" was also inflicted, at least according to some of the guideline skeptics (most notably the loss of low-density lipoprotein cholesterol [LDL-C] and non-HDL cholesterol [non-HDL-C] treatment targets).

Table 2.1 Four risk groups most likely to benefit from statin therapy, plus optional groups that may be considered for statin initiation

1	Secondary prevention	Clinical history of ASCVD
2	Primary prevention	LDL-C ≥190 mg/dL, age ≥21 years
3	Primary prevention	Diabetes: age 40–75 years, LDL-C 70–189 mg/dL
4	Primary prevention	No diabetes: ≥7.5 % 10-year ASCVD risk, age 40–75 years, LDL-C 70–189 mg/dL
Optional candidates for statin therapy		≥5 % 10-year ASCVD risk
		Family history of premature ASCVD
		hs-CRP ≥2.0 mg/L
		CAC score ≥300 or ≥75th percentile,
		Ankle-brachial index <0.9
		LDL-C ≥160 mg/dl

At the center of these new guidelines is the identification of four "statin benefit" groups (Table 2.1) which are as follows:

1. Individuals with a history of clinical ASCVD should receive statin therapy (high-intensity statin for persons ≤75 years and moderate for those >75 years).
2. Primary prevention individuals ≥21 years with LDL-C ≥190 mg/dL (which is in the range concerning for a genetic dyslipidemia) should receive statin therapy (preferably high intensity), and it is reasonable to achieve at least a 50 % reduction in LDL-C (additional non-statin therapy if needed to achieve this target may be considered).
3. Primary prevention individuals aged 40–75 years with diabetes and LDL-C ≥70 mg/dL should receive at least moderate statin therapy, and it is reasonable to consider high-intensity statins when ASCVD risk ≥7.5 % over the next decade.
4. Primary prevention individuals aged 40–75 years without diabetes but who have LDL-C ≥70 mg/dL and elevated ASCVD risk ≥7.5 % should receive moderate- or high-intensity statins after a clinician-patient discussion (moderate statins may also be considered for those with ASCVD risk 5–7.5 % or with elevated novel risk markers as described above). The patient with ASCVD risk >7.5 % who does not have diabetes or clinical evidence of ASCVD should not be given statin therapy without clinician-patient risk discussion. Patient preference needs to be considered in initiation of statin in this group of patients.

High-intensity statins include atorvastatin 40–80 mg and rosuvastatin 20–40 mg and should reduce LDL-C ≥50 %. Moderate-intensity statins should reduce LDL-C 30–50 % and include atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin 40 mg twice daily, and pitavastatin 2–4 mg (Chap. 28). Of note, the guidelines do not

recommend statins in persons on hemodialysis or those with advanced heart failure (due to lack of benefit in randomized clinical trials such as AURORA and CORONA).

While LDL-C targets are no longer endorsed by the guidelines, regular monitoring of statin therapy for adherence and safety is recommended. In order to monitor therapeutic response, a fasting lipid panel should be performed within 4–12 weeks of initiation and 3–12 months thereafter. Most clinicians will likely choose to recheck a lipid profile on a yearly basis in stable patients to assess compliance and to look for signs of new metabolic conditions (such as hypothyroidism) that may lead to worsening of the lipid profile. Individuals receiving statins should be monitored for new onset diabetes, especially those who are receiving high-intensity statin therapy and those with preexisting glucose intolerance [10]. While the guidelines do not routinely recommend non-statin therapies, it is reasonable to consider alternatives for persons who are completely statin intolerant or cannot achieve the recommended intensity of statin.

It is important to emphasize that a central tenet of these new cholesterol treatment guidelines is that, while four specific groups of "statin benefit" are endorsed for consideration of statin initiation, the final decision to start therapy should only occur after a full clinician-patient risk discussion (particularly for the fourth, primary prevention, group). This discussion should cover the following: heart-healthy lifestyle, the potential for ASCVD risk reduction, the potential for side effects, management of other risk factors, patient preferences, and whether any further testing may be necessary when the decision is unclear. This discussion is particularly important as there have been concerns for overuse of statin therapy based in these guidelines [8]. Patient preferences regarding lifelong preventive therapies should be given more priority [11]. A summary of the new cholesterol treatment recommendations is provided in Fig. 2.1.

While there is no doubt that these cholesterol treatment guidelines represent a major step forward in preventive cardiology, there have been some criticisms (Table 2.2). Most notably was the concern that statins may become overprescribed in the setting of overestimation of risk using the new ASCVD risk calculator, which is heavily influenced by chronologic age [12]. In addition, there have been concerns about the loss of LDL-C targets for therapy. The authors of the guidelines removed these targets because there was no randomized evidence that treatment to specific LDL-C targets is beneficial (statins in randomized trials were allocated based on intensity and dosage) and because there was concern that recommending specific targets may motivate the use of non-statin medications (which are mostly of unproven efficacy) just to get patients to arbitrary LDL-C levels. However, there is biologic rationale to justify LDL-C targets, particularly in higher-risk secondary prevention [13].

Similarly, monitoring of LDL-C may identify persons with high residual risk and also may justify consideration of non-statin medications (particularly in those with atherogenic dyslipidemia/metabolic syndrome). In addition, non-HDL-C targets

may better capture the treatment effect of statins and other therapies on triglyceride-rich remnant lipoprotein burden [14]. Further, these guidelines do not provide specific recommendations on the use of non-statin medications – only to recommend considering non-statin therapy in high-risk patients who have not responded to statins appropriately or are not able to tolerate statins. Finally, LDL-C targets remain in European, Canadian, and other national guideline recommendations, representing a current lack of international consensus on this issue [15]. However, despite these concerns, it is widely considered that implementation of these recent guidelines is likely to improve the cardiovascular health of the population overall.

Fig. 2.1 American Heart Association-American College of Cardiology Statin Initiation guidelines for the treatment of blood cholesterol to reduce ASCVD risk in adults. Colors correspond to the classes of recommendation (*green* = class 1, *yellow* = class 2a, *orange* = class 2b). *Percent reduction in LDL-C can be used as an indication of response and adherence to therapy but is not in itself a treatment goal. †The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin. ‡Consider moderate-intensity statin as more appropriate in low-risk individuals. §For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP 2 mg/L, CAC score 300 Agatston units, or 75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. ‖Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative risk reduction from the intensity of statin initiated (approx. 30 % for moderate-intensity statin or approx. 45 % for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. ¶Potential adverse effects. The excess risk of diabetes is the main consideration in approx. 0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and approx. 0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated. *ABI* indicates ankle-brachial index, *ASCVD* atherosclerotic cardiovascular disease, *CAC* coronary artery calcium, *hs-CRP* high-sensitivity C-reactive protein, *LDL-C* low-density lipoprotein cholesterol, *MI* myocardial infarction, *RCT* randomized controlled trial (Reproduced from open source reference [1]

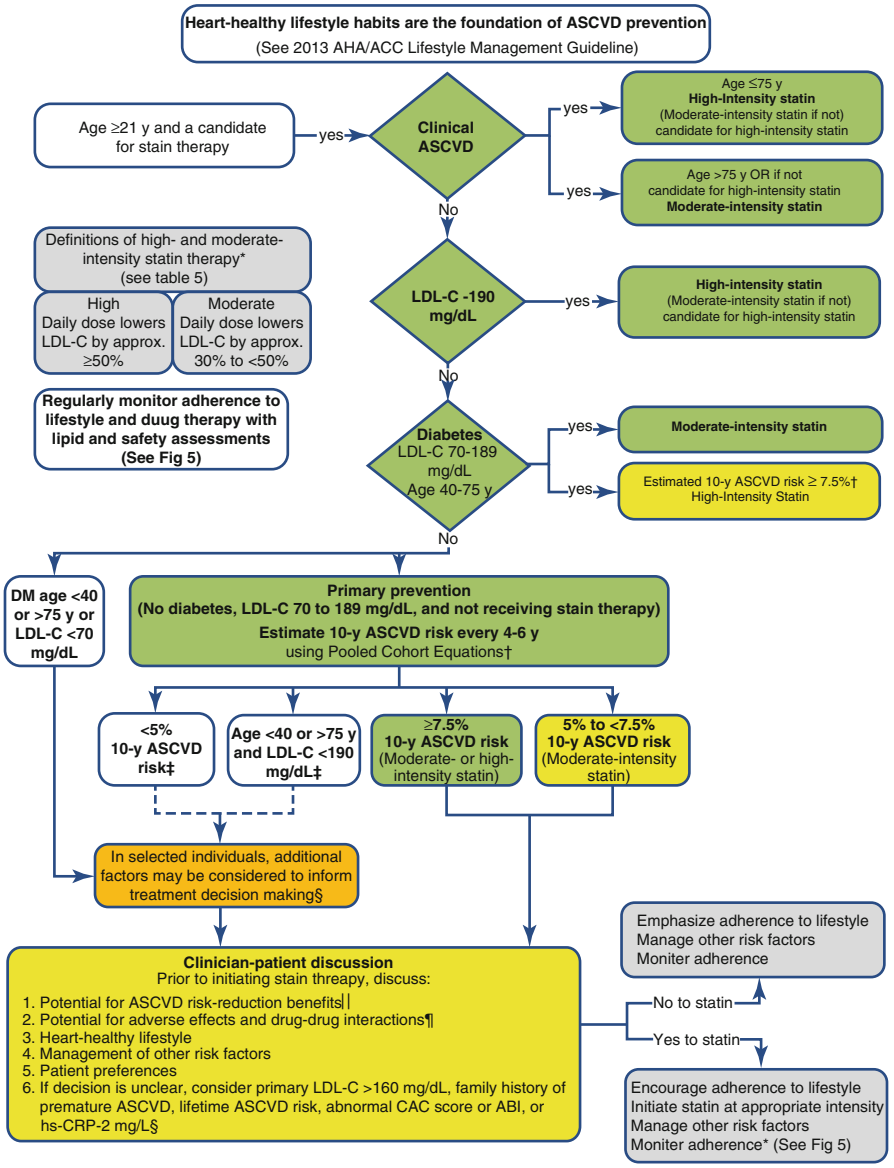
Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)
Age ≥21 y and a candidate for stain therapy
yes
Clinical ASCVD
yes
Age ≤75 y
High-Intensity statin
(Moderate-intensity statin if not) candidate for high-intensity statin
yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of high- and moderate-intensity statin therapy* (see table 5)
High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%
LDL-C -190 mg/dL
yes
High-intensity statin
(Moderate-intensity statin if not) candidate for high-intensity statin
No
Regularly monitor adherence to lifestyle and duug therapy with lipid and safety assessments (See Fig 5)
Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y
yes
Moderate-intensity statin
yes
Estimated 10-y ASCVD risk ≥ 7.5%†
High-Intensity Statin
No
DM age <40 or >75 y or LDL-C <70 mg/dL
Primary prevention
(No diabetes, LDL-C 70 to 189 mg/dL, and not receiving stain therapy)
Estimate 10-y ASCVD risk every 4-6 y
using Pooled Cohort Equations†
<5%
10-y ASCVD risk‡
Age <40 or >75 y and LDL-C <190 mg/dL‡
≥7.5%
10-y ASCVD risk
(Moderate- or high-intensity statin)
5% to <7.5%
10-y ASCVD risk
(Moderate-intensity statin)
In selected individuals, additional factors may be considered to inform treatment decision making§
Clinician-patient discussion
Prior to initiating stain threapy, discuss:
1. Potential for ASCVD risk-reduction benefits
2. Potential for adverse effects and drug-drug interactions¶
3. Heart-healthy lifestyle
4. Management of other risk factors
5. Patient preferences
6. If decision is unclear, consider primary LDL-C >160 mg/dL, family history of premature ASCVD, lifetime ASCVD risk, abnormal CAC score or ABI, or hs-CRP-2 mg/L§
Emphasize adherence to lifestyle
Manage other risk factors
Moniter adherence
No to statin
Yes to statin
Encourage adherence to lifestyle
Initiate statin at appropriate intensity
Manage other risk factors
Moniter adherence* (See Fig 5)

Table 2.2 Pros and cons of the new cholesterol treatment guidelines

Pros	Broadening of risk assessment to include consideration of stroke, with separate risk equations by gender and race
	Identifying statins as the first-line treatment
	Emphasizing the dose of statin and adherence to statin
	Education on managing statin side effects
	Collaboration between different writing groups and use of high-quality evidence from randomized trials
Cons	Abandonment of lipid goals without evidence for superiority of the new approach
	Strong reliance on a risk equation that is heavily weighted by chronological age (without consideration of family history or vascular age) and has only modest discriminatory capacity for events
	Use of additional testing like CAC only to up-classify risk but not to downgrade risk
	Little explicit integration of CAC and choice of threshold of >300 or >75th percentile rather than Agatston score of >100
	Ignores compelling observational evidence that supports LDL-C targets

2.5 Lifestyle Management Guidelines

As this textbook focuses on the pharmacotherapy of cardiovascular disease, we will only cover the highlights from guidelines on lifestyle management to reduce ASCVD risk (Chap. 30). Diet was a major focus of these guidelines, and overall, these guidelines emphasize dietary patterns rather than individual dietary components. Other critical questions addressed included the effect of dietary sodium and potassium on ASCVD risk and the effect of physical activity. Based on rigorous systematic review of the evidence, the working group endorsed the following lifestyle recommendations.

1. Persons who would benefit from LDL-C lowering should consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, and nuts; examples include the DASH diet, the USDA food pattern, or the AHA diet. Saturated fats (aim for <6 % of calories) and *trans* fats should be minimized.
2. For persons who would benefit from blood pressure (BP) reduction, the same dietary pattern should be recommended but also with <2,400 mg of sodium per day (and it is reasonable to aim for 1,500 mg).
3. With respect to exercise, it is reasonable to engage in aerobic physical activity to reduce LDL-C, non-HDL-C, and blood pressure: three to four sessions per week, lasting on average 40 min per session, and involving moderate- to vigorous-intensity physical activity.

2.6 Obesity Guidelines

Similar to the lifestyle management guidelines, the new guidelines for the management of obesity and overweight do not incorporate specific recommendations about pharmacology therapies for excess weight. Rather, this complex guideline document identified five critical questions to address:

1. Identification of patients who need to lose weight.
2. Matching obesity treatment with other cardiac risk profiles (BP, cholesterol, diabetes).
3. Dietary recommendations for weight loss (women should aim for an intake of 1,200–1,500 kcal/day and men 1,500–1,800 kcal/day, or alternatively a deficit of 500–750 kcal/day).
4. Recommendations for lifestyle interventions and counseling (advised that overweight and obese individuals should participate in a *comprehensive lifestyle program* for >6 months [inclusive of 200–300 min/week of high-level physical activity] with on-site high-intensity [≥14 sessions] weight-loss interventions, or alternatively electronically delivered programs are reasonable).
5. Recommendations for referral for bariatric surgical treatment of obesity (it is reasonable to refer patients with BMI ≥40 kg/m^2 and also those with BMI ≥35 kg/m^2 who have obesity-related comorbidities including diabetes). There was insufficient evidence for bariatric surgery in those with BMI <35 kg/m^2 at the time of writing; however, more recent trial data suggest that some diabetics in the 30–35 kg/m^2 BMI range may also benefit from weight-loss surgery, but more data on cost-effectiveness in this group are needed [16].

The above interventions should be targeted for a weight loss of ≥5 % of baseline weight and for improvements of other cardiovascular risk factors. Notably, the high-intensity *comprehensive lifestyle program* is a relatively new concept to many physicians and includes the following:

1. Prescription of moderately reduced caloric diet
2. A program of increased physical activity
3. The use of behavioral therapies (provided by a trained interventionist) to facilitate adherence to diet and exercise

Perhaps most pertinent to this pharmacologic text is that the expert panel did not choose to address various aspects of pharmacotherapy because at the time the guideline was written there was only one approved medication (orlistat, a gastrointestinal lipase inhibitor) for weight loss.

However, the guidelines did acknowledge that in overweight and obese adults with type 2 diabetes, orlistat with lifestyle intervention results in 2–3 kg greater weight loss at 1 and 2 years than placebo with lifestyle intervention. Similarly, the addition of orlistat is associated with greater reductions in fasting blood glucose,

averaging 11 mg/dL and 4 mg/dL at 1 and 2 years, as well as an average greater reduction in hemoglobin A1c of 0.4 % at 1 year [17]. Thus, it appears reasonable that this medication be considered in diabetics who are not losing weight after a *comprehensive lifestyle program* and who do not wish to undergo bariatric surgery.

2.7 Hypertension Treatment Recommendations from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Not long after the release of the above formal guidelines from the AHA/ACC, the panel appointed to JNC 8 released updated recommendations for the treatment of hypertension (Chap. 30). Similar to the AHA/ACC Guidelines, the JNC 8 panel had originally planned to release a new hypertension treatment guideline under the auspices of the National Institutes of Health (NIH). However, when the NIH withdrew from the process of generating guidelines, the JNC 8 panel decided to release their recommendations independently. It should be noted that their recommendations were not endorsed by any professional society and should, therefore, not be interpreted as formal guidelines by a major medical society or national organization. Moreover, the ACC and AHA are now in the process of appointing a new committee to formally update the JNC 7 guidelines, and this writing group will not restrict themselves to basing their recommendations only on randomized controlled trials.

Similar to the above documents, the JNC 8 panel also focused on high-quality evidence derived from randomized controlled trials and performed an independent systematic review of the evidence prior to formulating their recommendations. The major recommendations were as follows:

1. In persons aged ≥60 years, to initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥90 mmHg and treat to a goal SBP <150 mmHg and goal DBP <90 mmHg (with the important corollary that if pharmacologic treatment for high BP results in lower achieved SBP [e.g., <140 mmHg] and treatment is well tolerated and without adverse effects, treatment does not need to be adjusted).
2. In all persons <60 years, or in persons over 60 years with either diabetes or chronic kidney disease, to initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to a goal SBP <140 mmHg and DBP <90 mmHg.
3. In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic (Chap. 38), calcium channel blocker (CCB) (Chap. 37), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) (Chap. 36).
4. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.

5. In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes.
6. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug, and if goal BP cannot be reached with two drugs, add and titrate a third drug (but don't use an ACEI and an ARB together) (Chap. 41).
7. Referral to a hypertension specialist is recommended for patients in whom goal BP cannot be attained.

The main criticisms of these recommendations related to the lack of direction on both BP assessment (including ambulatory monitoring) and titration of medications, as well as the increased systolic BP goal for persons over 60 years of age (<150 mmHg). In fact, a minority group from the panel wrote a dissenting piece specifically addressing concerns about the higher systolic threshold [18]. In this critique, the authors pointed out that most other national BP guidelines recommend a target of <140 mmHg systolic for persons less than 80 years of age. The dissenting authors were also concerned that the evidence to change the threshold from 140 mmHg systolic to 150 mmHg systolic in persons over 60 years was not strong enough to justify the potential for harm in persons with elevated ASCVD risk, in addition to the potential for confusion about differing treatment thresholds (and targets) in different subgroups of the population among medical providers.

Extending their rationale, the authors of this dissenting article also cited data from three large trials (HYVET, SHEP, and FEVER) and other meta-analyses that suggested a benefit for a threshold of <140 mmHg in older persons [18]. In their conclusion, these authors made the point that the evidence to increase the threshold for treatment should be at least as strong as the evidence to decrease the threshold and that this evidence is either not in existence or not unanimously agreed upon. In the wake of these disagreements, some providers have chosen to wait for more formal recommendations (which are officially endorsed by professional medical bodies) and, in the meantime, to apply the higher systolic threshold of 150 mmHg to persons older than 80 years and/or who are frail. In addition, the AHA/ACC released an updated advisory in April 2014 declaring that the standard systolic BP treatment thresholds should be maintained (Fig. 2.2) [19]. It should also be noted that the evidence for renal denervation therapy, while initially promising, appears to demonstrate poor efficacy for this technique in the control of hypertension.

2.8 Concluding Remarks

These guideline documents are the result of years of diligent work by leaders in the field of cardiovascular medicine and are informed by comprehensive reviews of the literature for high-quality evidence. Thus, the validity of all these new guidelines is likely to be consistently stronger than their predecessors. For example, many prior guidelines relied on expert opinion when deciding on central tenets of the main recommendations. In such, we believe that the new guidelines will help to improve

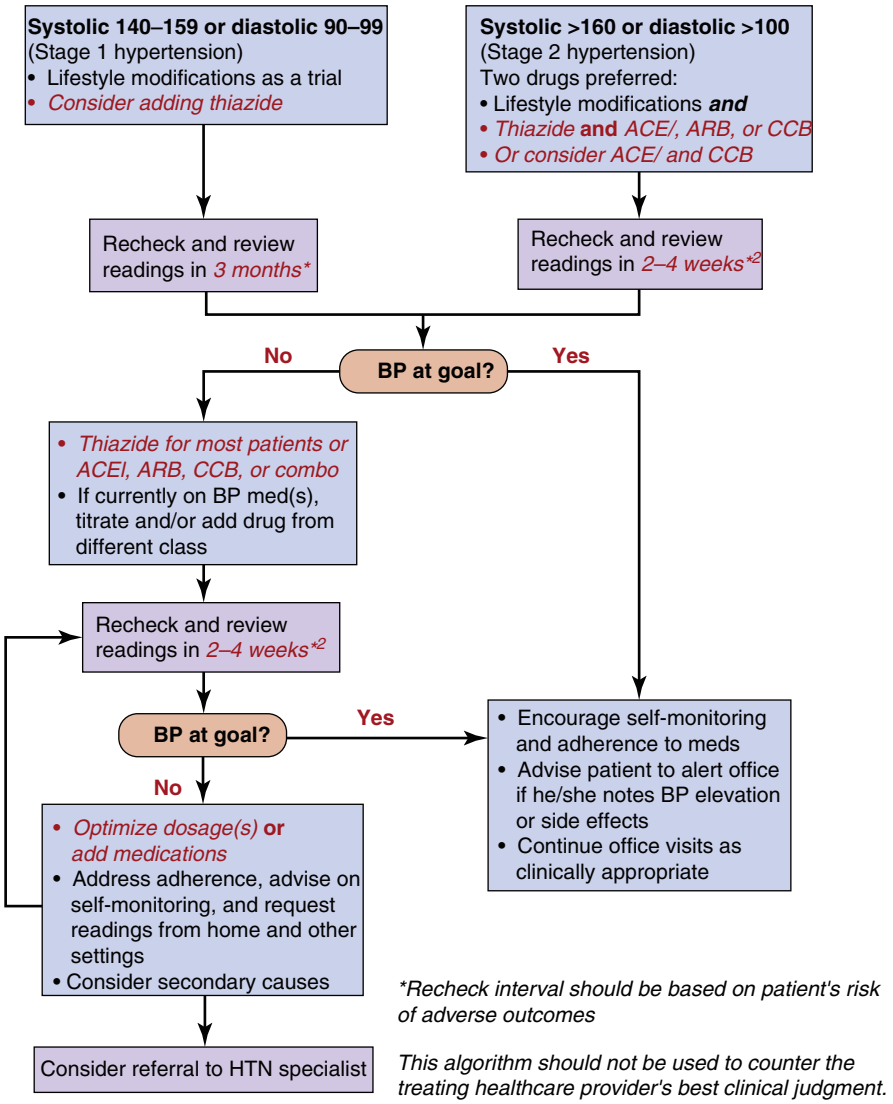

Fig. 2.2 American Heart Association-American College of Cardiology Treatment algorithm for controlling hypertension in adults (Reproduced from open source reference [19])

the health of the population and also provide a strong foundation for evidence-based guidelines of the future. However, the controversies generated by the new guidelines also teach us that consensus in the field (with widespread distribution of draft proposals for comment by external experts), prioritizing dissemination and implementation of recommendations, and also timely release and frequent update of recommendations are all critical components to future iterations of guideline

documents. In addition, while observational data should always be interpreted with caution, these recent guidelines also remind us that excluding compelling observational data from the synthesis of evidence-based recommendations may narrow our perspective and lead to missed opportunities to optimize care. Nonetheless, it is clear that these new guidelines represent a step forward in maximizing the health and wellness of our patients.

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Chapter 3
Pathophysiology of Heart Failure

Leany Capote, Ruth Nyakundi, Brandon Martinez, and Anastasios Lymperopoulos

Abstract Cardiac dysfunction precipitates changes in vascular function, blood volume, and neurohormonal status. These changes serve as compensatory mechanisms to help maintain cardiac output and arterial blood pressure. However, these compensatory changes over months and years can worsen cardiac function. Overall, the changes in cardiac function associated with heart failure (HF) result in a decrease in cardiac output. This results from a decline in stroke volume that is due to systolic dysfunction, diastolic dysfunction, or a combination of the two. Systolic dysfunction results from a loss of intrinsic inotropy (contractility), most likely due to alterations in signal transduction mechanisms responsible for regulating inotropy. Systolic dysfunction can also result from the loss of viable, contracting muscle as occurs following acute myocardial infarction (MI). Diastolic dysfunction refers to the diastolic properties of the ventricle and occurs when the ventricle becomes less compliant (i.e., "stiffer"), which impairs ventricular filling. Both systolic and diastolic dysfunctions result in a higher ventricular end-diastolic pressure, which serves as a compensatory mechanism by utilizing the Frank–Starling mechanism to augment stroke volume. In this chapter, we discuss the various types of cardiac insults and morbidities/conditions that can cause myocardial damage (directly or indirectly) in humans, thereby precipitating chronic systolic HF. Particular focus is given to the pathophysiological mechanisms by which they initiate or aggravate the development of clinical HF.

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3.1 Overview of HF Pathophysiology

HF has five million victims in the United States alone. It occurs equally in men and women and is more prevalent among African-Americans, Hispanics, and American Indians than among whites. About 75 % of these individuals are older than 65 years. The incidence of HF is increasing, as our population ages and the lives of our cardiac patients are extended by innovative interventions and therapeutics. In spite of advances in treatment, the damage to the myocardium leads to HF. In addition, the high rate of obesity in America has escalated the incidence of diabetes and high blood pressure, increasing the risk of HF. Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high (Chap. 1).

Myocardial damage regardless of etiology can cause a decrease in cardiac output, which stimulates a cascade of events dictated (mainly) by the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) in order to restore cardiac output and supply enough oxygen to meet the increasing demands (Fig. 3.1). The main pathological alterations preventing the heart from functioning properly, thereby causing HF, are decreased preload, increased afterload, and reduced contractility/force of contraction that insufficiently pumps blood to the periphery. The most common cause of left ventricular systolic dysfunction is end-stage coronary artery disease, either with a history of MI or with a chronically underperfused, yet viable, myocardium. Other common causes of left systolic dysfunction include idiopathic dilated cardiomyopathy, valvular heart disease, hypertension, toxin-induced cardiomyopathies (e.g., doxorubicin and other drugs, alcohol), and congenital heart disease. On the other hand, right ventricular systolic dysfunction is usually a consequence of left ventricular systolic dysfunction. It can also develop secondary to right ventricular infarction, pulmonary hypertension, chronic severe tricuspid regurgitation, or arrhythmogenic right ventricular dysplasia. A much less-common cause of heart failure is high-output failure caused by thyrotoxicosis, arteriovenous fistulae, Paget's disease, pregnancy, or severe chronic anemia. Diastolic dysfunction (i.e., impaired left ventricular relaxation) usually is related to chronic hypertension or ischemic heart disease. Diastolic (nonsystolic) HF presents with symptoms and signs of HF in a setting of normal left ventricular ejection fraction (>50 %) and the absence of valvular disease. Other causes of diastolic dysfunction may be restrictive, infiltrative, and hypertrophic cardiomyopathies. Inadequate filling of the right ventricle can result from pericardial constriction or cardiac tamponade. Often, both systolic and diastolic dysfunction may coexist, and all patients with systolic HF have some degree of diastolic dysfunction. In the following sections, we discuss the main risk factors/morbidities that result in the pathophysiological alterations, ultimately culminating in development of left ventricular systolic HF.

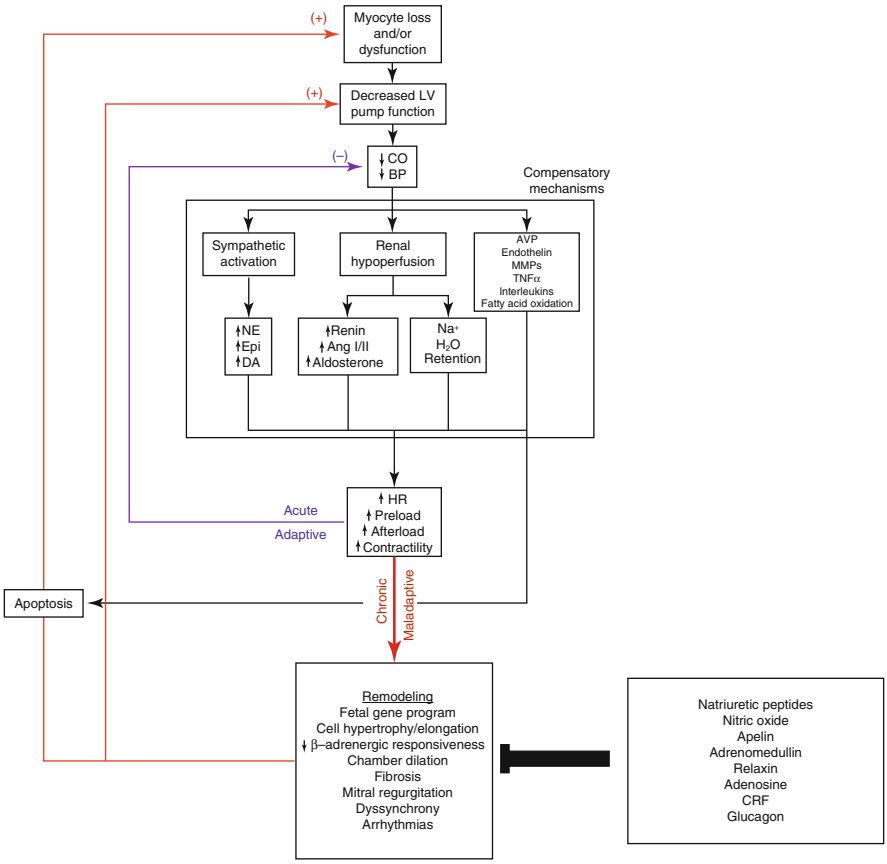

Fig. 3.1 Schematic depiction of the interrelated and (usually) opposing neurohormonal mechanisms/systems activated in acute and in chronic HF and their (patho)physiological actions for the circulation. *LV* left ventricular, *CO* cardiac output, *BP* blood pressure, *AVP* arginine vasopressin, *MMP* matrix metalloproteinase, *TNFα* tumor necrosis factor-alpha, *NE* norepinephrine, *Epi* epinephrine, *DA* dopamine, *Ang* angiotensin, *HR* heart rate, *CRF* corticotropin-releasing factor. See text for details

3.2 MI-Coronary Atherosclerosis and HF

Atherosclerosis is the gradual accumulation of lipids, blood cells, calcium, and other materials on the walls of the arterial vasculature. Stable plaque buildup can eventually cause ischemia, while unstable plaques, which are prone to rupture, can lead to thrombus formation or can detach, travel, and occlude downstream arteries [1]. Therefore, atherosclerosis has acute and long-term consequences on the body's vasculature ranging from acute coronary syndrome, sudden cardiac death, arrhythmias, transient ischemic attacks to cerebrovascular disease and beyond [2] (Chap. 25).

In the heart, one of the most serious manifestations of atherosclerotic plaques is that of the acute coronary syndrome known as ST-elevated MI (STEMI) or simply MI [3]. MIs are caused by complete occlusion of the arteries supplying the heart directly leading to myocardial tissue damage. In fact, the most common cause of MIs is ischemic heart disease, and in turn, MIs are one of the leading causes of HF because they directly alter the structure and function of the heart [4, 5]. Due to major advances in medicine, mortality due to MIs has decreased while complications such as recurrent MIs, arrhythmias, atrial fibrillation, and HF are on the rise [1, 6]. The incidence of post-MI HF has been reported to range from 5 to 50 % depending on the population being studied and study design [7–9]. However, up to half of patients may already have some degree of transient or chronic HF or may develop it while hospitalized for the MI. Others will likely develop it within 30 days of hospital discharge. Moreover, 40 % of MI patients will develop left ventricular systolic dysfunction after discharge. The progression to HF following an MI is more likely to occur in older patients, females, those with an anteriorly located infarct, and in individuals with coexisting comorbidities such as hypertension and diabetes (Chaps. 19 and 20).

HF often occurs as the terminal common pathway of any combination of cardiac conditions that affect the myocardium's productivity. It can be described as the inability of the heart to adequately fill or contract in order to meet the body's metabolic demands. MIs affect the ability of the heart to properly fill and eject blood depending on the location and extent of infarct. Directly following an MI, persistent ischemia directly leads to cardiomyocyte loss from necrosis, apoptosis, inflammation, and neurohormonal mechanisms which all contribute to cardiac remodeling as well as with long-term detrimental consequences (Fig. 3.1) [10–19]. Even with successful and timely revascularization after an MI, the occurrence of microvascular injury remains high. Critical factors for injury and repair processes are age, time to treatment, exaggerated platelet activation, presence of diabetes or other comorbidities, and severity of atherosclerotic heart disease [20, 21]. Induced by ischemia, cardiomyocyte death by apoptosis and necrosis peaks within 8 h after an infarction. While necrosis may be more prominent in the acute phase of MI, apoptosis seems to play a more important role in the long run.

Inflammatory processes play an important role in the body's response to an MI and are especially active in the first 2 weeks following the event. Ischemic-reperfusion injury or microvascular damage following restoration of blood flow, oxygen, and nutrients from the generation of free radicals, leukocyte, and inflammatory response to the infarcted tissues is a well-established phenomenon. Macrophages and neutrophils are rapidly recruited by chemokines and cytokines such as interleukins 1b, 6, 8, and 18 and tumor necrosis factor-α (TNFα) in order to initiate the healing process by phagocytosing necrotic cells, producing matrix metalloproteinase (MMP) to break down the extracellular matrix (ECM), secreting myeloperoxidase and other compounds [22–24]. Reactive oxygen species such as superoxide and peroxynitrite generation from inflammatory cells increases while there is decreased antioxidant activity furthering cardiomyocyte death [22]. Other mediators of inflammatory cells such as the pro-fibrotic cytokines tissue growth factor-beta1 (TGF-β_1) and

connective tissue growth factor (CTGF) are also involved in the clearing of necrotic cells [25–32]. However, an overwhelming inflammatory and immune response can also have deleterious effects on the affected myocardium such as by the generation of toxic by-products blocking sufficient perfusion of the infarcted areas [33, 34].

The RAAS, the SNS, and the vasopressin systems along with their effector hormones and compounds also play a pivotal role in the development of HF [2, 16] (Chaps. 5 and 35). As the main product of RAAS, angiotensin II is involved in regulating electrolytes and fluid volume, both of which have important consequences for the signs and symptoms of HF. Local angiotensin II and aldosterone concentrations are also increased in an infarcted heart influencing fibrosis and hypertrophy [2]. Aldosterone has been particularly associated with coronary vasculature damage as well as left ventricular dysfunction and promotion of fibrosis [2]. Higher levels of the catecholamines epinephrine and norepinephrine following MI are known to damage the endothelium and are associated with subsequent development of HF as well as death [21]. Furthermore, circulating levels of particular compounds may be important prognostic markers of progression to myocardial damage, development of complications, and mortality. Peak C-reactive protein (CRP) levels may also predict negative outcomes from an MI including HF [10]. Finally, serum levels of soluble tumor necrosis factor receptor (sTNFR), which is an important mediator of inflammation and apoptosis, have been found in post-MI patients to correlate well with the size of infarct and extent of left ventricular dysfunction [22].

Ventricular remodeling is strongly related to cell death, to inflammation, and to the neurohormonal responses of an MI (Fig. 3.2) [34]. It begins within days of an MI and may continue for months after the initial insult to the myocardium. Inflammatory and immune cells such as macrophages and neutrophils together with their pro-fibrotic cytokines can cause changes in the extracellular matrix due to collagen synthesis and deposition through myofibroblasts [34]. Because myocardial tissue has inadequate ability to regenerate, structural consequences of an MI often include hypertrophy of viable tissue due to collagen remodeling as well as myocardial scarring and stiffness in infarcted areas [34]. Ventricular remodeling therefore primarily consists of thinning at the infarcted sites, hypertrophy of the viable myocardium, and ventricular dilation. Fibrosis proximal and distal to the infarcted sites leads to scar formation and wall stiffness and is influenced by the presence of aldosterone and angiotensin II in addition to aforementioned compounds [2]. Both collagen generation and degradation in the extracellular matrix occur following an MI which will inevitably lead to changes in the shape and capacity of the affected heart chamber [2, 34].

In summary, myocardial injury can lead to cell death, inflammation, and neurohormonal responses, triggering pathological cardiac remodeling with deleterious long-term consequences such as HF. These adaptive mechanisms are an effort by the injured heart to maintain adequate cardiac output sufficient to adequately perfuse the body. However, their continued activation contributes to worsening cardiac function as the heart progressively fails in its ability to maintain cardiovascular homeostasis and the patient progresses through the stages of HF.

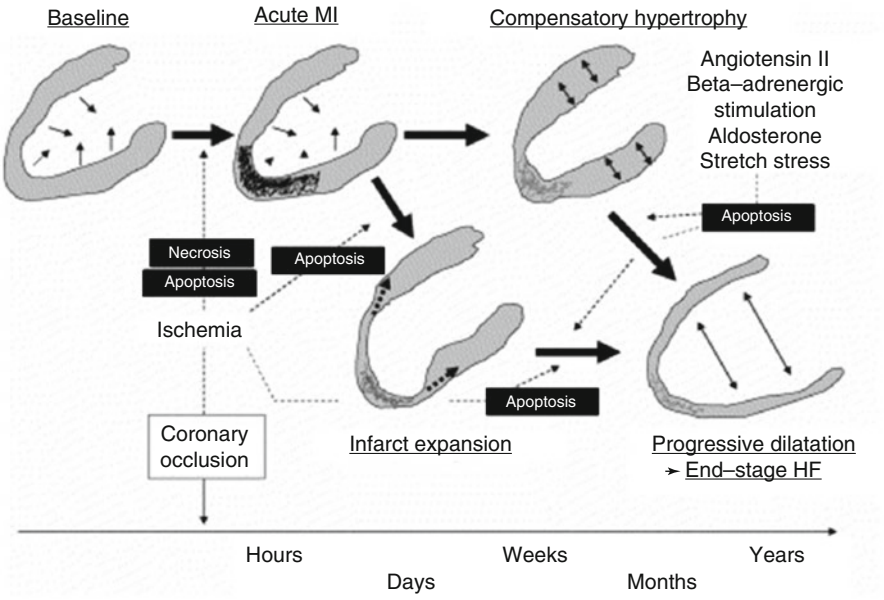

Fig. 3.2 Time course of ventricular remodeling and progression to HF (Reproduced with permission from Ref. [6])

3.3 Hypertension and HF Pathophysiology

Elevated blood pressure affects more than 65 million adult Americans and is a major risk factor for MI, stroke, renal failure, and HF [35, 36]. Long-term management of both systolic and diastolic hypertension can reduce the risk of developing HF by approximately 50 % [37–39]. Because HF due to hypertension is preventable, it is of paramount importance to educate those at risk on antihypertensive medications and lifestyle modifications. Activities such as weight loss, control of sodium intake, and exercise are steps in the right direction which reduce or eliminate progression to HF [40]. Before discussing the mechanisms by which chronic hypertension may lead to HF, it is essential to review the diagnostic criteria of hypertension and the particular categories of this chronic illness.

The recently released JNC8 guidelines define hypertension by age class. Those younger than 59 years old are considered hypertensive if presented with either a systolic blood pressure greater than 140 mmHg or a diastolic blood pressure above 90 mmHg. Those greater than 59 years old require a systolic pressure above 150 mmHg or a diastolic pressure greater than 90 mmHg to be diagnosed as hypertensive [41]. The cause of heightened blood pressure may also be used as a means to define the condition. A diagnosis of primary hypertension is given when the etiology is of unknown origin and is present in approximately 90–95 % of diagnosed individuals; whereas, a diagnosis of secondary hypertension implies that the origin is known and is found in 5–10 % of those diagnosed [42]. Although there are differences

between primary and secondary hypertension, the key pathophysiologies behind the two are similar and will be discussed as one (Chap. 30). This section will focus on hypertension-induced mechanisms leading to the eventual development of HF.

Cardiac output is a common biological marker used to diagnose HF. An increased stroke volume, heart rate, and blood pressure or decreased peripheral vascular resistance leads to heightened cardiac output. An increase in cardiac output, brought about through increased blood pressure, puts a strain on cardiomyocytes and may ultimately lead to cell injury and loss of elasticity from collagen deposition. This accumulation of collagen is due to changes in the myosin heavy chain causing a reduced contractility [43]. Loss of the myocardial cell count present in chronic, untreated hypertension is central to the development of HF. Furthermore, the damage induced by hypertension to the cardiac muscle often leads to an inflammatory response which perpetuates cell damage and loss. The overall loss of cell contractility leads to decreased stroke volume, cardiac output, and ejection fraction of the heart [19]. Once the heart's ejection fraction, or the amount of blood being pumped from the heart, falls to a level below 40 %, HF with reduced ejection fraction is diagnosed [44].

Certain populations pose with an increased risk of developing chronic HF as a result of hypertension. Age-related changes in the cardiovascular system place older adults in such a category [45]. Typically, a rise in blood pressure is sensed by the smooth muscles' lining vessel, which releases nitric oxide leading to vessel dilation and reduced resistance. Elasticity in blood vessels is gradually lost due to aging making it increasingly difficult to adjust vessel diameter and account for changes in blood pressure [46]. These vessels are constantly constricted causing increased pressure that erodes the cardiomyocytes and increases fibroblasts, collagen, and hypertrophy of cardiac tissue. Age-related changes alter ATP concentration, resulting in higher levels of calcium ions which increase norepinephrine and further stress the heart (Chap. 4). Finally, the RAAS has the potential to alter blood pressure levels, especially in males and in African-American populations. Hence, there are many mechanisms by which hypertension may ultimately lead to HF [43].

3.4 Renal Dysfunction and HF

An important bidirectional relationship exists between the kidneys and the heart. Each organ functions to maintain a homeostatic balance allowing the other organ to maintain optimal efficiency. Conversely, dysfunction in either organ system has the ability to cause or propagate disease in the other organ by means of common feedback pathways [47]. The clinical significance in this relationship has been studied and shown through observations of higher percentage of patients with cardiovascular disease in patients with a chronic kidney condition [48–51]. The 2013 US Renal Data System Report shows that 41 % of patients with stage 4 or 5 chronic kidney disease (CKD) developed HF compared to 7 % in non CKD patients in Medicare patients age 66 years or older [52]. Impaired renal function is also associated with

an increased risk of hospitalization due to HF as well as an increased risk of cardiovascular-related deaths [47, 53, 54].

Under normal conditions, the kidneys are perfused by the heart. In other words, the kidneys are reliant upon cardiac output for normal function. The kidneys sense the level of perfusion from the heart and adjust the blood pressure accordingly through the RAAS. In the presence of low perfusion or blood pressure (reduced cardiac output), the RAAS is activated to release renin from the juxtaglomerular apparatus of the kidneys. Renin cleaves angiotensinogen circulating from the liver to angiotensin I. Angiotensin-converting enzyme converts angiotensin I to the biologically active angiotensin II [55]. The effects of angiotensin II include direct vasoconstriction, sodium retention through a direct renal tubular effect and increased aldosterone secretion, and stimulation of water intake through the thirst center [56]. The net result of these physiologic mechanisms is an increase in fluid volume and blood pressure. Under normal physiological conditions, this mechanism between the heart and kidneys maintains blood pressure within a set range. It is when this system falls out of homeostatic balance that a dangerous cycle of failure in each system is observed (Chaps. 35 and 36).

In the presence of altered kidney function, the kidneys lose the ability to maintain sodium, potassium, water, and acid–base balance. This balance is lost due to improper filtering and clearance mechanisms within the kidney [57]. In relation to the cardiorenal system, these altered mechanisms lead to an imbalance of sodium. Water follows this increase of sodium resulting in an increase in intravascular volume. This increase in volume sequentially leads to a prolonged sense of hypoperfusion by the kidneys. Renal mechanisms compensate for this decreased perfusion by continuous activation of the RAAS. Once activated, the RAAS adds to the systemic imbalance of electrolytes, fluids, and intravascular volume by increasing aldosterone secretion. The activation of RAAS also leads to direct vasoconstriction, worsening the decline in the cardiorenal cycle. Increased levels of plasma renin and aldosterone are seen in patients with severe HF in whom the activity of the RAAS is increased [58].

The prolonged inability to stop this cycle of decreased renal perfusion and increased ventricular vascular resistance leads to the development and worsening of HF. The initial decrease in cardiac output leads to an inability of the kidneys to inhibit the RAAS. This system remains activated because of a constant sense of hypoperfusion by the kidneys. The prolonged activity of this system leads to several compounding factors affecting cardiac function including sodium and water retention, intravascular volume expansion, sympathetic activation, and electrolyte and acid–base imbalances (Fig. 3.3) [47, 60]. The body is fixed in a persistent hypertensive state coupled with increased intravascular volume, causing an increase in vascular resistance. This increase in vascular resistance increases cardiac workload. The initial mechanism of compensation in HF is activation of the SNS. In HF, peripheral alpha2-adrenoceptor function is lost contributing to higher levels of circulating norepinephrine [59]. Increased norepinephrine levels lead to an increase in cardiac inotropy and chronotropy as well as peripheral vasoconstriction. Though this compensatory mechanism is initially useful in maintaining stroke volume and cardiac output, eventually, the increased workload of the heart leads to negative effects on the heart muscle [56]. The additional stress placed on the heart can lead

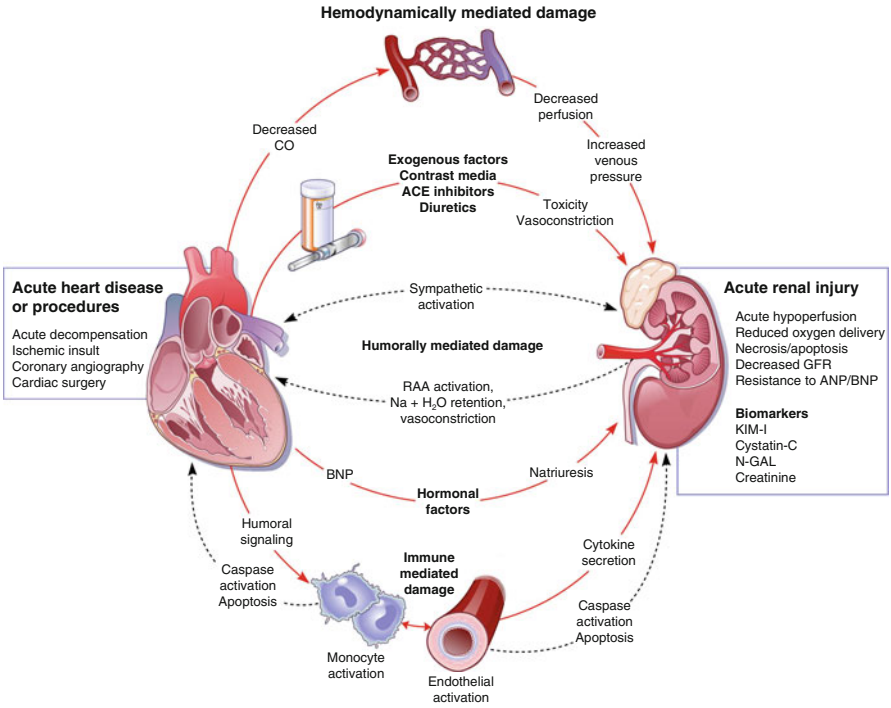

Fig. 3.3 Interplay between kidney injury (renal failure) and HF pathogenesis (Reproduced with permission from Ref. [59])

to myocyte hypertrophy and dysfunction [61]. Alterations of myocytes are fundamental in the cardiac remodeling process. When exposed to stress, the myocytes produce proteins altering their shape and structure in an attempt to adapt to maintain stroke volume and cardiac output. These alterations lead to increased ventricular wall thickness and further deterioration of cardiac function [62]. Research has led to the theory that angiotensin II may directly lead to myocyte hypertrophy, as well [63]. Progression of HF is dependent upon the severity and duration of these physiologic mechanisms. The predominant contribution of angiotensin II in HF development and progression illustrates the clinical importance of ACE inhibitors and angiotensin receptor blockers (ARBs) in the treatment of HF, wherein RAAS antagonists have shown to decrease mortality [64].

3.5 Central Nervous System (CNS) Disorders and HF

Approximately one in five HF patients is diagnosed with depression [65, 66]. Some studies have observed this number to be higher depending on the study and assessment method used [66, 67]. The incidence of a comorbid depressive condition

increases with worsening stages of HF with as many as 42 % of patients observed with this comorbidity in patients with NYHA class IV HF [68]. This patient population has also been observed to have worse clinical outcomes in terms of greater hospitalization and rehospitalization rates as well as increased morbidity and mortality [66–69]. Furthermore, depression has been associated as an independent predictive factor for hospital readmissions and mortality in HF patients, as well as increased health-care-associated costs and diminished quality of life [70–73]. Anxiety disorders are not as prevalent appearing in roughly 15 % of patients depending on the study and assessment tools used, but this percentage is still higher than the general population percentage [67, 74]. Depression and anxiety can both contribute to the development and progression of HF, as patients with these comorbid conditions become fixed in this pathophysiologic loop of disease progression [75].

The effects of depression potentiate a cascade of events which both directly and indirectly contribute to worsening cardiac function and cardiovascular disease progression. The mechanisms by which depression and anxiety lead to the development and progression of HF are precipitated through the activation of the hypothalamic–pituitary–adrenal (HPA) axis, dysregulation of the autonomic nervous system, impaired platelet function, and activation of the cytokine cascade [67, 68, 73, 76]. Overstimulation of the HPA axis increases the level of cortisol in the circulation leading to hypertension, increased levels of serum lipids, and insulin resistance, which all play a role by either direct or secondary pathways in worsening of cardiovascular disease [77]. Overstimulation of the HPA axis also causes an increase in sympathetic activity. As discussed in other pathological mechanisms of HF, an increase in circulating catecholamines first leads to maintenance of cardiac output but eventually leads to prolonged vasoconstriction and hypertrophy of the cardiac cells [67]. Increased sympathetic activity and decreased parasympathetic activity lead to increased heart rate and decrease heart rate variability (HRV) [77]. Decreases in HRV predispose patients to arrhythmias thus increasing the mortality in HF patients [76]. The prolonged increase of sympathetic activity and circulating cortisol also leads to the development of a hyper-coagulation state via increases in clotting factors, factor III and von Willebrand factor, and increases in circulating norepinephrine [75, 77] (Chap. 23). Researchers have also observed altered platelet function in depressed patients, further increasing the risk for a thrombosis formation [75–77]. Patients with depression have been shown to have increased levels of the pro-inflammatory cytokines TNF-α, interleukin-1, and interleukin-6 [75–77]. The overproduction of these cytokines leads to inflammation eventually causing left ventricular remodeling and contractile dysfunction [77].

Sleep plays an important part in the maintenance of normal cardiac function. Sleep abnormalities, such as sleep apnea, constitute another CNS disorder that, similarly to depression, can play a role in the development and progression of HF. Sleep disordered breathing (SDB), often seen in obstructive sleep apnea (OSA), is associated with an increase in morbidity and mortality in HF patients [78, 79]. The most common manifestations of OSA are respiratory abnormalities, but research has revealed a strong relationship between OSA and cardiovascular disease such as arrhythmias [80], hypertension, coronary artery disease, and HF [81, 82].

The pathophysiological relationship between OSA and HF includes oxidative stress, sympathetic activation [83], systemic inflammation, and endothelial dysfunction [84]. The physiological relationship between OSA and decline in cardiac function is further illustrated through the improvement of cardiac function shown in patients with OSA treated with nocturnal continuous positive airway pressure (CPAP) treatment. Patients treated with CPAP were shown to have an increase in left ventricular ejection fraction and significant decreases in daytime systolic blood pressure and heart rate [85].

During normal sleep, distinct physiologic changes in cardiovascular function take place. This includes a decrease in sympathetic nerve stimulation, heart rate, blood pressure, cardiac output, and systemic vascular resistance (SVR) [86]. OSA occurs when the upper way becomes partially or completely closed during sleep causing either partial or complete lack of airflow [87]. This increased airway resistance leads to altered sleep and awakening patterns which ultimately result in significant changes in cardiac function. Studies have identified the mechanisms of OSA resulting in cardiovascular disease as four factors, including a prolonged exaggeration of negative intrathoracic pressure, development of hypoxia and hypercapnia during apnea, repetitive arousal from sleep at the end of apneic episodes, and altered endothelial function or vascular wall injury [88]. Extreme decreases in intrathoracic pressure are seen in patients with OSA. This decrease in pressure causes an increase in left ventricular transmural pressure, which leads to an increase in cardiac afterload and impaired left ventricular relaxation [86–89]. The blockage of the upper airway in OSA causes a hypoxic and hypercapnic state. The recognition of this state of decreased oxygenation causes intermittent states of arousal to take a breath [81]. These episodes of brief wakefulness cause an increase in myocardial oxygen demand [89]. When awake, there are bursts of sympathetic activity, which result in increased blood pressure and heart rate [86–89]. Blood pressures as high as 200/120 have been recorded post apneic episodes in patients suffering from OSA, and it is thought that this process occurring several times per night leads to hypertrophy of smooth muscle and increased peripheral resistance [81]. The repetitive reoxygenation from a hypoxic state also leads to the production of free radicals. The increase of reactive oxygen species (ROS) contributes to endothelial damage through oxidative stress [81, 86, 90]. This stress exacerbates the inflammatory response leading to an increase in inflammatory cytokines and endothelin. Increased levels of pro-inflammatory cytokines have been observed in patients with OSA [90]. The ensuing inflammation is associated with endothelial damage, increased arteriole resistance, and atherosclerotic plaque formation which can worsen the progression of HF (see above and Refs. [82, 87]).

3.6 Substance Abuse and HF

Nicotine's addictive nature poses a major health hazard among those who regularly consume tobacco products. Cigarette smokers are twice as likely to develop HF, compared to nonsmokers, and those exposed to secondhand smoke increase their

heart disease risk by 25–30 % [91]. These negative effects of smoking hold possible detrimental long-term consequences. In fact, a smoker who decides to quit will still remain at an increased risk of heart disease for up to 15 years after their quit date [92]. This is because cigarette smoking alters the circulatory system dramatically and sufficient time is needed for recovery. In those who chronically smoke cigarettes, a state of hypertension is induced through catecholamine release resulting in peripheral vascular resistance and increased heart rate [93]. Additionally, the nicotine in cigarettes increases antidiuretic hormone (ADH) levels with a greater augmentation in those with developed chronic HF [94]. An increase in ADH (vasopressin) levels leads to a decrease in diuresis, which increases water retention (hyponatremia) and raises blood pressure [95]. Furthermore, cigarette smoke has been associated with an increased risk for developing coronary artery disease (atherosclerosis), an additional risk factor for HF [96]. In summary, smoking increases chance of developing various risk factors of HF and worsens conditions once HF is established.

In addition to nicotine (tobacco), alcohol (ethanol) is another very important and common substance of abuse. Chronic ethanol consumption (alcoholism) has been studied extensively and often leads to myocyte loss. The region of the heart most affected in past studies is the left ventricle [97], needed for pumping blood and nutrients from the heart to organs. Damage to this site is associated with reduced cardiac output, a key factor in the development of chronic HF with reduced ejection fraction [98]. High alcohol consumption has also been associated with irregular levels of norepinephrine and calcium, which add strain to the cardiomyocytes through collagen formation and eventual elasticity loss [99, 100]. Over time, the loss of cardiac myocyte elasticity leads to contraction weakening, or a negative inotropic effect, which signifies progression to HF [101]. Additionally, alcohol has been associated with dilated cardiomyopathy, or ventricular dilation with decreased cardiac output, a major cause of HF that is reversible through abstinence [102]. Conversely, moderate alcohol consumption appears to be protective against coronary heart disease [103, 104]. This positive outcome may be due to reduced clotting factors, endogenous fibrinolytic activity, glucose metabolism, higher HDL (high-density lipoprotein-"good cholesterol") levels, and inflammation with increased endothelial function [105, 106]. Thus, only chronic alcohol consumption (abuse) has been found to aggravate the onset and progression of HF.

With regard to other recreational drugs that can cause addiction or can be abused, there are many known complications that can lead to HF exacerbations. In particular, the use of agents such as cocaine and amphetamines (e.g., methamphetamine) is well recognized as potential cause of HF, based on their potential for increasing cardiac stress, blood pressure, and heart rate. These drugs place the body in a state of fight-or-flight and are so-called sympathomimetics for their ability to mimic this classic sympathetic response. Their inherent ability to increase stress on the heart may have detrimental consequences.

Methamphetamine usage releases norepinephrine from nerve terminals [107], raising catecholamine levels. This results in microvascular spasms and possible focal myocarditis [108, 109]. Hypertrophy is found in many of the pathways leading to HF and is not a distinctive marker indicating causation. Definitive characteristics

of HF as a result of methamphetamine abuse include cell deformities like vacuolization and nuclear atypism [110]. A lesion across the myocardium is a clear indication of catecholamine-associated degeneration and is commonly observed in patients who die abruptly during a stressful situation or from illicit drug abuse [111].

As with alcohol and tobacco abuse, chronic cocaine usage has led to dilated cardiomyopathy, a condition reversible through abstinence [112]. Cardiomyopathy is the most frequent cause of HF and is characterized by ventricular chamber enlargement, systolic dysfunction, and normal left ventricular wall thickness [113] (Chap. 16). Cases of HF from short-term usage of cocaine are rarely witnessed [112] but are often associated with endothelial alterations, thrombus formation [114], hypersensitivity, or inotropic depression caused by decreased sodium output [115]. Overstimulation of α_1- and β-adrenergic receptors by catecholamines increases oxygen demand, loss of coronary reserve, and vasoconstriction of the coronary arteries [116].

Finally, the effects on the heart of another drug of abuse gaining huge popularity of late due to its legalization for medical and recreational uses in several US states, marijuana (cannabis), are currently under intense investigation. Currently, there is no clear consensus regarding the extent of cardiac damage caused by smoking marijuana (or its cardiac safety) [117]. More studies are needed to unequivocally establish its cardiac effects in humans and its potential HF risks. Overall, however, substance abuse can have detrimental consequences for the heart, precipitating HF onset or progression, and thus, it should be advised against in heart disease (including HF) patients.

3.7 Concluding Remarks

HF is a clinical syndrome that develops in response to an insult resulting in a decline in the pumping capacity of the heart. This insult can be a direct damage to cardiac tissue (MI), conditions that reduce blood flow to and from the heart (atherosclerosis, angina, coronary artery disease, hypertension), and even environmental insults that disturb the systemic circulation in general (smoking, diabetes, obesity, alcohol and substance abuse, etc.). Once the cardiac damage has set in, it is subsequently characterized by the continuous interaction between the underlying myocardial dysfunction and the compensatory neurohormonal mechanisms that are activated. These systems are initially able to compensate for the depressed myocardial function and preserve cardiovascular homeostasis. However, their long-term activation has deleterious effects on cardiac structure and performance, leading to cardiac decompensation and HF progression. Substantial progress in identification and characterization of the pathophysiological mechanisms (insults) that can lead to HF in humans has taken place over the past few decades. Unfortunately though, this progress has not led to significant advances in treatments for the causes of this syndrome and chronic HF treatment is still largely symptomatic, aiming at prolonging life of the patient (without necessarily improving quality of life). Therefore, it is absolutely imperative that future research in the field of HF continues to focus on

its pathological mechanisms, especially at the molecular, biochemical, and cellular levels, if the hope of discovering a cure for this devastating syndrome is to be materialized one day.

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Chapter 4
Calcium Signaling in Cardiovascular Physiology and Pathology

Nadjib Hammoudi and Djamel Lebeche

Abstract Calcium (Ca^{2+}) plays a critical role in cardiac function. Abnormalities in cardiomyocyte intracellular Ca^{2+} dynamics contribute to the pathophysiological changes observed in several cardiac diseases including cardiac hypertrophy, chronic heart failure, ventricular arrhythmias, and vascular remodeling. In addition to its key role in maintaining cardiac excitation–contraction coupling, it is increasingly apparent that changes in myocardial Ca^{2+} also contribute to the regulation of normal and pathological signal transduction that controls myocyte growth, hypertrophic signaling, and transcriptional gene expression. Interestingly, experimental evidence suggests that these multifarious Ca^{2+}-dependent responses are spatially and temporally mediated by distinct cellular Ca^{2+} pools (i.e., microdomains) which are generated by diverse channels, calcium-binding proteins, and molecular signals with widely differing timescales of activation and localization. These concepts will be discussed in this chapter alongside the emerging role of endoplasmic reticulum stress in myocardial Ca^{2+} dynamics and cardiac physiology.

Keywords Calcium signaling • Calcium microdomains • Hypertrophy • Heart failure • Arrhythmia • Vascular • ER stress

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4.1 Introduction

Calcium (Ca^{2+}) is vital for the proper functioning of a healthy heart. Abnormalities in the regulation of Ca^{2+} homeostasis are associated with cardiovascular pathologies such as hypertrophy (Chap. 16), heart failure (Chap. 3), ventricular arrhythmias (Chap. 52), hypertension (Chap. 31), and atherosclerosis (Chap. 25) [1, 2]. Intracellular Ca^{2+} concentrations are therefore tightly regulated by a number of Ca^{2+}-handling enzymes, channels, and transporters, located in the plasma membrane and in Ca^{2+} storage organelles, which work in concert to fine-tune a temporally and spatially precise Ca^{2+} signal during each contraction and relaxation cycle. Physiological maintenance of a proper cardiomyocyte Ca^{2+}-signaling system is not only vital for cardiac cell contraction but is also crucial for controlling long-term myocyte responses, such as metabolism, transcription, and growth. Emerging studies reveal that these Ca^{2+}-dependent responses are temporally mediated by distinct Ca^{2+} pools (i.e., microdomains) which are generated by diverse channels with widely differing timescales of activation [3, 4]. In this chapter, we will discuss how myocardial Ca^{2+} signaling is essential for the proper and coordinated cardiomyocyte function as aberrant Ca^{2+}-dependent responses are linked to debilitating human diseases such as pathological cardiac hypertrophy, heart failure, and vascular remodeling. We will also highlight the emerging role of endoplasmic reticulum (ER) stress response in the dynamic control of myocardial Ca^{2+}-signaling system.

4.2 Calcium Cycling in Cardiac Physiology

4.2.1 Ca^{2+}-Induced Ca^{2+} Release

Excitation–contraction (EC) coupling is a well-described, fundamental principle by which a myocyte's ionic (excitation) properties tightly coordinate its mechanical (contraction) function (Fig. 4.1). In the mammalian heart, a number of ion channels and transporters ensure that Ca^{2+} release and uptake in myocytes is carefully regulated during the process of contraction since excessive quantities can lead to deleterious pathological consequences [5]. The sarcoplasmic reticulum (SR) plays an important role in orchestrating the movement of Ca^{2+} during each contraction and relaxation.

Excitation leads to the opening of voltage-gated L-type Ca^{2+} channels, allowing the entry of a small amount of Ca^{2+} into the cell [5]. Through a coupling mechanism between the L-type Ca^{2+} channel (LTCC) and the SR Ca^{2+} release channel (ryanodine receptor 2 – RyR2), a larger amount of Ca^{2+} is released through a process termed Ca^{2+}-induced Ca^{2+} release (CICR), activating the myofilaments, leading to contraction [5]. This process increases intracellular Ca^{2+} concentration from approximately 10 nM during diastole to about 1 μM during systole. The relatively increased Ca^{2+} concentration in the T-tubular SR junctions inactivates the LTCC by a Ca^{2+}-dependent inactivation and consequently terminates Ca^{2+} influx to avoid Ca^{2+} overload and arrhythmias [5, 6].

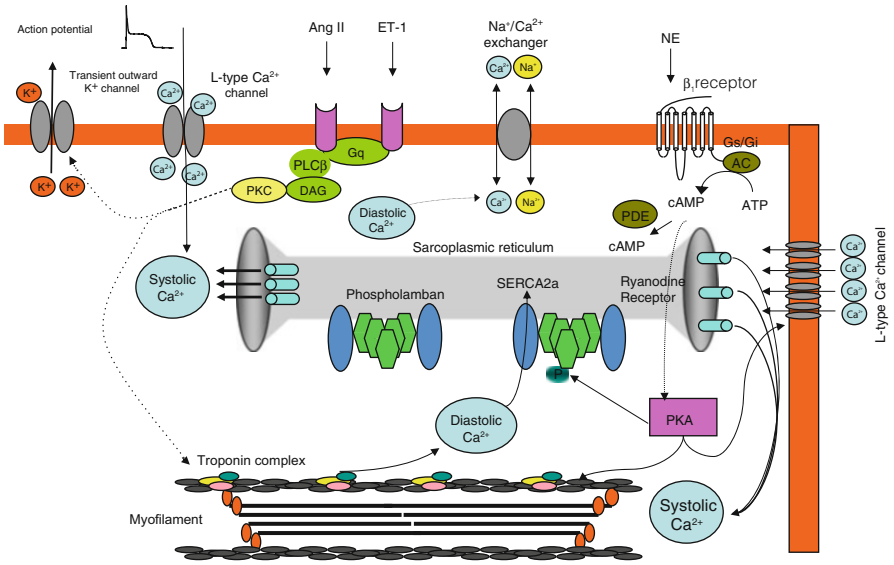

Fig. 4.1 Excitation–contraction coupling: Ca^{2+} cycling is regulated by transporters and channels on the plasma membrane and sarcoplasmic reticulum. Under pathological conditions, such as hypertrophy and heart failure, defects in EC coupling manifest as depressed outward K^+ currents (particularly I_{to}), L-type Ca^{2+} current, Na^+/Ca^{2+} exchange, SR Ca^{2+} uptake due to SERCA2a down-regulation, impaired ryanodine receptor function, depressed β-adrenergic receptor signaling, and phospholamban phosphorylation. β-Adrenergic receptor signaling is depressed mostly through a decrease in expression of β-1 receptors. Ca^{2+}-induced Ca^{2+} release is diminished in part because of reduced sarcoplasmic reticulum Ca^{2+} content – systolic Ca^{2+} – stemming from increased RyR2 leak. Diastolic Ca^{2+} transient is prolonged in part because of reduced expression of SERCA and increased inhibition from phospholamban. A decrease in SR Ca^{2+} load leads to a decrease in the amount of Ca^{2+} released through RyR2 and subsequently lower cytosolic Ca^{2+}. Contraction and relaxation are also slowed by shifts in myofilament regulation (e.g., decreased troponin I phosphorylation) and myosin isozyme expression (e.g., increased MHCβ). Abnormalities in myocardial PKC and PKA activities regulate many of these events. *Abbreviations*: *β-1* β-1 adrenergic receptors, *Ca^{2+}* calcium, *Gq* G-protein subunit q, *GαS/Gi* G-protein subunits αS/i, *K^+* potassium, *Na^{2+}* sodium, *PLCβ* phospholipase C subunit beta, *cAMP* cyclic adenosine monophosphate, *PKA* protein kinase A, *PKC* protein kinase C, *DAG* diacylglycerol, *P* phosphate, *AC* adenylyl cyclase, *PDE* phosphodiesterase, ATP adenosine triphosphate, *NE* norepinephrine, *Ang II* angiotensin II, *ET-1* endothelin 1, *SERCA2a* sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase

During relaxation, Ca^{2+} is re-accumulated back into the SR by the SR Ca^{2+}-ATPase pump (SERCA2a) and extruded extracellularly primarily by the sarcolemmal Na^+/Ca^{2+} exchanger-1 (NCX1). The plasma membrane Ca^{2+}-ATPase (PMCA) pump and the mitochondrial uniporter may also contribute to this process, albeit minimally [5]. The contribution of each of these mechanisms for lowering cytosolic Ca^{2+} varies with species and is mostly determined by the abundance and activity of SERCA2a and sarcolemmal NCX1, by $[Na+]_i$ and $[Ca^{2+}]_i$, and by the membrane potential [5]. In humans ~75 % of the Ca^{2+} is removed by SERCA2a and ~25 % by the NCX1 [7]. The Ca^{2+} pumping activity of SERCA2a is influenced by

phospholamban (PLN) [8] and sarcolipin [9]. In the unphosphorylated state, PLN inhibits SERCA2a activity, whereas phosphorylation of PLN by cAMP-dependent protein kinase A (PKA) and by Ca^{2+}/calmodulin-dependent protein kinase (CaMKII) reverses this inhibition [8]. CaMKII can also directly phosphorylate SERCA2a and enhances its activity [10]. Sarcolipin on the other hand inhibits SERCA2a through direct binding and through stabilization of SERCA2a–PLN interaction in the absence of PLN phosphorylation and through the inhibition of PLN phosphorylation [9]. Disease-induced malfunction of several of these key EC coupling proteins and the subsequent alterations in intracellular Ca^{2+} homeostasis result in mechanical and electrical dysfunction at the molecular level, cellular level, and the entire organ.

Although Ca^{2+} regulation of EC coupling is fundamental for cardiac physiology, Ca^{2+} is also essential for the regulation of an array of Ca^{2+}-dependent regulatory processes associated with cardiac remodeling. There is emerging evidence that the induction of this Ca^{2+}-dependent remodeling is not affected by the rapid elevation in the contractile Ca^{2+} stimulus but is mediated by a more sustained Ca^{2+} signal. Several reports have now described the existence of spatially restricted and distinct Ca^{2+} pools in cardiomyocytes that influence contractility and Ca^{2+}-dependent signaling pathways. How the cardiac myocyte distinguishes between contractile Ca^{2+} and signaling Ca^{2+} has been a matter of debate and few hypotheses have been put forward to explain this conundrum [3, 4]. However, a picture is now emerging that emphasizes how spatially restricted Ca^{2+} signals in local Ca^{2+} nanodomains, microdomains, and macrodomains can selectively recruit certain transcription factors and not others, or activate certain metabolic molecules and not others, through activation of diverse Ca^{2+}-permeable ion channels with widely differing timescales of activation.

A classic example of the concept of Ca^{2+} microdomains is represented by the maintenance of a very close approximation of LTCC and RyR2 in the dyads between T-tubular sarcolemma and the junctional SR that promotes contraction [11]. A similar microdomain also exists between mitochondria and the SR that facilitates an efficient and rapid mitochondrial Ca^{2+} uptake to meet the bioenergetic demand of the beating myocyte [12]. Other examples of Ca^{2+} microdomains involve local Ca^{2+} pools provided and regulated by (1) LTCC [13], T-type Ca2+ channels (TTCC), and plasma membrane Ca^{2+}-ATPase isoform 4 (PMCA4) in non-junctional sarcolemmal caveolae [14]; (2) transient receptor potential channel (TRPC) proteins [15]; and (3) inositol 1,4,5-triphosphate receptor (IP_3R) localized to the nuclear membrane [16], which are all believed to be implicated in mediating diverse Ca^{2+}-responsive signal transduction in hypertrophy and heart failure.

4.2.2 Ca^{2+}-Induced Ca^{2+} Entry

Although calcium signaling is a combination of a highly organized Ca^{2+} release from intracellular Ca^{2+} stores – SR – and Ca^{2+} entry across the plasma membrane, extracellular Ca^{2+} influx is necessary to maintain cytosolic Ca^{2+} levels.

In non-excitable cells, the mechanism that controls Ca^{2+} entry is triggered by intracellular Ca^{2+} store depletion which activates plasma membrane Ca^{2+} channels and elicits a prolonged increase in intracellular Ca^{2+} in a process now termed store-operated Ca^{2+} entry (SOCE). This mechanism of Ca^{2+} influx plays a critical role in replenishing Ca^{2+} stores and providing a sustained and precise local Ca^{2+} signals that are critical in determining a spectrum of downstream cellular responses.

STIM1 (stromal interacting molecule), a recently identified single-span ER membrane molecule, has a unique and essential role in mediating Ca^{2+} entry through SOCE [17, 18]. STIM1 contains four low-Ca^{2+}-affinity luminal EF hands which are sensitive to ER Ca^{2+} concentration; when ER Ca^{2+} is high, Ca^{2+} binds to STIM1 EF hands and inactivates it. However, when ER Ca^{2+} is decreased, Ca^{2+} dissociates from the EF hands and causes conformational changes that result in the activation of STIM1. So, STIM1 functions as sensor of Ca^{2+} levels in the lumen of the ER and activator of the SOCE channel(s) in the plasma membrane [19]. STIM1, through its Ca^{2+}-binding EF hands, can detect small changes in ER Ca^{2+} levels and responds by rapidly oligomerizing and translocating into specialized regions close to the ER–plasma membrane junctions where it interacts with and activates plasma membrane Orai channels [20, 21]. Interaction of STIM1 with Orai Ca^{2+} channels then triggers entry of Ca^{2+} and replenishment of intracellular Ca^{2+} homeostasis and activation of Ca^{2+}-dependent signaling pathways [22]. As Ca^{2+} levels increase in the ER lumen or at ER–plasma membrane junctions – microdomains – STIM1–Orai coupling is turned off and STIM1-induced Orai channel activation is terminated, leading to STIM1 protein de-oligomerization [23, 24].

Whether cardiomyocytes possess a similar functional SOCE mechanism is not clear since Ca^{2+} entry through SOCE requires depletion of SR/ER Ca^{2+} store content, a condition which is hardly achieved in vivo in physiological conditions. However, SOCE has emerged as a potential mechanism regulating Ca^{2+} transients in cardiomyocytes, and a number of recent studies have provided evidence that SOCE is, for instance, operational in neonatal cardiomyocytes [25, 26]. Hulot et al. have reported that STIM1 is abundant in neonatal cardiomyocytes but marginally expressed in adult cardiomyocytes [26]. Interestingly, these studies also reported that STIM1 manipulation did not have any influence on cardiac EC coupling. These observations were further confirmed by Luo et al. who have also demonstrated that SOCE is nearly absent in adult cardiomyocytes but highly active in neonatal myocytes or adult cardiomyocytes under pathological cardiac remodeling [27]. This latter study also demonstrated that STIM1 expression levels correlate with the magnitude of SOCE activation and the subsequent increase in Ca^{2+} entry [27].

Although the SOCE process has been initially reported to mainly result from the coupling of STIM1 with Orai Ca^{2+} channels [25], STIM1 is now known to interact with and activate several transient receptor potential (TRP) channels, which have long been linked to SOCE [28]. Recent evidence suggests, for example, that TRPC1, TRPC3, and TRPC6 are implicated in cardiac hypertrophic responses [29, 30]. Moreover, studies have reported that STIM1 interacts with and controls the function of Cav1.2 voltage-operated Ca^{2+} channel in smooth muscle and neuron [31, 32]. STIM1 interacts with the C-terminal end of the LTCC and inhibits its function and

decreases its surface expression, thus leading to its inactivation [32]. Interestingly, this action of STIM1 on LTCC is thought to favor Ca^{2+} entry via Orai channel [32]. Given the importance of LTCC in Ca^{2+} signaling in cardiac hypertrophy, it is not known whether STIM1 has a similar effect on LTCC in cardiomyocytes, an observation that remains to be determined.

Although STIM1 appears to function as a master regulator of SOCE protein complexes, many questions pertaining to its role in cardiomyocytes remain to be answered. For instance, what are the coupling partners of STIM1 in the heart? Do Orai and TRP channels act synergistically or redundantly and do they have different timescales of activation? Do they activate a common Ca^{2+} pool and/or do they elicit different Ca^{2+}-dependent signaling pathways? What is the role of STIM2, Orai1, Orai2, Orai3, and other TRP channels in the heart? However, emerging results from a number of studies show that adult cardiomyocytes may not need SOCE per se to regulate SR Ca^{2+} loading or contractile Ca^{2+} pools, but this process has a functional significance in fetal and neonatal cardiomyocytes and during cardiac growth and remodeling [15].

4.3 Calcium Signaling in Hypertrophy and Heart Failure

4.3.1 Intracellular Ca^{2+} Handling in Hypertrophy and Heart Failure

The remarkable low cytosolic Ca^{2+} gradient is tightly maintained, as noted earlier, by the concerted activity of several highly conserved families of Ca^{2+}-handling pumps, channels, and transporters that regulate a balance between Ca^{2+} entry, extrusion, and storage. Although initial modifications of Ca^{2+} handling are beneficial, several lines of evidence now suggest that Ca^{2+} dysregulation contributes to pathological hypertrophy and heart failure (Chaps. 3 and 16).

4.3.1.1 SERCA2a, PLN, and Ca^{2+} Regulation

Heart failure is characterized by a number of abnormalities at the cellular level in the various steps of EC coupling. The major abnormality in Ca^{2+} cycling that occurs in heart failure is the observation that SR Ca^{2+} stores are significantly reduced. When this store is depleted, SR Ca^{2+} release is curtailed, in terms of both its amplitude and duration, and as a result reduced contraction force is generated. The likely cause of this deficiency (depressed SR load) is the differential changes in gene expression and activity of key Ca^{2+} regulatory proteins. Ca^{2+} transients recorded from failing human myocardial cells or trabeculae reveal a significantly prolonged Ca^{2+} transient with an elevated end-diastolic intracellular Ca^{2+}. A decrease in SERCA2a activity and Ca^{2+} uptake have been shown to be responsible for abnormal

Ca^{2+} homeostasis in both experimental and human failing hearts [33]. Associated with a defective Ca^{2+} uptake, there is a decrease in the relative ratio of SERCA2a/PLN in these failing hearts. With a decrease in SERCA2a expression and an increase in PLN expression, the SERCA2a/PLN ratio is significantly decreased, leading to a slower relaxation.

Using transgenic and gene transfer approaches in isolated rat cardiac myocytes and failing human myocytes, increasing levels of PLN relative to SERCA2a significantly altered intracellular Ca^{2+} handling by prolonging the relaxation phase of the Ca^{2+} transient, decreasing Ca^{2+} release, and increasing resting Ca^{2+} [7, 8, 34]. Furthermore, in neonatal rat myocytes in vitro, overexpression of SERCA2a largely "rescued" the phenotype created by increasing the PLN to SERCA2a ratio [35]. More importantly, in human cardiomyocytes isolated from the left ventricle of patients with end-stage heart failure, gene transfer of SERCA2a resulted in an increase in both protein expression and pump activity and induced a faster contraction velocity and enhanced relaxation velocity, thereby restoring these parameters to levels observed in nonfailing hearts [36]. In an animal model of pressure-overload hypertrophy in transition to failure, where SERCA2a protein levels and activity are decreased and severe contractile dysfunction is present, overexpression of SERCA2a by gene transfer in vivo restored both systolic and diastolic function to normal levels [33]. These studies provide strong evidence that overexpression of SERCA2a to rescue disturbed Ca^{2+} cycling and myocardial function of the failing heart is indeed possible, validating the feasibility of cardiac gene transfer in heart failure patients [37].

The recent successful and safe completion of a phase 2 trial targeting the cardiac SERCA2a has the potential to open a new era for gene therapy for heart failure [38]. In contrast to SERCA2a, most studies from hypertrophied and failing hearts have shown an increase in both NCX1 mRNA and protein [39], suggesting that enhanced NCX1 function compensates for defective SR removal of Ca^{2+} from the cytoplasm in the failing heart, but at the cost of further depleting the SR releasable pool of Ca^{2+} and further increasing the probability of arrhythmogenecity. However, the exact role of NCX1 in disease and whether it participates as a compensatory or maladaptive mechanism remains controversial.

4.3.1.2 Multi-beneficial Effects of SERCA2a

In addition to its effects on cardiac contractility, SERCA2a overexpression has other ancillary cardiovascular effects that collectively improve its therapeutic effects in heart failure which are summarized in Fig. 4.2:

- *Metabolism and mechano-energetics*: A number of studies in preclinical heart failure models demonstrated a beneficial metabolic remodeling following SERCA2a overexpression in the heart. Adeno-associated virus-mediated SERCA2a gene transfer significantly improved cardiac metabolism (as measured by the ratio of creatine phosphate to ATP) and energy utilization (as measured by

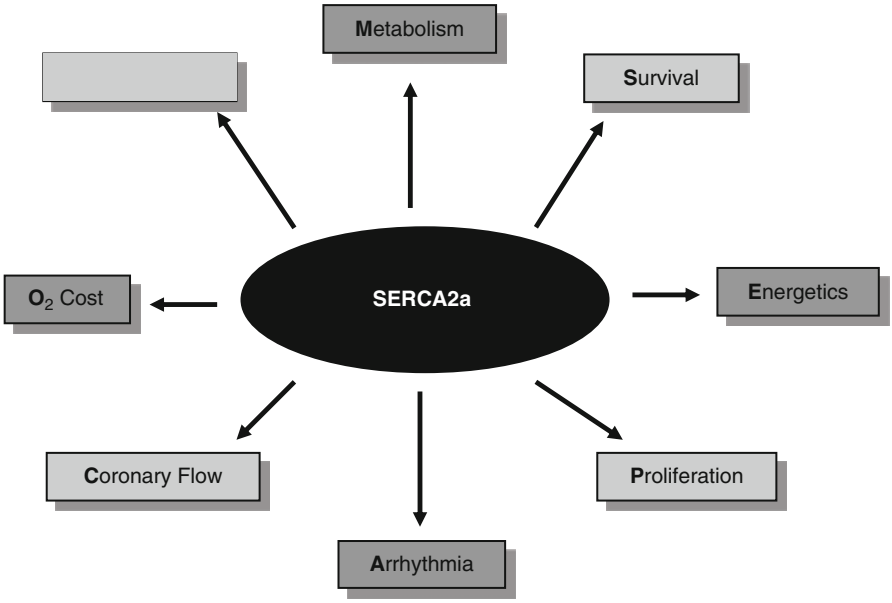

Fig. 4.2 Beneficial effects of SERCA2a overexpression. SERCA2a has various other effects on the cardiovascular system in addition to its well-established effects on myocardial contractility. SERCA2a's effects on metabolism and energetics, survival and arrhythmia, and vascular remodeling are discussed in the text. Although individual effect of SERCA2a promotes well-established benefits, it is believed that the combination of all SERCA2a's effects contributes to the improvement of its therapeutic effects

restoration of the O_2 consumption to EC coupling relationship to normal levels) in addition to mechanical properties [33, 40]. The normalization of myocardial energetic function by SERCA2a is an important issue because increased myocardial contractility and hemodynamics are associated with greater energy demands. This improved energy utilization by SERCA2a overexpression must have contributed to the improvement of mortality and energy reserve in heart failure [33].

- *Coronary outflow and myocyte hypertrophy*: We have found that transcoronary gene transfer of SERCA2a increases coronary flow and reduces cardiomyocyte size in failing hearts [41]. The improved left ventricular relaxation induced by SERCA2a transfer may increase coronary blood flow via wall-dilated coronary vessels due to a more efficient relaxation because coronary blood flow occurs primarily during the diastolic phase. Increased SERCA2a activity decreases diastolic Ca^{2+} via increasing SR Ca^{2+} uptake leading to inactivation of Ca^{2+}-regulated phosphatase, calcineurin, which plays a central role in transducing environmental signals that control gene expression and hypertrophic growth in cardiomyocytes.
- *Vascular reactivity*: We found that human endothelial cells overexpressing SERCA2a exhibit enhanced eNOS expression and eNOS promoter activity, with increased Ser1177 eNOS phosphorylation in basal state [42]. Furthermore, we demonstrated by co-immunoprecipitation that SERCA2a and eNOS are

associated in functional protein–protein complex. This indicates that both proteins are localized in a similar Ca^{2+} environment and also suggests that SERCA2a may directly control eNOS activity. These findings suggest that increased coronary flow occurring after intracoronary SERCA2a gene transfer in a heart failure model may be also due to increased eNOS expression and activity in coronary artery endothelial cells [41].

- *Proliferation*: In human and animal vascular smooth muscle cells (VSMCs), proliferation is controlled by alteration of Ca^{2+} cycling mediated by loss of SERCA2a and RyR2 [43]. In hamsters' VSMC, basal voltage-independent Ca^{2+} influx is required for activation of the nuclear factor of activated T-cell (NFAT) signaling pathway and induction of proliferation. Restoration of SERCA2a expression in proliferating cell leads to complete inhibition of basal Ca^{2+} influx, NFAT transcriptional activity, and proliferation of VSMC. Furthermore, SERCA2a gene transfer prevents migration of cultured VSMC. In vivo and ex vivo studies conducted in animals and humans demonstrated that SERCA2a gene transfer prevents injury-induced restenosis and vascular remodeling, inhibits inflammation in injured segments, and allows complete re-endothelization.
- *Ionic imbalance and arrhythmias*: SERCA2a overexpression was found to decrease ventricular arrhythmias in a rodent model of ischemia–reperfusion [44] and in a large animal model of ischemia–reperfusion [45]. More recently, another group found that overexpression of SERCA2a suppresses electrical alternans, interrupting an important pathway leading to cardiac fibrillation. These findings are further discussed below. Although there were early concerns with SERCA2a overexpression because of the additional SERCA2a pumps, the SR would trigger Ca^{2+} release especially with leaky ryanodine receptors [46] and as such expression of SERCA2a can induce pro-arrhythmogenic effects. However, the aforementioned studies provided strong evidence that SERCA2a restoration in the setting of heart failure is rather anti-arrhythmogenic and beneficial (Chap. 48).

4.3.1.3 RyR2 and Ca^{2+} Regulation

It was demonstrated that RyR2 phosphorylation is highly increased in heart failure and this "hyperphosphorylation" increases the RyR2 open probability to cause a persistent leak of Ca^{2+} from the SR, further impairing the SR Ca^{2+} load. Usually, the RyR2 is closed during diastole to allow for SERCA2a Ca^{2+} uptake. Ca^{2+} release through RyR2 is regulated in part by the interaction of RyR2 with calstabin2 (also known as FKBP12.6). Protein kinase A (PKA)-induced hyperphosphorylation of RyR2 in failing hearts causes calstabin2 to dissociate from RyR2 channel complex and destabilizes the closed state of the channel, resulting in increased spontaneous diastolic RyR2 activity, elevated diastolic SR Ca^{2+} leak, reduced SR Ca^{2+} load, and decreased Ca^{2+} transients [1, 47]. Other suggested mechanisms for increased RyR2 open probability include oxidative modification of the RyR2 and increased RyR2 phosphorylation by CaMKII [48]. Furthermore, the gating of RyR2 is also controlled by a score of other Ca^{2+} regulatory proteins including triadin/junction/

calsequestrin complex, sorcin, calmodulin, and the protein phosphatases PP1 and PP2A.

Diastolic leak of SR Ca^{2+} has been proposed as the mechanism responsible for delayed after polarization, triggered ventricular arrhythmias, and sudden death in heart failure. Although substantial data have accumulated in support of the RyR2 hyperphosphorylation hypothesis, many reports have questioned it and, using a similar canine model of heart failure (in addition to human tissue), have found that the Ca^{2+} sensitivity of the RyR2 opening was unaffected [49]. Furthermore, the association of calstabin2 with RyR2 has been reported to be insensitive to the degree of PKA phosphorylation. Although impaired RyR2 function is likely to be involved in the abnormal Ca^{2+} handling commonly observed in heart failure, the exact alterations in RyR2 function in heart failure have yet to be defined.

4.3.1.4 IP_3R and Ca^{2+} Regulation

Another mechanism for aberrant Ca^{2+} signaling in heart failure is the function of inositol 1,4,5-triphosphate-gated Ca^{2+} release channels (IP_3R) located in the SR and nuclear envelope. Although the physiological role of IP_3R in cardiomyocytes has been a matter of debate, recent evidence supports a prominent role in EC coupling and SR Ca^{2+} release; their location near the RyR2 within the dyadic functional microdomains suggests that they can trigger CICR and enhance EC coupling [50–52]. The expression of IP_3R, which is typically manyfold less abundant than RyR2 in normal cardiomyocytes [52, 53], increases significantly in both human and animal models of hypertrophy and heart failure, particularly their expression in the dyadic junction, suggesting that these channels may be associated with pathological signaling [54]. Studies in neonatal rat ventricular myocytes suggest that activation of IP_3R may be linked to α1-adrenergic receptor-induced Ca^{2+} spark rate and global Ca^{2+} oscillations and catecholamine-induced cardiomyocyte hypertrophic growth. Heart-specific genetic manipulations of IP_3R signaling demonstrated that IP_3R expression enhances cardiac hypertrophy remodeling in vivo in response to agonists stimulation [16]. Increased IP_3-induced Ca^{2+} release in the perinuclear region can directly activate Ca^{2+}-dependent transcriptions factors that permit expression of hypertrophic genes [51, 55]. However, enhanced SR Ca^{2+} release through IP_3R has the potential to trigger arrhythmogenic events [55].

4.3.2 Electrical Remodeling in Hypertrophy and Heart Failure

Although changes in many ion channel currents have been reported in cardiac hypertrophy, reduction in the density of the transient outward K^+ current (I_{to}) is the most prominent ionic current change resulting in prolongation of the action potential duration (APD) in a process referred to as electrical remodeling [56, 57]. Prolongation of the APD is consistently observed in experimental models of cardiac

hypertrophy and failure. APD prolongation and downregulation of I_{to} are also observed in compensated hypertrophy and in end-stage human heart failure [58]. In the mammalian heart, I_{to} is encoded by Kv4.2 or Kv4.3 or a combination of the two [59]. Associated with the reduction in I_{to} density, downregulation of Kv4.2 and/or Kv4.3 mRNA and protein expression levels has been observed in cardiac tissue derived from diseased hearts [60, 61]. APD has been shown to strongly influence Ca^{2+} transient amplitude in normal and hypertrophied myocytes [61] which may help to support contraction of the compromised myocardium but may also harm the myocardium by increasing the propensity to develop arrhythmias [59] and by activating hypertrophic signaling pathways (Chaps. 46 and 48).

The relationships between reductions of I_{to} and concomitant APD prolongation and cardiac hypertrophy and heart failure have been explored using a number of techniques. Cardiac-specific ablation of I_{to} by overexpression of a Kv4.2 channel with a single missense mutation (W362F) did not induce cardiac hypertrophy [62]. However, cardiac-specific overexpression of dominant-negative Kv4.2 channel (truncated channel: Kv4.2N) resulted in hypertrophy and cardiomyopathy along with a prolonged APD. APD prolongation is associated with an enhanced propensity to develop cardiac arrhythmias which may contribute to the high incidence of sudden death observed in patients with heart failure [59, 63].

The mechanism by which APD prolongation contributes to arrhythmogenesis might be related to the intracellular Ca^{2+} overload it generates. APD prolongation can elevate $[Ca^{2+}]i$ and several groups have demonstrated that modulation of APD is an important determinant of Ca^{2+} influx through LTCC. We have shown that cardiac gene transfer of Kv4.3-based I_{to} can increase I_{to} density, shorten APD, decrease Ca^{2+} influx, and attenuate cardiac hypertrophy in vitro [64] and in vivo [65]. Interestingly, restoration of the otherwise downregulated expression of the potassium channel-interacting protein 2 (KChIP2, a K_V4 subunit) in hypertrophied hearts evoked similar effects [66]. Therefore, a reduction in I_{to} density and APD prolongation represent early electrical remodeling events in the diseased myocardium, pointing toward a potential role in disease initiation and progression.

4.4 Calcium Signaling in Cardiac Arrhythmia

4.4.1 Pathogenesis and the Role of Ca^{2+} Overload During Cardiac Arrhythmia

Ventricular arrhythmias are a major cause of death in patients with heart failure. The role of abnormal cytoplasmic Ca^{2+} regulation is thought to be a critical and perhaps a common mechanism underlying cardiac dysfunction and the genesis of ventricular arrhythmias [67]. In fact the well-described phenomenon of Ca^{2+}-mediated arrhythmias was originally observed as a result of digitalis intoxication. By raising intracellular Na^+, cardiac glycosides reduce Ca^{2+} efflux by NCX and favor net Ca^{2+} uptake by the SR. At high doses, these agents can produce Ca^{2+} overload of the SR

and result in the spontaneous release of Ca^{2+} by RyR2, thereby generating a net depolarizing transient inward current mediated by NCX.

Spontaneous increases in membrane potential caused by the activation of the transient inward current manifest as delayed afterdepolarizations (DADs) that can be of sufficient magnitude to produce a full-blown premature action potential. A variety of complimentary changes occurring as a result of left ventricular dysfunction in heart failure can reduce the threshold for the induction of DAD-mediated triggered beats, among which is the upregulation of NCX and the increased open probability of PKA-hyperphosphorylated RyR2 channels.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) and arrhythmogenic right ventricular dysplasia (ARVD), both of which are characterized by mutations in RyR2 genes, are two forms of familial cardiomyopathy-associated arrhythmias. Wehrens et al. demonstrated that CPVT mutant RyR2 channels have a decreased binding affinity for calstabin2. Although these mutant channels are indistinguishable from wild-type channels at rest, they exhibit exaggerated calstabin2 dissociation from RyR2 in response to PKA-mediated phosphorylation, causing more SR Ca^{2+} release and diastolic Ca^{2+} leak [48].

In addition to DADs, early afterdepolarizations (EADs) are another source of triggered activity in cardiomyocytes, which is secondary to abnormal Ca^{2+} cycling and which results from the reactivation of LTCC during conditions of prolonged action potential repolarization. Furthermore, abnormal Ca^{2+} cycling by the SR has also been implicated in the pathogenesis of reentrant arrhythmias by promoting action potential alternans and/or spiral wave breakups leading to the degeneration of ventricular tachycardia and ventricular fibrillation [68, 69]. As such, changes in Ca^{2+} handling in general, and Ca^{2+} overload in particular, are thought to form the triggers for lethal arrhythmias at the cellular level, which under appropriate conditions might produce sustained arrhythmias at the organ-system level.

4.4.2 Targeting Myocardial Ca^{2+} Cycling to Prevent Arrhythmia

To highlight the importance of SR Ca^{2+} in the regulation of ventricular arrhythmias, we have addressed the issue of restoring Ca^{2+} load of the SR through SERCA2a overexpression using genetic strategies [44]. We and others have demonstrated that targeted delivery of SERCA2a to the heart can, as discussed above, significantly improve contractile function in vitro and in vivo, normalize metabolism and intracellular signaling pathways, and improve survival and mechano-energetic properties at no cost of O_2 [33, 40, 70]. Whether these potential benefits of SERCA2a can be further extended to improve cardiac arrhythmias was addressed using a well-documented Ca^{2+} overload rat model of ischemia/reperfusion (IR). Cardiac IR induces ventricular arrhythmias, including ventricular premature beats, ventricular tachycardia, and ventricular fibrillation in both experimental animal models and in

humans [5]. Using continuous telemetry, we found that SERCA2a overexpression significantly decreased ventricular arrhythmias during IR and 24 h later [44]. In addition, SERCA2a overexpression significantly reduced infarct size and improved wall thickening in the anterior wall which may have contributed to the decrease in ventricular arrhythmias because the size of the infarct is associated with the incidence and frequency of arrhythmias. A decrease in diastolic Ca^{2+} and better handling of intracellular ions during the rush of reperfusion are both associated with improved survival of the cardiomyocyte. The reduced incidence and severity of threatening arrhythmias of IR in the SERCA2a-overexpressing animals also corresponded to a preservation of muscle function, as shown by improved wall thickening and hemodynamic measurements. These findings were recently extended by other studies which demonstrated that SERCA2a gene transfer in animal models of heart failure significantly reduced arrhythmogenic cardiac alternans [71], reduced SR Ca^{2+} leak – through reduction of RyR2 phosphorylation – and attenuated ventricular arrhythmias in vivo [37].

Although targeting SR Ca^{2+} cycling proteins can abrogate Ca^{2+}-mediated adverse electrophysiological remodeling associated with IR injury, other candidates have also been shown to exert beneficial anti-arrhythmic effects. For instance, protein kinase C epsilon (PKCε) activation confers cardioprotection from IR injury in various cell cultures, isolated perfused heart models, and transgenic mice. Furthermore, in vivo activation of PKCε was shown to protect the ischemic myocardium from reperfusion arrhythmias, while its inhibition exacerbates their incidence [72]. CaMKII has been functionally implicated in the mediation of (1) frequency-dependent acceleration of relaxation, (2) RyR2-mediated SR Ca^{2+} leak, and (3) Ca^{2+} current facilitation, which all lead to perturbations in intracellular and SR Ca^{2+} balances and triggered arrhythmias. In addition, CaMKII expression and activity are known to increase in patients and in many animal models of structural heart disease. Hence, its inhibition has been shown in several studies to reduce hypertrophy, cardiac dysfunction, and importantly ventricular arrhythmias [73].

4.5 Calcium Signaling in Vascular Biology

4.5.1 Role of Ca^{2+} Cycling in the Modulation of Arterial Vascular Smooth Muscle Cell Phenotype

Vascular proliferative disorders such as atherosclerosis and hypertension are the most common causes of severe cardiovascular diseases, the current leading cause of death in the United States. The proliferative response of VSMC is essential in injury recovery after coronary angioplasty and stent implantation. Although VSMCs are normally located in the arterial media and maintained in a contractile/quiescent state, injury or mechanical stress of arteries causes migration of VSMCs into the intima layer of the arterial wall, where the VSMCs switch their phenotype and start

to proliferate and synthesize extracellular matrix proteins, resulting in expansion of the arterial intima [74]. Changes in phenotype have been well characterized at the level of contractile proteins and more recently at the level of Ca^{2+}-handling proteins. Indeed, the LTCC are replaced by the TTCC [75], store-operated channels and TRP1 channels are upregulated [76], and a decrease in expression of RyR2 and SERCA2a in proliferating VSMC in culture has been shown [77].

4.5.2 Regulation of Intracellular Ca^{2+} Concentration in VSMC

Chronic alteration in intracellular Ca^{2+} signaling may play an important role in determining a new contractile state and new phenotype of the VSMC. The intracellular Ca^{2+} concentration in VSMCs is tightly regulated by a complex interaction of several Ca^{2+} influx and efflux pathways providing a wide range of possibilities for controlling Ca^{2+} concentration in a spatial and temporal manner [78].

The intracellular Ca^{2+} concentration is regulated by pumps and channels located on the plasma membrane or on the membrane of intracellular stores. The sarco-/endoplasmic reticulum is the main intracellular store which forms a network going from the perinuclear space to the plasma membrane. The view that a spatially homogeneous elevation in cytosolic Ca^{2+} concentration is necessary for effective Ca^{2+} signaling has been radically modified by the discovery of local Ca^{2+} transients in cardiac, skeletal, and smooth muscle cells. Ca^{2+} sparks are due to the opening of the RyR2. A single Ca^{2+} spark is capable of producing a very high (10–100 μM) increase in Ca^{2+} in a small region of the cell representing less than 1 % of its volume [79]. Ca^{2+} sparks regulate the membrane potential by activating large conductance Ca^{2+}-regulated potassium channels. The resulting increase in K^+ conductance promotes membrane hyperpolarization, thus reducing the activity of the voltage-gated Ca^{2+} channels and opposing vasoconstriction [80]. Furthermore, a Ca^{2+} spark has the potential to modulate Ca^{2+}-dependent processes that are not responsive to global Ca^{2+} increase such as activation of kinases and phosphatases which also are unevenly distributed in the cytoplasm.

In the VSMC, the two SERCA2 isoforms, 2a and 2b, are present, but their respective roles are still not elucidated. Ca^{2+} cycling in contractile VSMCs requires the expression of the SERCA2a isoform, whereas the Ca^{2+} cycling in synthetic VSMCs is associated only with the expression of the ubiquitous isoform SERCA2b [81]. Moreover, a synergistic role of protein phosphatase inhibitor 1 (I-1) and SERCA2a in the acquisition of the VSMCs contractile phenotype was recently reported [82]. Disappearance of SERCA2a in proliferating VSMCs may be important in terms of propagation of the Ca^{2+} signal which itself controls gene expression via differential activation of Ca^{2+}-regulated transcription pathways. SERCA2a and I-1c gene transfers appear to be promising strategies for preventing vascular proliferative disorders [43, 81, 82].

4.5.3 Ca^{2+}-Regulated Transcription Factors and Control of Proliferation and Growth of VSMC

The mode of Ca^{2+} entry is critical in transducing changes in excitability to changes in gene expression (Fig. 4.3). Transient Ca^{2+} influx through the LTCC is particularly effective in activating the cAMP-responsive element-binding protein (CREB), via Ca^{2+}/calmodulin-dependent phosphorylation by Ca^{2+}/calmodulin kinase (CaMK) or by mitogen-activated protein kinase (MAPK) [83]. By contrast, a sustained increase in cytosolic Ca^{2+} obtained by activation of the IP_3R or activation of the SOCE is necessary to activate calcineurin. Calcineurin is a Ca^{2+}/calmodulin-dependent phosphatase which dephosphorylates many proteins including the transcription factor

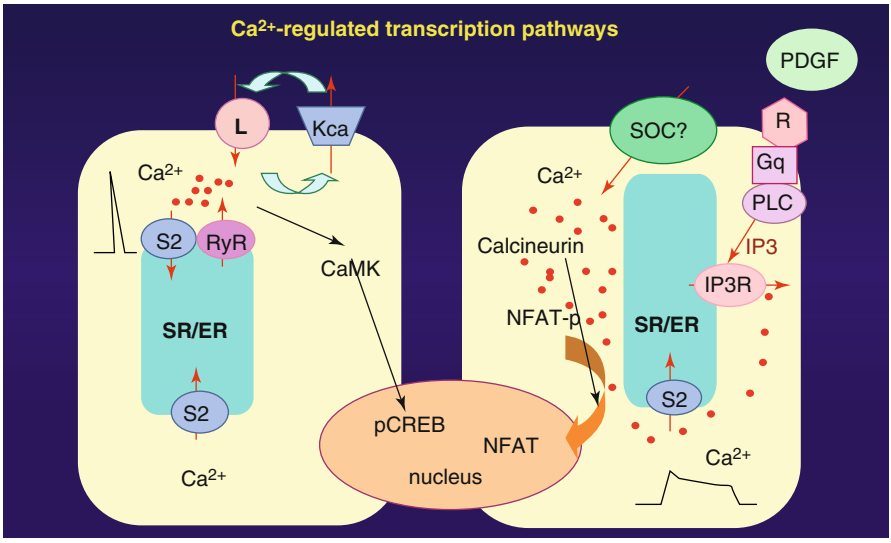

Fig. 4.3 Schematic representation of CREB and NFAT transcription pathways: calcium-regulated pathways controlling proliferation in vascular smooth muscle cells. Transient Ca^{2+} influx through the L-type voltage-activated Ca^{2+} channel (L) activates CREB, the cAMP-responsive element-binding protein, via Ca^{2+}/calmodulin-dependent phosphorylation by Ca^{2+}/calmodulin kinase. By contrast, a sustained increase in cytosolic Ca^{2+} obtained the activation of the store-operated channels (SOC) or by stimulation of phosphoinositide-coupled receptors by mitogens (i.e., PDGF) and generation of inositol-1,4,5-trisphosphate (IP3), leading to activation of IP3R and Ca^{2+} release from intracellular stores, is necessary to activate calcineurin. Calcineurin dephosphorylates the transcription factor NFAT, the nuclear factor of activated T cells, leading to its translocation into the nucleus. *CREB* cAMP-responsive element-binding protein, *CaM* calmodulin, *CaMK* CaM kinase, *Gq* G-protein subunit q, *L* L-type calcium channel, *PLC* phospholipase C, *NFAT* nuclear factor of activated T lymphocytes, *NFAT-p* phospho-NFAT, *R* receptor, *IP3 inositol 1,4,5-trisphosphate*, IP3R inositol 1,4,5-trisphosphate receptor, *S2 SERCA2* (sarcoplasmic/endoplasmic Ca^{2+} ATPase), *SR/ER sarcoplasmic*/endoplasmic reticulum, *SOC* store-operated channel, *PDGF* platelet-derived growth factor

NFAT. When dephosphorylated, NFAT is then translocated to the nucleus [84] (Fig. 4.3). SERCA2a gene transfer inhibits NFAT signaling pathway and prevents post-injury restenosis and vascular remodeling while allowing re-endothelialization in a small animal model [43].

4.6 Calcium Signaling and ER Stress in the Heart

4.6.1 ER Stress and the UPR

The sarco-/endoplasmic reticulum (SR/ER), a multifunctional organelle, plays a crucial role in cell homeostasis and survival. In addition to being the major storage organelle of intracellular Ca^{2+}, it is also involved in protein folding and lipid and sterol biosynthesis. Perturbations in the normal function of the ER trigger a network of signaling cascades that lead to stress and the activation of the unfolded protein response (UPR) and ER stress [85]. The UPR has been associated with a wide range of human diseases, and many lines of evidence indicate that the UPR and ER stress also play an important role in cardiovascular pathologies [86–93]. The UPR triggers a set of signal transduction pathways aimed at ameliorating ER function and reestablishing ER homeostasis by reducing protein synthesis in the ER, accelerating protein degradation of accumulated misfolded proteins, and selectively increasing production of protective proteins – chaperones [92, 94].

It is widely accepted that initially the UPR is an adaptive protective response to restore homeostasis and enhance cell survival; however, severe or prolonged stress may lead to loss of ER function and apoptosis in the heart and other tissues. The ER stress response is generally initiated within the ER/SR lumen and membrane when accumulation of misfolded and damaged proteins in the ER is detected by the chaperone protein GRP78 (glucose-regulated protein) that binds Ca^{2+} and initiates the activation of three ER transmembrane sensors: the protein kinase-like ER kinase (PERK), the inositol requiring kinase (IRK)1α, and the transcription factor-activating transcription factor 6 (ATF6). Each of these UPR mediators then activates a cascade of different downstream cytoplasmic and nuclear signaling pathways that either promote pro-survival or pro-apoptotic responses [85, 92].

4.6.2 Ca^{2+} Cycling and Myocardial ER Stress

Perturbations in any of the ER/SR function can result in ER stress. However, since this chapter is dedicated to Ca^{2+} signaling, we will focus our discussion to Ca^{2+} cycling contribution to ER stress in the heart; readers are encouraged to consult other excellent broader reviews on the subject [90, 91].

The ER/SR plays an important role in regulating the cytoplasmic Ca^{2+} concentration by actively taking up Ca^{2+}, through SERCA2, and storing it and releasing it, through the IP_3- and ryanodine-sensitive channels, on receiving the appropriate

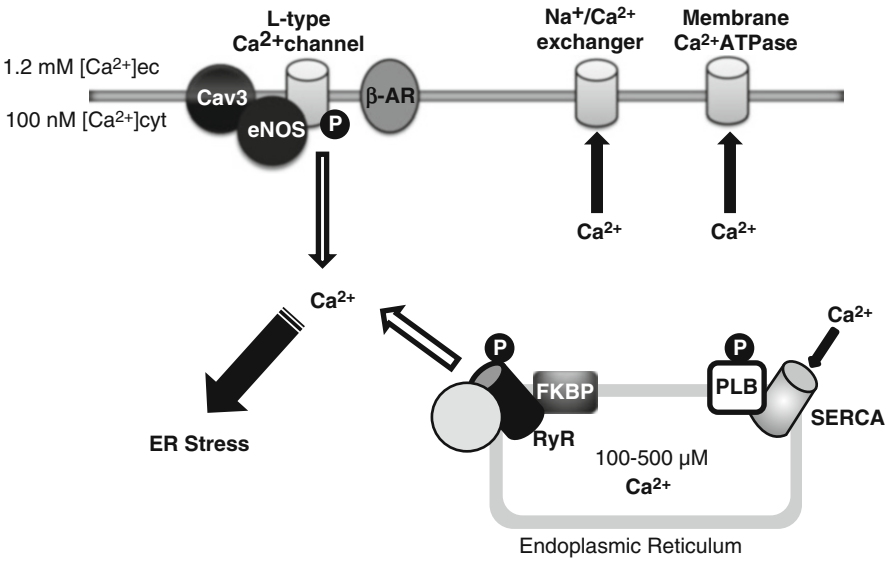

Fig. 4.4 Calcium handling in the ER in normal cells: Ca^{2+} concentration is very tightly regulated in normal cells by key calcium-handling proteins at the plasma membrane, such as L-type calcium channel and its interaction with Cav3-eNOS system, and in the sarcoendoplasmic/endoplasmic reticulum, such as SERCA and ryanodine receptors (RYR). Low intracellular calcium is closely kept in the nanomolar range, compared to the extracellular space, by the concerted actions of these Ca^{2+}-handling players. Alterations in the function and/or expression of these proteins lead to aberrant intracellular Ca^{2+} levels which trigger abnormal cell function and ER stress. *ER* endoplasmic reticulum, [Ca^{2+}]*ec* extracellular Ca^{2+} concentration, [Ca^{2+}]*cyt* cytosolic Ca^{2+} concentration, *Cav3* caveolin 3, *eNOS* endothelial nitric oxide synthase, *nNOS* neuronal NOS, *β-AR* beta-adrenergic receptor, *FKBP* FK506-binding protein, *PLB* phospholamban

signal. The Ca^{2+} content within the ER lumen, determined by electron probe X-ray microanalysis, is estimated to be in the order of hundreds of micromolar to about 5 mM, depending on conditions [95]. The concentration of Ca^{2+} in the ER is known to influence ER proteins in a number of ways. The reduction of ER Ca^{2+} affects protein folding, secretion out of the ER, and the binding and release of ER proteins by chaperones within the ER. Since Ca^{2+} storage within the ER/SR is required for proper ER homeostasis and signaling, disruption of the ER/SR Ca^{2+} levels have been demonstrated to trigger the UPR and ER stress (Fig. 4.4). Recent evidence shows that a major cause of ER stress is attributed to reduction in the SERCA2 activity, since SERCA2 dysfunction leads to elevated cytoplasmic Ca^{2+}, causing ER stress-induced toxicity. Indeed, an association between altered Ca^{2+} cycling, a common observation in heart failure patients, and ER stress response has been reported, and UPR activation has been seen in both hypertrophic and failing hearts [87, 88] and in ischemic myocardium [93, 96].

ER resident chaperone and folding proteins, GRP78 and protein disulfide isomerase (PDI), play an important role as Ca^{2+} buffers in the lumen of ER and studies have demonstrated their utility in controlling ER stress-induced cardiac damage.

GRP78 and PDI expression were upregulated after ischemic events [93, 96] or in hypertrophic cultured cardiomyocytes [97]. Furthermore, PDI was shown to promote survival and limit myocardial infarction-induced ischemic injury, and in mice subject to chronic hypoxia, PDI expression is increased in cardiac endothelial cells, suggesting a role for PDI in neoangiogenesis in scar areas.

Similarly, overexpression of activated ATF6 in transgenic mouse hearts attenuated ischemic damage and improved contractility most likely through upregulation of GRP78, while a dominant-negative mutant of ATF6 leads to increased apoptosis, ventricular dilatation, and reduced functional recovery followed by heart failure and death. This is consistent with the finding that a decline in ER Ca^{2+} triggers an increase in GRP78 in cardiomyocyte and activates ATF6 and that oxygen, serum, and glucose deprivation or shortly following myocardial infarction, ATF6 expression is upregulated [96], suggesting that ATF6 is essential in promoting cardiac protection in this context.

Interestingly, thrombospondin 4, an ER/Golgi membrane Ca^{2+}-binding protein whose level and secretion are controlled by ER Ca^{2+} content, was demonstrated to augment ER function and promote ER stress cardioprotection through activation of ATF6 [98]. Recent evidence also demonstrates that ischemia preconditioning of neonatal cardiomyocytes activates mild ER stress destined to reduce ER stress-induced cell death stimulated by hypoxia/reoxygenation and prevent ischemia-induced cytoplasmic Ca^{2+} overload [99]. It appears that the heart uses ER stress as a means to protect against the consequences of Ca^{2+} overload; however, prolongation of the stress typically leads to apoptosis and heart failure.

4.6.3 Ca^{2+} Cycling in ER Stress-Induced Atherosclerosis

The UPR and ER stress are also activated in atherosclerotic lesions, and ER stress-associated cell death of macrophages and smooth muscle cells is a central event in plaque instability and rupture [100], inciting an inflammatory response that further promotes vascular injury [90]. Interestingly, decreased MEK/ERK (mitogen-activated or extracellular signal-regulated protein kinase kinase) signaling and defects in SERCA2b activity and Ca^{2+} mobilization were demonstrated to be primarily responsible for the activation of UPR/ER stress in macrophages and sensitization to ER stress-associated apoptotic stimuli [101]. Restoration of defective MEK signaling rescued SERCA2b dysfunction and enhanced phospho-PERK expression and partly attenuated ER stress-induced apoptosis in macrophages [101].

Another mechanism that may contribute to the ER stress-initiated cell death involves the pro-apoptotic transcription factor C/EBP homologous protein (CHOP). CHOP expression is significantly increased in macrophages undergoing apoptosis and further increases as atherosclerotic lesions progress [102], while deficiency of CHOP reduced lesion area and apoptosis and necrosis in advanced atherosclerotic plaques [103]. CHOP-stimulated apoptosis was demonstrated to be primarily caused by depleting ER Ca^{2+} stores through enhancement of IP_3R1 Ca^{2+} channel activity mediated by the CHOP transcriptional target ER oxidase (ERO)1α [104, 105].

Elevations in cytosolic Ca^{2+} can provide a stimulus for the induction of apoptosis and possibly tissue/cell damage since a variety of kinases, receptor, and signaling cascades are directly activated by Ca^{2+} or use Ca^{2+} as a cofactor. In addition to macrophages and smooth muscle cells, ER stress is also activated in endothelial cells subject to atherosclerosis-promoting sheer stress. Attenuation of AMPK (adenosine monophosphate (AMP)-activated protein kinase) signaling and subsequent reduction of SERCA activity and depletion of ER Ca^{2+} stores were shown to be key mechanisms underlying induction of UPR and ER stress response [106].

4.7 Concluding Remarks

In heart physiology, Ca^{2+} is a double-edge sword for both life and death. While required for maintenance of proper cardiac function, abnormalities in Ca^{2+} cycling and signaling are the "heart" of contractile deficiency and the progression to cardiac hypertrophy and heart failure. Understanding the normal and pathophysiological myocardial Ca^{2+} signaling is important for devising adequate and appropriate strategies to correct Ca^{2+}-stimulated maladaptive remodeling. Clinical trials targeting normalization of SR Ca^{2+} uptake (SERCA2a gene therapy) and reduction of SR Ca^{2+} leak (RyR2 stabilizers) are currently underway in heart failure patients. Likewise, it is expected that new advances in myocardial Ca^{2+}-dependent therapies will emerge in the near future, such as defining the sources of signaling Ca^{2+} and ER stress-based pathways involved in the induction of heart failure and arrhythmias.

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Footnote Due to the publisher's imposed limit on the total number of references, we were unable to cite all relevant articles. We truly apologize to our readers and to colleague authors for not citing their valuable works.

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Chapter 5
Sympathetic Nervous System Signaling in Heart Failure and Cardiac Aging

Gaetano Santulli

Abstract Heart failure represents the leading cause of death, especially among the elderly. Despite the development of numerous therapeutic strategies, heart failure prevalence is still increasing. Ergo, exploring the molecular mechanisms underlying aging-related heart failure seems to be of particular relevance. Intriguingly, the fields of cardiovascular disease and aging, which have remained largely separate hitherto, seem to have a common point in the sympathetic nervous system. Indeed, mounting evidence indicates that adrenergic receptors are functionally involved in numerous processes underlying both aging and cardiovascular disease. This chapter will review the pathophysiological role of the sympathetic nervous system in heart failure and cardiac aging.

Keywords Sympathetic nervous system • Adrenergic receptors • Aging • Heart failure • Hypertension • GRKs • Cardiomyocytes • Endothelium • Arrhythmias

5.1 Introduction

Aging is associated with a progressive decline in physiological processes, eventually leading to an increased risk of health complications and disease. Among the elderly, cardiovascular disease, and heart failure in particular, remains the leading cause of death. Despite the development of evidence-based therapeutic strategies including the inhibition of the activity of the β-adrenergic signaling and renin–angiotensin–aldosterone system, heart failure prevalence is still increasing, while morbidity and mortality have not been satisfactorily ameliorated. Additionally, recent advances in the diagnosis and treatment of such a disease have led to improved survival rates. However, the number of patients with failing hearts has been augmenting and is estimated to increase in the near future [1] (Chaps. 1 and 2).

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Therefore, especially with the tendency of global aging (by 2030, ~20 % of the population will be aged 65 or older), it is necessary to go deeper in exploring the molecular mechanisms underlying aging-related heart failure. In this age group, cardiovascular disease will result in 40 % of all deaths, ranking as the leading cause of mortality. Cardiac aging is characterized by a series of complex events of modifications including diastolic dysfunction, valvular degeneration, left ventricular hypertrophy, increased risk of atrial fibrillation, and overall decreased maximal exercise capacity. Of interest, the fields of cardiovascular disease and molecular and cellular biology of aging have remained largely separate hitherto. The sympathetic nervous system seems to play a crucial role in both aging and cardiovascular disease. Indeed, adrenergic receptors are involved in numerous pathophysiological processes, and mounting evidence indicates their participation in aging and cardiovascular physiopathology.

In this chapter, the literature in this field is summarized, providing an overview of the major studies investigating the pathophysiological role of the sympathetic nervous system in heart failure and cardiac aging.

5.2 Cardiovascular Aging

Aging triggers modifications in the cardiovascular system that most likely reflect perturbations of biochemical and biological adaptive mechanisms. The incidence of cardiac disorders including heart failure, atrial arrhythmias, and left ventricular hypertrophy increases considerably with age [1]. Elderly people appear to be particularly predisposed to the development of heart failure: such a diagnosis is undeniably the leading cause of hospitalizations in people >65 years of age [1, 2]. Additionally, alterations in ventricular relaxation and filling have been described with aging [3, 4], including a reversal of the early and late mitral inflow velocities (E/A ratio), a prolongation of the isovolumetric relaxation time, and a modification of the dynamic longitudinal wall relaxation and diastolic suction (propagation velocity of early mitral inflow). Atrial fibrillation is diagnosed in ~4 % of subjects without clinical coronary artery disease over age 60 years, a rate tenfold higher than the general adult population [5]. The overall prevalence of atrial fibrillation reaches values of 17.8 % in people aged 85 years and above [1]. Notably, the development of an irregular pattern of electrical activity might have detrimental consequences in hearts that are relatively stiff and relax slowly [1, 6, 7]. The prevalence of cardiac hypertrophy increases with rising blood pressure and body mass index [8, 9], and enlargement of cardiomyocytes has been observed at autopsy in aged subjects without cardiovascular disease in whom overall cardiac mass was not increased. Consistently, cross-sectional studies in normotensive people indicate that left ventricular wall thickness increases progressively with age [10].

At the vascular level there is an age-associated increase in intimal thickening (the intimal–medial thickness increases nearly threefold between 20 and 90 years of age) accompanied by luminal dilatation and reduction in compliance or

distensibility, eventually resulting in augmented vessel stiffness [11]. Similarly, pulse wave velocity, a noninvasive index of vascular stiffening, increases with age and has been associated to structural alterations in the media, including calcification, increased collagen, reduced elastin content, and elastin fractures [3, 12]. Thus, vascular stiffness seems to rely not only on the structural changes within the matrix, as noted above, but also on endothelial regulation of smooth muscle tone [13, 14]. Indeed, endothelial aberrations have been shown to occur in early stages in hypertension, atherosclerosis, and diabetes mellitus [15–18] (Chaps. 25 and 31).

5.3 Adrenergic Signaling: Established Pathways and Novel Insights

Adrenergic receptors (also known as adrenoceptors, ARs) belong to the guanine nucleotide-binding G protein-coupled receptor (GPCR) superfamily, membrane receptors that activate heterotrimeric G proteins after their ligand binding. G proteins typically stimulate (via G_s protein) or inhibit (via G_i protein) the enzyme adenylyl cyclase or activate (via G_q protein) phospholipase C (Fig. 5.1). GPCRs consist of one extracellular N-terminal domain, seven membrane-spanning domains, three intra- and three extracellular loops, and one intracellular C-terminal tail [19]. These heptahelical transmembrane sensors account for roughly 4 % of the total protein-coding genome and are considered the most important drug targets in medicine and physiology. An updated and detailed appraisal of the main cardiovascular GPCRs has been recently published [20]. GPCR signaling is terminated by phosphorylation of the intracellular domains of the receptor by the family of G protein-coupled receptor kinases (GRKs) [21, 22]. GRK-mediated phosphorylation increases the affinity of GPCRs for the arrestin class of proteins, which uncouples the phosphorylated receptor from G protein and successively targets the receptor for internalization. Downregulation of GPCRs reduces the functional activity of classical signaling paradigms up to 80 % [23] (also see Chap. 34).

There are two classes of ARs: αAR and βAR. Phenylephrine is considered a selective pharmacological agonist of αAR, whereas isoproterenol is a nonselective agonist for βAR [24]. The α_1AR subfamily (a G_q-coupled receptor) consists of three highly homologous subtypes, including α_1A-, α_1B-, and α_1D-AR [25]. The α_2AR subfamily (coupled to G_i) comprises three subtypes: α_2A-, α_2B-, and α_2C-AR [26]. Some species other than humans express a fourth α_2D-AR as well [27]. In the βAR family there are three receptor subtypes: β_1AR is found at its highest levels in the heart [28], β_2AR is distributed extensively throughout the body [29], and β_3AR is mainly expressed in the white and brown adipose tissue [30]. All three βARs couple primarily to $G\alpha_s$ and subsequent cAMP-related pathways, although under certain conditions can also couple to $G\alpha_i$ [31]. β_2AR and β_3AR signaling can also occur via G protein-independent mechanisms [17, 32]. In particular, cardiac β_3AR causes negative inotropic effects mainly mediated by activation of nitric oxide (NO) synthase (Fig. 5.1), serving thereby as a brake in sympathetic overstimulation. These

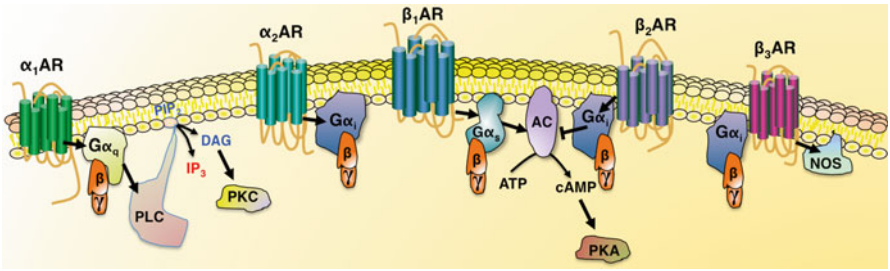

Fig. 5.1 Signaling pathways of α- and β-adrenergic receptors. Note that α_2AR is not expressed in cardiomyocytes. β_2AR can be coupled with both $G\alpha_s$ and $G\alpha_i$. Other receptors are coupled with $G\alpha_q$, including angiotensin II receptor type 1; acetylcholine M_1, M_3, and M_5 muscarinic receptors; vasopressin receptors 1A and 1B; calcitonin receptor; 5-HT_2 serotonergic receptors; histamine H_1 receptor; and metabotropic glutamate receptor, Group I. Other receptors are coupled with $G\alpha_i$, including M_2 and M_4 muscarinic receptors; adenosine A1 and A3 receptors; $GABA_B$ receptor; histamine receptors H_3 and H_4; opioid and nociceptin receptors δ, κ, and μ; apelin receptors; cannabinoid receptors CB1 and CB2; niacin receptors $NIACR_1$ and $NIACR_2$; melatonin receptors MT_1, MT_2, and MT_3; Ca^{2+}-sensing receptor; chemokine CXCR4 receptor; prostaglandin receptors EP1, EP3, FP, and TP; serotonin receptors 5-HT_1 and 5-HT_5; somatostatin receptors sst_1, sst_2, sst_3, sst_4, and sst_5; dopamine receptors D_2, D_3, and D_4; and glutamate receptors (mGluR2, mGluR3, mGluR4, mGluR6, mGluR7, and mGluR8). Other receptors are coupled with $G\alpha_s$, including arginine vasopressin receptor 2; adenosine receptor types A_{2a} and A_{2b}; dopamine receptors D_1-like family (D_1 and D_5); 5-HT receptor types 5-HT_4 and 5-HT_7; histamine H_2 receptor; gastric inhibitory polypeptide receptor; glucagon receptor; corticotropin-releasing hormone receptor; FSH receptor; thyrotropin receptor; parathyroid hormone receptor 1; melanocortin receptor MC_1R, MC_2R (ACTH receptor), MC_3R, MC_4R, and MC_5R; trace amine-associated receptor 1; prostaglandin receptor types D_2 and I_2; luteinizing hormone/choriogonadotropin receptor; secretin receptor; box jellyfish opsin; and calcitonin receptor and calcitonin gene-related peptide receptor. *AC* adenylyl cyclase, *AR* adrenergic receptor, *DAG* diacylglycerol, *NOS* nitric oxide synthase, *IP3* inositol 1,4,5-trisphosphate, *PIP2* phosphatidylinositol 4,5-bisphosphate, *PKA* protein kinase A, *PKC* protein kinase C, *PLC* phospholipase C

paradigms of signaling can be observed in the same cell type based on the functional state of the cell. Henceforth, the response to GPCR stimulus can be modified by various conditions, including chronic stimulation, acidosis, cell hypoxia, and aging [33].

5.4 Functional Involvement of Adrenergic Receptors in the Aging Process

The age-associated decrease in catecholamine responsiveness in the elderly is well established and widely acknowledged. In particular, an age-related reduction in βAR sensitivity and density has been clearly shown in the myocardium and has been essentially attributed to downregulation and impaired coupling of βARs to adenylyl cyclase [34]. More specifically, the age-linked decline in cardiac βAR response appears to be principally due to a downregulation of β_1ARs, as reported in aged

explanted human hearts [35]. Additionally, a decreased sensitivity of βARs, measured by isoproterenol-induced changes in the catecholamine-stimulated adenylyl cyclase activity, has been demonstrated in the myocardium and in pulse rate and blood pressure [29]. βAR compartmentalization may also participate in the age-associated decreased βAR responsiveness [36, 37]. Indeed, whereas β_1ARs are widely distributed on the plasma membrane, β_2ARs are usually located in the transverse tubules, invaginations of the plasma membrane containing several proteins that couple membrane depolarization (excitation) to calcium-mediated myofilament shortening (contraction) [29, 38]. Henceforward, the peculiar localization of β_2AR in cardiac cells leads to the generation of spatially restricted cAMP production, affecting Ca^{2+}-dependent proteins that control the contraction of myofilaments [39]. Interestingly, a disrupted localization of β_2AR has been recently described in chronically failing cardiomyocytes, with considerable functional consequences [40]. Numerous conditions presenting a depressed cardiac function elicit activity from the sympathetic nervous system that ultimately increases cardiac output and diverts blood flow to critical organs. The main actors of this system are catecholamines, whose release is strictly orchestrated by the GPCR system, relating the adrenal gland and the heart [41]. Most of the modifications in the sympathetic nervous system occurring with aging, including decreased βAR responsiveness, increased circulating catecholamines, and overall hyposensitivity to adrenergic stress, are also common in patients with heart failure. Moreover, young people are more reactive to isoproterenol-induced increase in blood flow than elderly subjects [42].

Vascular tone is finely regulated by the intimal (endothelial cells, EC) and the medial (vascular smooth muscle cells, VSMC) layers [14, 43], and both EC and VSMC express β_2AR [44, 45]. Therefore, such a receptor is expected to play a key role in the reduced vasoreactivity observed in the elderly [46]. Of interest, the age-related decline in β_2AR function and successive cAMP generation is a common factor to several cardiovascular disorders, including hypertension, atherosclerosis, vascular insufficiency, and orthostatic hypotension, all conditions with significant mortality and morbidity [15, 47–49]. The increased incidence of atherosclerosis and restenosis in aged people may also rely on the age-associated deterioration in βAR-mediated cAMP production, since cAMP may inhibit VSMC proliferation [50]. A reduced responsiveness with age has been also reported for αAR in healthy subjects [51], with potential implications for reduced muscle blood flow and augmented blood pressure during exercise [52].

5.5 Adrenergic Signaling in Cardiovascular Aging and Heart Failure

The sympathetic nervous system exerts various effects on the cardiac physiology, including increase in atrioventricular conduction (positive dromotropy), heart rate (positive chronotropy), cardiac contractility (positive inotropy), and cardiac relaxation (positive lusitropy). Likewise, it plays a crucial role in the regulation of

vascular tone due to its ability to control at the same time both peripheral resistances and cardiac output [53].

Heart failure is a chronic clinical syndrome in which the heart is incapable of pumping a sufficient supply of blood to meet the metabolic requirements of the body or requires elevated ventricular filling pressures to accomplish this goal. Heart failure leads to a debilitating illness characterized by poor exercise tolerance and chronic fatigue, representing one of the most important causes of morbidity and mortality worldwide. Notwithstanding considerable advances in its treatment, heart failure still represents a severe social and clinical burden [54, 55]. A complex neurohormonal regulatory system exists between the heart and multiple organ systems, including feedback loops mediated through a variety of vasoactive substances secreted by the adrenals, kidneys, lungs, and endothelium. Perturbations of function in any of these organs affect the others. Accordingly, the cardiovascular system must be perceived in a dynamic manner, continually adapting in order to optimize organ perfusion. During heart failure, diverse neurohormonal mechanisms get triggered in order to maintain cardiac output. Heart failure is indeed a progressive disease that begins long before symptoms or signs become evident. It is initially characterized by a complex adaptive neurohormonal activation, which includes the nervous system, renin–angiotensin–aldosterone system, natriuretic peptides, endothelin, and vasopressin. These and other regulatory mechanisms are required to compensate for cardiac dysfunction [56]; however, when the left ventricular dysfunction persists, the process progressively becomes maladaptive, eventually leading to increased mechanical stress on the failing heart, causing detrimental electrical and structural events, further impairment of systolic and diastolic function, and progressive cardiac fibrosis and apoptosis [57] (Chap. 3). Thus, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II AT_1 receptor blockers, and mineralocorticoid receptor antagonists represent cornerstones for the treatment of patients with failing hearts [58] (Chaps. 8, 36, and 38).

The central part of the adrenal gland, called adrenal medulla, constituted of groups of adrenergic and noradrenergic chromaffin cells and in the minor part of ganglionic neurons, is the main source of catecholamines. Here the chromaffin cells secrete around 80 % adrenaline (epinephrine) and 20 % noradrenaline (norepinephrine), whereas this proportion is reversed in the sympathetic nerves, which contain predominantly noradrenaline [41]. The adrenergic and noradrenergic secretion in different groups of chromaffin cells relies on the different α_2AR subtypes' expression [59]. The adrenal gland can be compared to a specialized sympathetic ganglion, receiving inputs from the sympathetic nervous system via preganglionic fibers. However, it directly secretes neurohormones into the bloodstream. Indeed, chromaffin cells are postganglionic sympathetic neurons that have lost part of their characteristics as axons and dendrites and are able to secrete their hormones into the blood by exocytosis. The suggestive link between the adrenal gland and the heart has become quite interesting and stimulating in the last few years, with several studies investigating the molecular mechanisms underlying such a complex relationship, especially in the pathophysiology of heart failure [41].

Adrenaline and noradrenaline generally have similar effects, although they differ from each other in certain actions. In particular, noradrenaline constricts almost all

blood vessels, while adrenaline causes constriction in many networks of minute blood vessels but dilates the vessels in the skeletal muscles and the liver [60]. Both sympathomimetic agents increase heart rate and myocardial contractility, thereby augmenting cardiac output and blood pressure [61]. Sympathetic overdrive observed in heart failure correlates with a higher risk of arrhythmias and left ventricular dysfunction [62]. Plasma concentrations of noradrenaline are negatively associated with survival in heart failure patients [63]. Augmented levels of circulating catecholamines can cause myocardial damage via an enhancement of the cardiac oxygen request and by increasing peroxidative (and lipoperoxidative) metabolism and ensuing free radical production [64, 65]. They lead to structural alterations in the myocardium, including focal necrosis and inflammation, increased collagen deposition, and subsequent interstitial fibrosis [66, 67]. Noradrenaline can also increase cardiac oxygen consumption and cause apoptosis, ultimately leading to dilated cardiomyopathy [68, 69].

At the vascular level, systemically circulating or locally released catecholamines [44] trigger two main classes of ARs: α_1AR and β_2AR, causing vasoconstriction and vasodilatation, respectively [45, 70]. With aging, such a fine equilibrium is progressively shifted toward increased vasoconstriction, most likely due to a defective vasodilatation in response to βAR stimulation. Supporting this hypothesis, βAR agonist administration in the human brachial artery induces vasodilatation, and this response appears to be attenuated in hypertensive patients [42]. The mechanistic role of β_2AR in the vasculature is also corroborated by the fact that genetic variants of β_2AR causing excessive desensitization have been shown to lead to reduced vasodilatation, promoting the development of atherosclerosis [71].

Increased basal levels of circulating catecholamines have been observed both in heart failure and with advancing age [72], mirrored by a decrease in the number of high-affinity βARs [73], suggesting that these alterations might be due to βAR desensitization rather than actual reduction in βAR density [74]. As mentioned above, βAR affinity for the ligand is mainly dependent upon GPCR phosphorylation, which in turn is in the domain of GRKs [75]. Modulation of sympathetic nervous signaling via GRK-mediated downregulation of βARs in the heart plays a key role in heart failure. In particular, heterozygous GRK2 knockout mice display augmented cardiac contractility and function, whereas transgenic mice overexpressing cardiac GRK2 exhibit decreased myocardial function due to βAR dysfunction [76].

GRK2 expression and activity increase in vascular tissue with aging [20]. Equally important, an impairment in βAR-mediated vasorelaxation has been observed in hypertensive patients [42] and in animal models of hypertension [16, 77]: such alteration has been related to the increased GRK2 abundance and activity. Transgenic overexpression of GRK2 in the vasculature causes impaired βAR signaling and vasodilatative response, eliciting a hypertensive phenotype in rodents. This aspect has been confirmed in humans: GRK2 expression correlates with blood pressure and impaired βAR-mediated adenylyl cyclase activity [20]. Besides, genetic variants of the β_2AR affecting its translational efficiency have been associated with longevity [78]. The decrease in βAR-mediated responses has been attributed to different mechanisms, including an attenuation of protein kinase A (PKA) activation, an impaired generation of cyclic AMP, a decreased receptor density, and a less

efficient coupling to adenylyl cyclase [29]. Variations in cyclooxygenase expression and vasoactive prostanoid levels have also been suggested as potential mechanisms. However, currently there is not a single molecular or cellular factor that can fully explain the decline in βAR function. Nevertheless, the etiology seems to be most likely associated with alterations in the ability of βAR to respond to agonists at the cellular level.

5.6 Therapeutic Implications: Pharmacologic and Non-pharmacologic Options

5.6.1 β-Adrenergic Receptor Blockade

Based on receptor-level activity, β-blockers can be classified into three generations (Table 5.1): (1) first generation, nonselective drugs that block both β_1AR and β_2AR; (2) second generation, cardioselective agents, with higher affinity for β_1AR; and (3) third generation, β-blockers with vasodilatative properties, mediated by α_1AR blockade, β_2AR agonism, or NO synthesis. Both selective and nonselective β-blockers have negative inotropic and chronotropic effects. The reduced inhibitory effect on β_2ARs makes the selective β-blockers less likely to cause peripheral vasoconstriction. Therefore, exercise performance may be impaired to a lesser extent by β_1AR selective drugs, at least in part because β_2AR blockade tends to blunt the exercise-induced increase in skeletal muscle blood flow [3]. Exercise training has been shown to improve βAR signaling and function, augmenting cardiac inotropic reserves, increasing peak oxygen uptake, and restoring normal sympathetic outflow and circulating catecholamine levels [3, 98].

β-Blockers differ in their physicochemical properties. For instance, lipophilic compounds, including metoprolol, carvedilol, nebivolol, and bucindolol, are rapidly adsorbed in the gastrointestinal tract and are extensively metabolized in the liver (first-pass metabolism), resulting in a shorter half-life when compared to other β-blockers [99]. Furthermore, the high lipophilicity leads to an enhanced penetration across the blood–brain barrier, which may justify the increased number of central nervous system-related effects as well as the membrane-stabilizing properties of antiarrhythmic molecules, which are independent of the βAR blockade [100].

The most common adverse events of β-blockers are attributable to the blockade of sympathetic stimulation, resulting in acute or chronic consequences at cardiovascular, metabolic, and respiratory levels [101, 102]. In the heart, acute blockade of catecholamine effects worsens myocardial contractility and induces bradycardia. Starting with low doses and slowly titrating up is a commonly used approach to reduce these risks. Patients may experience worsening of their symptoms during β-blocker titration, often requiring increased diuretic doses. Since a prolonged β-blocker treatment may enhance the sensitivity to catecholamines, an abrupt withdrawal should be avoided. At the respiratory level, β-blockers can cause bronchoconstriction, due to β_2AR blockade. Therefore, β-blockers, especially nonselective

Table 5.1 Classification and pharmacology of β-adrenergic receptor blockers

	β_1AR selectivity	α_1AR blockade	ISA	MSA	Half-life (hours)	Bioavailability (%)	Comment	Reference
First generation (nonselective)								
Carteolol	–	–	+	–	6–8	85	Used to treat glaucoma	[79]
Levobunolol	–	–	–	–	20	75	Used to treat glaucoma	[80]
Nadolol	–	–	–	–	10–20	35	Low lipid solubility	[81]
Penbutolol	–	–	+	–	5–6	90	5-HT_1A antagonist	[82]
Pindolol	–	–	++	±	3–4	75	Long-lasting hemodynamic effects	[83]
Propranolol	–	–	–	++	3–5	25	Treatment of performance anxiety	[84]
Sotalol	–	–	–	–	12	95	Inhibition of K^+ channels	[85]
Timolol	–	–	–	–	3–5	65	Reduces intraocular pressure	[86]
Second generation (cardioselective)								
Acebutolol	+	–	+	+	3–4	40	Used in Smith–Magenis syndrome	[87]
Atenolol	+	–	–	–	5–8	50	Almost exclusive renal excretion	[88]
Betaxolol	+	–	–	±	14–22	89	Used to treat glaucoma	[89]
Bisoprolol	+	–		–	9–12	90	Minor effects on insulin sensitivity	[90]
Esmolol	+	–	–	–	0.15	99	Ultrashort acting	[91]
Metoprolol	+	–	–	±	3–7	12	Available as succinate or tartrate	[92]
Third generation (vasodilators)								
Bucindolol	–	+	±	–	3–4	30	Debatable results in clinical trials	[93]
Carvedilol	–	+	–	–	7–10	30	Ameliorates insulin sensitivity	[94]
Celiprolol	+	–	+	+	5	50	β_2AR agonist	[95]
Labetalol	–	+	+	±	4–6	20	Used to treat high blood pressure	[96]
Nebivolol	+	+	–	–	10–30[a]	12–96[a]	Nitric oxide vasodilatatory effect	[97]

ISA intrinsic sympathomimetic activity, *MSA* membrane-stabilizing activity
+ yes, – no, ± moderate effect
[a]Depending on CYP polymorphisms

agents, are contraindicated in patients suffering from asthma or chronic obstructive pulmonary disease. A risk/benefit assessment should be performed in each single patient in order to avoid undertreatment of heart failure [103, 104].

Counteracting adrenergic overdrive through means of βAR antagonists has been shown to reduce cardiac workload and increase O_2 sparing in patients with failing heart. However, β-blockers have also noteworthy metabolic implications, including alterations in the lipoprotein profile, namely, a reduction in high-density lipoprotein (HDL) cholesterol and an increase in triglycerides, and a deranged glucose homeostasis, which is essentially attributed to the blockade of β_2AR-dependent insulin release from the pancreatic islets of Langerhans [17]. β_1AR selective antagonists should thereby be preferred in patients with diabetes and heart failure [49]. The variability in the response to β-blockers has been at least in part attributed to polymorphisms in CYP2D6 gene, which is highly polymorphic in humans [105]. Indeed, many β-blockers are partially or totally metabolized by CYP2D6, and opportune dose modifications should be accurately considered in patients treated with drugs processed by the same CYP isoforms, including antipsychotics and antidepressants [106]. Equally important, half-life and peak plasma concentration are influenced by the formulation of the molecule. For instance, metoprolol is available in two different formulations: metoprolol succinate [107], with a long-lasting action (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure – MERIT-HF), and metoprolol tartrate [108], which has a short half-life and demonstrated a reduced efficacy when compared to carvedilol (Carvedilol or Metoprolol European Trial – COMET study). The FDA has approved metoprolol succinate for the treatment of subjects with failing hearts [109, 110].

5.6.2 α-Adrenergic Receptor Blockade

As potent vasodilators, α_1AR blockers were initially thought to be promising to treat heart failure. However, chronic administration of the α_1AR blocker prazosin caused an increase in catecholamine levels. Two clinical trials demonstrated that the hypothesis of using α_1AR blockers to treat heart failure was not pursuable. First, in the Veterans Administration Cooperative Study (V-HeFT), patients receiving prazosin experienced worse outcomes than those receiving the combined vasodilator therapy of isosorbide dinitrate and hydralazine [111]. Then, in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study, the doxazosin arm was terminated early because of the higher incidence of heart failure [112]. Mounting evidence indicates that the central nervous system plays a crucial role in the sympathetic excitation observed in heart failure. Moreover, the association between the degree of sympathetic activation and mortality raised the possibility that a more complete adrenergic blockade might produce better outcome. Since the excitation of central α_2AR inhibits the activation of the sympathetic nervous system, such a receptor has been considered as a possible target in the treatment of heart failure [113].

Clonidine is a centrally acting drug with α_2AR agonist action that at modest doses has been shown to markedly attenuate cardiac and renal sympathetic tone in patients with failing hearts in a small and short-term clinical study. However, a clinical trial (Moxonidine in Congestive Heart Failure – MOXCON) investigating the centrally acting sympatholytic agent moxonidine had to be terminated early [114] because the drug was associated with an increased mortality (+38 %) and hospitalizations for heart failure and myocardial infarction, despite a significant dose-related reduction in plasma noradrenaline (−18.8 %). These results suggest that peripheral receptor inhibition may be better tolerated than central suppression of the sympathetic nervous system (Chap. 39). A marked sympatholytic effect has been also associated with adverse outcomes in the Beta Blocker Evaluation of Survival Trial (BEST), where patients in which bucindolol induced a significant decrease in noradrenaline levels exhibited a 169 % increase in mortality [115]. Intriguingly, one of the oldest drugs used to treat heart failure, digoxin, which mainly acts by indirectly increasing intracellular Ca^{2+} available in the sarcoplasmic reticulum, has been shown to modulate the adrenergic nervous system by improving baroreceptor function and decreasing sympathetic tone [116].

5.6.3 RAAS Interruption

The renin–angiotensin–aldosterone axis (RAAS) is another key system involved in the pathophysiology of heart failure, and the degree of its activation correlates with prognosis [117]. Angiotensin II and aldosterone production have been shown to enhance the release (and inhibit the uptake) of noradrenaline at the nerve endings. Plasma aldosterone levels may be elevated as high as 20-fold in heart failure patients, primarily because of augmented production by the adrenal glands following stimulation by the high circulating levels of angiotensin II [118]. Together with its metabolic and electrolyte effects, aldosterone causes endothelial dysfunction, increases plasminogen activator inhibitor-1 levels, and induces the development of cardiac fibrosis, accelerating the remodeling process and disease progression [119, 120]. Undoubtedly, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers represent cornerstones in heart failure therapy [121] (Chap. 36). Furthermore, two clinical trials (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and Randomized Aldactone Evaluation Study (RALES)) have demonstrated the benefits of aldosterone antagonists in heart failure, probably also related to their effect on the sympathetic nervous system [122, 123].

5.6.4 Non-pharmacologic Options

Recent evidence suggests that the modulation of the sympathetic nervous system can also be achieved via non-pharmacologic routes, including sympathetic denervation, baroreflex sensitization, and vagal nerve stimulation [124, 125] (Chap. 6).

However, randomized clinical trials are required to address the potential benefits of these treatments in patients with heart failure. Of note, cardiac resynchronization therapy has been shown to improve sympathetic function in patients with reduced systolic function [57, 126]. Biventricular pacing can indeed reduce cardiac sympathetic nerve activity and revert autonomic remodeling, at least in part by upregulating presynaptic receptor function [127–129].

5.7 Adrenergic System in the Heart: Beyond the Regulation of Contractility

The activation of the sympathetic system leads to noteworthy metabolic responses, including increased gluconeogenesis and lipolysis with subsequent elevated plasma levels of free fatty acids and glucose [47, 130]. Essentially, the extra amount of glucose and free fatty acids can be used by the organism as fuel in times of stress or danger, when increased exertion or alertness is required [131]. Different therapeutic approaches targeting myocardial metabolism have been suggested to regulate metabolic pathways in the failing heart and improve cardiac function and metabolic elasticity [132] (Chap. 17).

During the flight-or-fight response, sympathetic activation causes α_1AR-mediated vasoconstriction in less vital vascular beds, such as splanchnic and skin, to divert the blood to the skeletal muscle in exercise. AR activation also mobilizes blood from the capacitance veins, involving α_1 and α_2 ARs [133]. These acute physiological responses, typical of the stress conditions, are disadvantageous when they become chronic. Actually, a common feature of many pathological conditions involving sympathetic system hyperactivity is the development of metabolic alterations, including insulin resistance, impaired glucose and lipid metabolism, and mitochondrial dysfunction [3, 134]. The myocardium has high metabolic demands, among the highest in the body: with minimal ATP reserves and complete ATP turnover approximately every 10 s, the heart heavily depends on a continuous energy supply [135]. Though, the heart possesses a strategic metabolic flexibility that allows maintaining its function during stressful conditions. The cardiac muscle generates ATP almost exclusively via oxidative phosphorylation by using different metabolic substrates: in healthy state cardiac ATP production mainly relies on free fatty acid oxidation, whereas the relative contribution of glucose increases during stress or injury [136].

Imbalance in adrenergic activation and cardiac energy metabolism represents a risk factor for the development of cardiac disease. Therefore, heart failure represents a classical hallmark in the study of metabolic alterations related to the sympathetic system. Indeed, under pathological conditions, the heart presents a malfunction of various metabolic pathways, including the tricarboxylic acid cycle and β-oxidation. Metabolic remodeling observed in failing hearts is characterized by a lower oxidative capacity, contractile dysfunction, and insulin resistance [137, 138]. In both type 2 diabetes mellitus and heart failure,

circulating insulin levels are chronically augmented, leading to persistent stimulation of insulin receptors [49, 139]. Such increase in insulin signaling in the heart promotes free fatty acid uptake, ensuing lipotoxicity [140]. Moreover, hyperactive insulin signaling has been also demonstrated to accelerate adverse left ventricular remodeling [9, 141]. Insulin itself can directly impair adrenergic signaling pathways required for contractile function via an insulin receptor/β_2AR signaling complex [137], providing a potential innovative mechanism underlying cardiac dysfunction in heart failure. Of interest, insulin resistance has been shown to highly correlate with neuroadrenergic function [16], and the onset of type 2 diabetes is associated with increased central sympathetic outflow [142]. In addition to that, both nutritional sympathetic responsiveness and baseline sympathetic drive have been demonstrated to be important prognostic biological markers for dietary weight loss outcome in obese subjects with metabolic syndrome [143].

The prevalence of sympathetic over parasympathetic activity might be initially responsible, at least in part, for an increased metabolic state. However, as in different hormone-regulated pathways, such a state is subsequently followed by a decrease in βAR metabolic responsiveness, with a reduced basal metabolic rate and an increased tendency toward anabolic processes, leading to insulin resistance and reduced ability to dissipate energy, with an overall weight gain, particularly at the visceral level [144]. This particular aspect can eventually cause a vicious circle, in which insulin resistance further stimulates sympathetic activity, worsening insulin resistance itself. A sustained βAR stimulation is widely known to induce insulin resistance [145]. β_2AR and β_3AR seem to play a pivotal role in regulating, although not exclusively, glucose and lipid homeostasis, respectively: whereas β_2AR acts on both pancreatic β-cell hormone secretion and peripheral glucose metabolism [17], β_3AR is more involved in the modulation of free fatty acid metabolism [146]. GRKs actively participate in this complex scenario.

GRKs have been proposed as pleiotropic proteins involved in the regulation of countless cellular functions, not exclusively via the classic phosphorylation pathway. Mounting evidence indicates that GRKs exert different effects within the cell depending on cell type, localization, stimuli, and pathophysiological context. For instance, Iaccarino and colleagues were the first researchers to demonstrate the mitochondrial localization of GRK2 [147], later confirmed by other investigators [148], with important functional significances. Insulin has been shown to cause upregulation of GRK2, which in turn inhibits insulin signaling and glucose extraction [20, 149]. Various conditions associated to insulin resistance including hypertension and diabetes are characterized by elevated GRK2 levels [20]. In murine failing hearts, GRK2 inhibition has been demonstrated to be beneficial, preventing the derangement of insulin signaling and significantly delaying the reduction of glucose uptake and preserving myocardial function. In the clinical setting, lymphocyte GRK2 levels have been shown to be significantly augmented in patients with end-stage heart failure [150] and in patients with myocardial infarction, significantly correlating with a worse systolic and diastolic function [75].

5.8 Concluding Remarks

Notwithstanding important insights into the role of the sympathetic nervous system in heart failure and aging, several issues remain to be clarified. For instance, whether the activation of the adrenergic system is the driver of heart failure or, on the contrary, a consequence of the disease has not yet been clearly established. Future investigations could help in understanding the molecular mechanisms underlying hyperactivation of the sympathetic system, providing new pharmacological targets and machineries to be leveraged in the clinical scenario.

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Chapter 6
The Parasympathetic Nervous System and Heart Failure: Pathophysiology and Potential Therapeutic Modalities for Heart Failure

Brian Olshansky, Renee M. Sullivan, Wilson S. Colucci, and Hani N. Sabbah

Abstract Congestive heart failure is associated with essential perturbations in the autonomic nervous system. Early in the development of heart failure, there may be defective parasympathetic cardiac control. This may occur before, or in parallel with, elevation in sympathetic tone. Here, we consider alterations that occur in the parasympathetic nervous system during the initiation and development of congestive heart failure. We also consider targets in the parasympathetic nervous system at various levels that may affect and improve clinical outcomes (survival, measures of progressive heart failure and debilitation, and cardiac remodeling, to name a few) by unique mechanistic effects that the parasympathetic nervous system exerts on heart rate, inflammation, remodeling, endothelial nitric oxide synthase activity, inhibition of the sympathetic nervous system, and other potential mechanisms. We consider approaches to vagus nerve stimulation, the designs and early outcomes of trials, and some of the drug interventions that have been attempted. In this rapidly emerging field, with little clinical data, we discuss issues regarding study designs and outcome measures of importance.

Keywords Parasympathetic activation • Heart failure • Vagus nerve • Inflammation • Parasympathetic nervous system • Baroreceptor

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6.1 Introduction

The relationship between the sympathetic nervous system (SNS) and the development and progression of congestive heart failure (CHF) in patients with left ventricular (LV) systolic dysfunction, or heart failure with reduced ejection fraction (HFrEF), is well established. Long-term, sympathetic overstimulation is detrimental to the myocardium [1]. Beta-adrenergic blockers improve many important outcomes, including CHF hospitalization and total mortality, but also ameliorate LV remodeling and improve functional class (Chaps. 3 and 5).

On the other hand, the relationship between parasympathetic innervation and CHF is less well defined. Although there may be a dynamic inverse relationship between the SNS and parasympathetic nervous system (PNS), it is difficult to measure parasympathetic (vagus) nerve efferent and afferent activity directly. As a result, it is difficult to quantify the effects of parasympathetic activation, and its withdrawal, with regard to definable CHF outcome parameters. Furthermore, there are no specific drugs that can activate the vagus nerve preferentially, reproducibly, reliably, and measurably without having other undesirable side effects.

Measures of vagus nerve activity often include peripheral markers, such as reduced circulating levels of norepinephrine, brain natriuretic peptide (BNP), and change in heart rate and heart rate variability. These markers, however, do not necessarily provide detailed, accurate, or specific information with regard to targeted and localized vagus nerve activation in the ventricles and atria of patients with CHF. This extent of sympathetic or parasympathetic activation may differ by disease type and pathological lesion distribution. Vagus nerve activation may differ by location of myocardial infarction. It is not completely known how parasympathetic activation, and its inhibition, affects initiation and progression of CHF.

Here, we address the potential effects of parasympathetic nerve activity in the development and reversal of HFrEF. We consider the PNS as a potential target for therapeutic intervention to improve outcomes in patients with LV systolic dysfunction.

6.2 Organization of the Parasympathetic Nervous System

Parasympathetic innervation is complex and affected by local influences. The effects are abrupt in onset and offset (although persistent vagal tonicity also exists) which makes them distinct from the more global (slow on and slow off) effects of sympathetic activation. While the effects can be rapid and/or phasic (e.g., varying with respiration), they can be more prolonged or tonic (related to localized central processing or ganglionic gating) [2] with continuous effects on ventricular muscle, for example. Selective neural and hormonal modulation occurs at various levels from the central nervous system through the ganglia and down to the level of intracellular signaling in specific target cardiac cells.

Central efferent extensions of the PNS begin at medial medullary sites (nucleus ambiguus, nucleus tractus solitarius, and dorsal motor nucleus) and are modulated

by the hypothalamus. All activity then extends through the vagus nerves to the postganglionic neurons, located in the peripheral ganglia (in fat pads around the heart), activated via nicotinic receptors and then postsynaptically via muscarinic end-organ receptors. Through cardiac mechanoreceptors, baroreceptors, and aortic arch receptors, vagal afferent activation provides feedback from the cardiovascular system to the central nervous system. Baroreceptor activation sends signals to the nucleus tractus solitarius that can be activated tonically, which in turn can then activate the dorsal nucleus of the vagus nerve to affect efferent cardiac vagal responses.

In the normal state, at rest, parasympathetic activity predominates to regulate the heart rate via the sinus node; sympathetic effects are minimal. Physical activity can enhance vagal activation and suppress resting sympathetic tone. However, in CHF, sympathetic activation can supersede to various degrees any and all effects from the PNS.

Several types of parasympathetic nerve fibers coexist in the vagus nerve. A fibers are myelinated, the largest and the fastest conducting. Afferent fibers include slow-conducting unmyelinated C fibers and small-diameter A-delta fibers, whereas small, thin, nonmyelinated postganglionic C fibers and intermediate-diameter and intermediate-conducting preganglionic myelinated B fibers in efferent fascicles contribute to cardioinhibition mediated at the heart by muscarinic receptors. Efferent fascicles contain large myelinated A-beta fibers that belong to the laryngeal bundle and cardioinhibitory A-delta fibers that excite postganglionic neurons in the cardiac fat pads via nicotinic receptors. Nicotinic receptors affect ganglionic transmission and ultimately are responsible for parasympathetic activation via local neurons. Vagal efferent activation may differ (tonic or phasic) depending on where the fibers originate (nucleus ambiguus or dorsal motor nucleus of the vagus).

Predominantly, the PNS innervates the sinus node and AV nodes (Fig. 6.1). However, extensions of fibers are also present nonuniformly in atrial and ventricular muscle in a nonuniform epicardial/endocardial and regional distribution such that anatomical relationships are not in direct relationship to sympathetic innervation. Parasympathetic activation can inhibit sympathetic activation pre- and postsynaptically. Likewise, sympathetic activation can inhibit parasympathetic activation.

Postganglionic parasympathetic cholinergic fibers affect the heart through cardiac muscarinic (generally, M2) receptors. These, and other, muscarinic receptors (M3 and M4) are present in cardiac muscle with density varying by location and cell type. Muscarinic receptors are concentrated in the sinus and AV nodes. While fewer fibers project into the ventricles, they are denser in the endocardium than in the epicardium. Most of the effects from the PNS are modulated through M2 receptors. Under normal, physiologic conditions, parasympathetic stimulation will inhibit tonic sympathetic activation with or without exercise. This is known as "accentuated antagonism." Muscarinic receptor stimulation opposes sympathetic activation by the G_i-mediated signaling pathway that opposes adenylyl cyclase and works via guanosine triphosphate.

In those with heart disease, there can be defective parasympathetic cardiac control, and in those with CHF, the influence of the PNS diminishes even at rest [3–5]. This may actually occur before, or in parallel with, elevation in sympathetic "tone"; the two are related [6, 7]. The mechanisms responsible for this and the causal relationships between withdrawal of parasympathetic tone and CHF progression remain uncertain. Several other changes occur during the development of

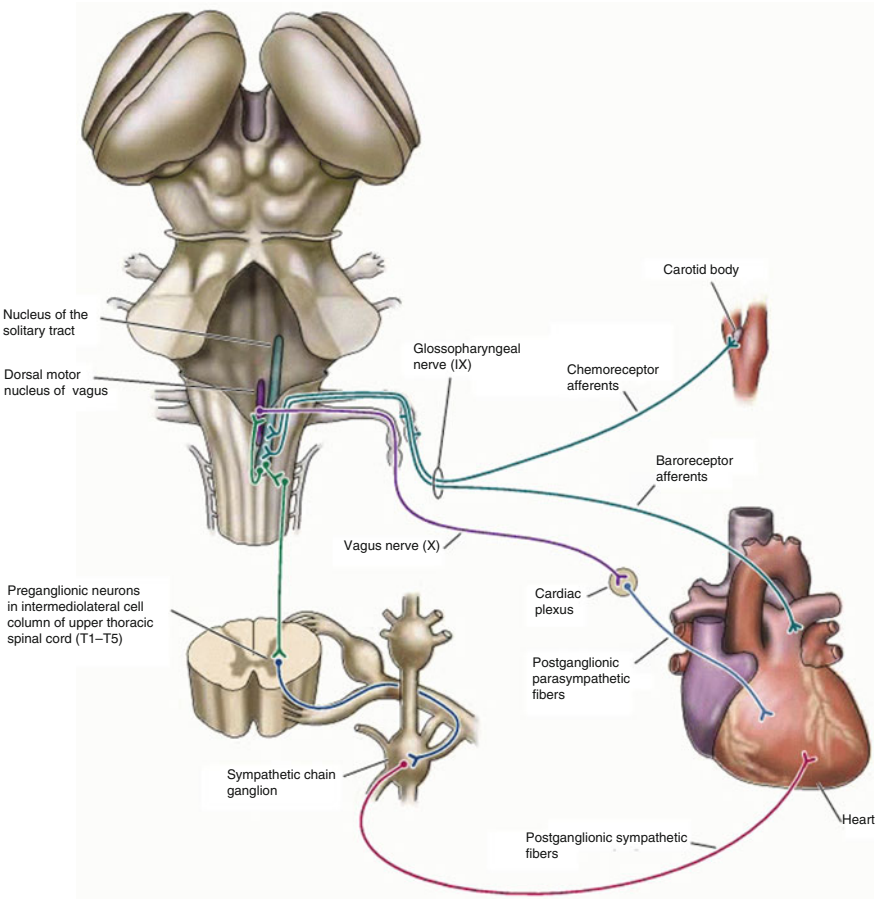

Fig. 6.1 Innervation of the heart by the autonomic nervous system – from central to peripheral inputs. The sympathetic and parasympathetic (vagus) nerves are marked. Vagus afferents (sensory nerves) are also present (Reproduced with permission from Sinauer and associates and Springer Publishing Company. The figure is from Dale Purves et al., Principles of Cognitive Neuroscience, second edition, Figure 21.7 page 461)

CHF. There is a decrease in nicotinic receptor number with reduced ganglionic transmission and a decrease in M2 receptor density and sensitivity, partly due to formation of M2 receptor antibodies. In an animal model, autoantibodies to M2 receptors have been associated with remodeling in CHF [8] although the clinical significance of this is questioned [9, 10]. Additionally, M3 and/or M4 receptors co-localized on cardiac structures may increase in lieu of decreasing M2 receptor density [11]. The effects from these changes are uncertain clinically. Also, sympathetic activation increases, in part, due to withdrawal of parasympathetic "tone."

Various muscarinic receptors have different cellular expression, signaling pathways, functions, and molecular subtypes. Several forms appear to be present in the heart [12]. M1, M3, and M5 receptors couple Gq/11 to phospholipase C [13] to form two key second messengers, inositol trisphosphate and diacylglycerol [14].

M2 and M4 receptors couple pertussis toxin-sensitive G protein (Gi/Go) to inhibit adenylyl cyclase [15]. The receptors have differential effects on K^+ and Ca^{2+} channels. The interactions of the receptors and other factors may explain why muscarinic agonists at high concentrations can induce a positive inotropic effect.

During CHF, parasympathetic control of the heart is attenuated, ganglionic transmission is reduced, muscarinic receptor density is increased [16], and acetylcholinesterase activity is decreased. Perhaps, as a consequence of the withdrawal of parasympathetic tone, muscarinic receptor density is increased [16] with a shift to novel muscarinic receptors at least in animal models. Thus, during CHF, once parasympathetic withdrawal is established, several maladaptations develop which include increased heart rate, excess release of pro-inflammatory cytokines [17], development of arrhythmias, and dysregulation of the nitric oxide (NO) signaling pathways [18].

Parasympathetic activation, on the other hand, inhibits sympathetic activity presynaptically [19] and reduces the heart rate. It is anti-inflammatory, limits cytokine release, and promotes normalization of NO expression and signaling. Additionally, parasympathetic activation inhibits the renin-angiotensin system, improves baroreflex sensitivity, and reduces the burden of life-threatening arrhythmias [18].

6.3 Potential Benefits of Vagus Nerve Stimulation: Animal Data

Parasympathetic activation in CHF has several potential therapeutic benefits (although the targets are not completely known). Firstly, the PNS can inhibit sympathetic activation, above and beyond that accrued by beta-adrenergic blockade. Secondly, the PNS can slow the sinus rate, thus lowering myocardial oxygen consumption. Thirdly, the PNS can improve cell-to-cell conduction and thus be antiarrhythmic. Fourthly, the PNS can normalize expression of several nitric oxide synthase (NOS) isoforms and provide potent anti-inflammatory and antioxidant effects. Inhibition of sympathetic overdrive in CHF can also elicit suppression of renin and vasopressin release and enhance intracellular calcium handling.

Much of the understanding on the beneficial influences of parasympathetic nerve activation in CHF has come from animal models. In these models, the effects of vagus activation are distinct from the effects of sympathetic activation or inhibition.

6.3.1 Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) can be antiarrhythmic and protect against ventricular fibrillation independent of muscarinic receptor activation [20]. In a canine ischemic model of ventricular fibrillation, Vanoli et al. compared a control group to those who underwent vagus stimulation [21]. Ventricular fibrillation occurred in controls who underwent a second coronary artery occlusion but was suppressed following coronary artery occlusion in almost all who had vagal stimulation beforehand. These data were also supported by murine CHF and post-myocardial infarction models

showing that right vagus stimulation slowed heart rate 20–30 bpm, improved hemodynamics, and reduced the risk of death (73 % relative risk reduction) [22]. In a post-myocardial infarction model, ventricular ectopy was markedly suppressed [23].

6.3.2 *Inflammatory Cytokines*

In CHF, there is an increase in inflammatory cytokines including TNF-alpha, IL-1 beta, IL-6, and IL-18 [17, 24]. Vagus nerve activation inhibits cytokine release and attenuates the inflammatory response. Cytokine release is associated with increased mortality and morbidity in CHF patients [25]. In the dog, protein expression and plasma levels of TNF-alpha increase with induced CHF versus a normal animal. Similarly, protein expression of IL-6 and plasma levels of IL-6 increase compared with a normal animal. However, with an effective stimulation of the vagus, levels of TNF-alpha and IL-6 decrease toward baseline values. Ruble et al. in a canine model of CHF have shown that TNF-alpha is elevated compared with normal animals and is decreased toward control values by VNS [26]. Borovikova et al. have described that acetylcholine can attenuate release of cytokines (TNF-alpha, IL-1beta, IL-6, and IL-18) and that direct electrical stimulation of the vagus nerve in vivo during lethal endotoxemia in rats inhibits TNF-alpha synthesis, attenuates serum TNF-alpha, and prevents septic shock [25].

VNS inhibits cytokine release and attenuates the inflammatory response, which includes the release of TNF-alpha, IL-1-beta, IL-6, and IL-18. Tracey has considered complex peripheral/central mechanisms between the cholinergic and anti-inflammatory pathways as it involves the nicotinic alpha-7 acetylcholine receptor. Work performed by his group has shown a relationship in CHF patients between cytokine release and mortality and morbidity [27]. In fact, signal transduction by the nicotinic alpha-7 acetylcholine receptor subunit regulates intracellular signals that control cytokine transcription and translation [28] and thus is an essential regulator of inflammation [29].

Sabbah et al. have shown a relationship between TNF-alpha, IL-1-6, and CHF in an animal model [30, 31]. Vagal nerve stimulation reduced the level of inflammation back to normal. Similarly, C-reactive protein increases in a pacing model of CHF and is reduced to baseline levels with VNS. VNS reduces norepinephrine and angiotensin II. VNS, in the canine CHF model, has been associated with reduction in elevations of C-reactive protein, IL-6, TNF-alpha, pro-ANP, and NT-proBNP.

6.3.3 *NO Modulation*

Parasympathetic nerve stimulation affects NO synthases (eNOS, nNOS, and iNOS) that are altered during CHF [32–40] and that affect ventricular function [32]. eNOS, which is reduced in CHF, exerts a number of beneficial actions that promote relaxation, modulate contractility, and inhibit myocardial hypertrophy and apoptosis. On

the other hand, iNOS, which increases in CHF, exerts several adverse actions that promote apoptosis, fibrosis, hypertrophy of the myocardium, heart block, and sudden death [37, 41]. nNOS, also increased in CHF, modulates calcium cycling and reduces contractility, in addition to increasing sensitivity to beta-adrenergic stimulation [39]. In an animal model of CHF, altered NOS expression is normalized by VNS.

6.3.4 Gap Junctions

It is known that gap junctions, essential for cell-cell communication with regard to electrical depolarization and repolarization, can be impaired in CHF. In particular, there has been focus on connexin-43 which is reduced during CHF. Slowed myocardial conduction, altered repolarization, and increased risk of arrhythmias and sudden death follow [42, 43]. VNS improves LV connexin-43 expression in a dog model of CHF and thus may be antiarrhythmic. VNS can protect against ischemia-induced arrhythmias, specifically by preserving connexin-43 [44].

6.3.5 Anti-apoptotic

VNS may be anti-apoptotic as shown in an animal model in which active caspase-3, elevated in CHF, is downregulated with VNS [45, 46]. VNS has been shown to improve the activity and expression of the sarcoplasmic reticulum SERCA-2a pump which is downregulated in CHF, a maladaptation that leads to both systolic and diastolic LV dysfunction. VNS can also affect the degradation and synthesis of collagens I and III in the heart and thus indirectly impact LV compliance. Furthermore, with VNS TGF-beta-1 protein expression may decrease, thereby decreasing interstitial fibrosis.

6.3.6 Heart Rate

A fundamental action of VNS is a reduction in heart rate and the mechanism of this is fairly well understood. Heart rate is a major determinant of myocardial oxygen consumption and is known to be associated with increased mortality and morbidity in CHF [47]. The importance of heart rate reduction in CHF is supported by the results of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I*f* inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial and SHIFT (Systolic Heart failure treatment with the I*f* inhibitor ivabradine Trial) [48–51], in which ivabradine, a specific and selective inhibitor of the I*f* current, was studied. In the BEAUTIFUL trial, ivabradine did not influence cardiovascular death or admission to hospital for heart failure. Ivabradine did reduce admission to

hospital for fatal and nonfatal myocardial infarction and coronary revascularization (Chap. 1). In the SHIFT, higher resting heart rate was shown to be a risk factor for adverse outcome, and heart rate reduction with ivabradine was an important predictor of an improvement in the primary composite endpoint of mortality and CHF hospitalization (mainly driven by CHF hospitalization). One should be aware, however, that the benefits of VNS may be mediated by effects independent of heart rate reduction.

6.3.7 Effects Independent of Beta-Blockade

VNS may lead to an improvement in ejection fraction over that which occurs with beta-adrenergic blockade alone. Sabbah et al. [30, 31] in a CHF model, showed that VNS, on top of beta-adrenergic blockade, caused a greater improvement in ventricular function than did beta-blockade alone. The best way to activate the PNS is not completely certain. While most data would support right vagus nerve stimulation, other approaches have been utilized including carotid sinus baroreceptor stimulation in a dog model [52], spinal cord stimulation in a canine model [53], and spinal cord stimulation in a porcine model [54]. The effects of left vagus nerve stimulation in CHF are less well studied.

VNS appears to improve ventricular remodeling in advanced CHF and thereby improve outcomes, though there are little human data as yet to substantiate this. Unanswered questions include which vagus (right, left, or both) is best to stimulate and at which intensity, frequency, and duration.

6.3.8 Carotid Baroreflex Activation

Alternatives to VNS as targets for PNS activation have been studied. Sabbah et al. examined the role of carotid sinus baroreflex activation in 14 dogs (eight experimental and six controls) with an LV ejection fraction of 25 % [52]. Over the course of 3 months, those receiving baroreflex activation were found to have an increase in ejection fraction (4.0 ± 2.4 %), while the controls had further decline (-2.8 ± 1 %) ($p < 0.05$). Biomarkers and LV remodeling also improved in the experimental group.

6.3.9 Other Effects of Vagus Activation

VNS (vs. control) can reduce infarct size, improve ventricular function, decrease ventricular fibrillation, and attenuate cardiac mitochondrial reactive oxygen species production, depolarization, and swelling. This effect appears modulated through muscarinic receptor modulation during VNS. The protective effects of VNS could be due to its protection of mitochondrial function during ischemia-reperfusion [55]. In

another experiment in swine, VNS applied 30 min after left anterior descending occlusion, but not at reperfusion, markedly reduced ventricular fibrillation and infarct size (~59 %); improved cardiac function; attenuated cardiac mitochondrial reactive oxygen species production, depolarization, swelling, and cytochrome c release; and increased the amount of phosphorylated connexin-43 and IL-4 vs. controls [56].

6.4 Parasympathetic Activation in Clinical Trials

The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study included patients post-myocardial infarction [57] and measured autonomic tone and reflexes to predict outcomes with regard to abnormalities in heart rate variability as measured by "standard deviation of normal to normal R-R intervals" (SDNN) >70 and baroreflex sensitivity >3 (a measure suggesting relatively high vagus nerve tone). While these particular parameters measure different things and may be associative rather than causal, the results suggested that vagus activation may improve mortality post-myocardial infarction. Low heart rate variability was associated with poor survival and low baroreflex sensitivity was associated with better survival. Other data support these findings [58]. Similarly, the CIBIS II (Cardiac Insufficiency Bisoprolol Study II) trial showed that diminished vagus nerve activity and increased heart rate predicted higher mortality in CHF [59]. The mechanisms responsible for this association remain unclear, and while increased heart rate alone may be a causative factor for higher mortality, the association is robust, but the causal nature is suspect.

Various approaches have been used to modulate the autonomic nervous system utilizing novel devices, particularly as relates to parasympathetic activation including spinal cord stimulation, selective right (or even left) vagus stimulation, baroreflex stimulation, and other innovative and as yet unapproved devices. This has led to the development of several ongoing clinical trials.

The CardioFit device, made by BioControl, attempts to selectively stimulate efferent cardioinhibitory B (A-delta) vagus fibers. An initial pilot study with a primary endpoint of safety in 32 CHF patients with LV ejection fraction $\leq$0.35, otherwise medically stable, was performed. VNS led to improvement in 3- and 6-month outcomes with regard to the New York Heart Association (NYHA) Functional Classification, 6-min walk, and quality of life, as well as structural/functional improvements in LV ejection fraction and end-diastolic and end-systolic volumes [60].

The INcrease Of VAgal TonE in HF (INOVATE HF) trial is a multicenter pivotal trial of CHF patients evaluating survival based on right vagus stimulation versus no vagus stimulation (no implant) and based on preliminary data [61]. The INOVATE trial is an open-label prospective, randomized comparative trial that involves 650 patients (80 investigative sites) followed for 5.5 years or until 400 events have occurred. The study is enrolling NYHA Functional Class III patients with LV ejection fractions $\leq$0.40 with an efficacy endpoint of total mortality or unplanned CHF hospitalization. In this trial, there is no specific measure of long-term VNS efficacy. The heart rate is not considered an important endpoint in this trial.

The Neural Cardiac TherApy foR Heart Failure (NECTAR-HF) study (Boston Scientific) of a right-sided vagus nerve implant system evaluated the primary endpoint of change in LV end-systolic dimension and mortality at 3 months, as well as a safety and several secondary endpoints, with the device "on" versus the device "off" in a 2:1 randomization of 96 patients with NYHA Functional Class III heart failure, an LV ejection fraction ≤35 %, and a narrow QRS complex [62]. The stimulation amplitude and frequency (0.1–4.0 mA and 20 Hz frequency, 300 μs pulse width, duty cycle 10 s "on" and 50 s "off") differ from CardioFit and the device uses a different electrode design. The device itself is approved for spinal cord stimulation for pain and is being used off-label for this trial. While the patients receiving vagus stimulation were noted to have improvement in quality-of-life scores and most had at least one point improvement in NYHA Functional Class, the study failed to show improvement in primary or secondary measures of cardiac remodeling (evaluated blindly) or functional capacity (European Society of Cardiology 2014; Barcelona, Spain).

The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) trial (Cyberonics) evaluated stimulation of the left ($n=31$) or right ($n=29$) vagus for 6 months in 60 patients (mean age = 51) with systolic heart failure on a stable medical regimen [63]. This was an open-label feasibility trial of patients with NYHA Functional Class II–III CHF and an LV ejection fraction ≤40 %. The primary efficacy endpoint was change in left ventricular ejection fraction (LVEF) and left ventricular end-systolic volume (LVESV) at 6 months; the secondary endpoints involved evaluating the effect on (1) left ventricular end-systolic diameter (LVESD), (2) NYHA Functional Class, (3) 6-min walk distance, (4) quality of life (Minnesota Living with Heart Failure Questionnaire), (5) heart rate variability, and (6) biomarkers (brain natriuretic peptide (NT-proBNP and hs-CRP)). Stimulation was at 10 Hz, the pulse amplitude was 2.0 ± 0.6 mA, the duty cycle was 17.5 % (14 s on, 66 s off), and the pulse width was 130 ms. The intensity was titrated over a 10-week period (European Society of Cardiology 2014; Barcelona, Spain). The LV ejection fraction improved by a mean of 4.5 % (similar with left or right vagus stimulation). There was a mean improvement in the 6-min walk test of 56 m (significantly less with left vs. right vagus stimulation) and a mean improvement in Minnesota Living with Heart Failure Questionnaire scores of 18 points. There was no significant improvement in LV end-systolic volume.

A canine model of post-infarct CHF has shown to benefit from spinal cord stimulation [53]. Stimulation caused reduction in norepinephrine, serotonin, and BNP, as well as evidence for reverse remodeling with an improved LV ejection fraction when combined CHF medications. In a porcine model [54], spinal cord stimulation reduced myocardial oxygen demand substantially despite increase in LV dP/dT. The Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF) trial (Medtronic) is a feasibility trial evaluating spinal cord stimulation vs. control in 70 ICD patients with NYHA Functional Class III CHF and an LV ejection fraction <35 %, a QRS duration <120 ms, and an endpoint of LV end-diastolic volume index [64]. St Jude is working on a spinal cord stimulator study (SCS Heart, 20 patients) [65]. To be enrolled, patients must have an LV ejection fraction of 20–35 %, NYHA Functional Class III or ambulatory Class IV CHF, a St. Jude implantable cardioverter defibrillator or CRT-D device, and an LV end-diastolic diameter of 55–80 mm.

Carotid baroreflex stimulation is another approach being evaluated in the Barostim HOPE4HF (Hope for Heart Failure) trial to assesses safety, efficacy, and feasibility of baroreflex activation as a therapy in CHF with preserved LV function (ejection fraction ≥40 %) and hypertension in 60 patients with elevated brain natriuretic peptide or NT-pro-brain natriuretic peptide and creatinine ≤2.5 mg/dL [66].

There are many important issues of concern with all of these clinical trials: (1) No definitive data has yet proved that vagal activation is better than no vagal activation in patients with CHF. (2) The optimal approach to vagal activation for increasing parasympathetic tone is not well defined (intensity, frequency, duration, etc.). (3) The best endpoint to measure adequate and long-lasting VNS is not certain. (4) The proof that parasympathetic activation is actually occurring remains difficult to comprehend. (5) The proper endpoint to measure, i.e., heart rate reduction or some other parameter, such as, an inflammatory marker, is not clear. (6) It is not clear which fibers of the vagus are most important to stimulate, whether they are the A-delta, the B fibers, or the unmyelinated C fibers. Further, it is unclear if afferent activation may be of benefit as well.

6.5 Drugs That Can Modulate the PNS in CHF

To date, no drug acting solely to activate the PNS has been shown to benefit patients with CHF. Drugs that target the PNS in CHF are given in Table 6.1 and are briefly described below.

6.5.1 Digoxin

Perhaps the most widely used PNS-activating drug is digoxin. While digoxin may have a potential role as a vagal activator, the mechanism of action and the intensity of the PNS effects are uncertain. Any direct effect on the vagus by digoxin is at best speculative and not well studied. It appears, however, that vagal afferents are sensitized by drugs similar to digoxin and these drugs also inhibit renal sympathetic nerve activity [67–69]. Also, digitalis can beneficially affect baroreflex sympathetic control in normal humans [70]. However, despite an increase in plasma norepinephrine with chronic digoxin therapy, heart rate variability changes and heart rate reduction suggest a substantial increase in parasympathetic activity [71].

Digoxin inhibits sodium/potassium ATPase, thereby increasing intracellular calcium that mediates a positive inotropic effect which could nullify any direct benefit of digoxin due to vagal activation. The Digitalis Investigation Group (DIG) trial showed no benefit of digoxin regarding mortality outcomes in CHF; digoxin only had an effect on reducing the rate of hospitalization overall and CHF hospitalization [72]. Although it is likely that digoxin does have an effect on vagus activity, the clinical evidence suggests that this effect is either not adequate to affect mortality or is counterbalanced by other adverse actions.

Table 6.1 Drugs that can target the PNS in CHF

Drug class	Site of action	Mechanism of action	Remarks
Cardiac glycosides, e.g., digitalis	Uncertain	Sensitizes vagal afferents Inhibits renal sympathetic nerve activity Affects baroreflex sympathetic activity Increases plasma norepinephrine Inhibits Na/K ATPase to increase intracellular Ca^{2+}	Mixed effects may nullify each other (parasympathetic, inotropic, sympathetic)
ACE inhibitors, e.g., enalapril and captopril	Indirect effects	Improvement in heart failure	Unlikely to have direct parasympathetic effect
I_f blockers, e.g., ivabradine	Funny channel of the sinus node	Slows sinus rate directly via the I_f channel	No specific parasympathetic effects
Muscarinic agonists	Muscarinic receptors		
Carbachol		Can prevent beta-receptor-stimulated apoptosis in cardiac myocytes, suggesting muscarinic activation	Could affect the rate of disease progression in CHF
Pirenzepine		Selective muscarinic receptor antagonist, works as an anticholinergic. At lower doses, it can have a cholinergic affect	Could augment vagal activity in CHF
Scopolamine		Blocks muscarinic receptors but, at lower doses, enhances parasympathetic activity. Relatively nonselective	Can affect HR variability (increased time/frequency domain parameters of HR variability in CHF) Not tested with regard to outcomes in patients with CHF Reduces average HR and increases time domain measures of HR variability Exercise performance did not improve but HR at submaximal exercise reduced Enhances tonic and reflex cardiac vagal activity during acute phase of MI measured by baroreflex sensitivity, HR variability, and respiratory sinus arrhythmia

Nicotinic agonists	Nicotinic receptors	Parasympathetic ganglia repeated exposure to nicotinic agonists during CHF development resulted in preserved or even supernormal effects of parasympathetic stimulation	Can prevent loss of parasympathetic control of CHF
Pyridostigmine bromide		An acetylcholinesterase inhibitor – works in the synaptic cleft. Does not cross the blood-brain barrier. It prolongs the effect of acetylcholine	In animals, reduces HR, increases vagal tone, reduces sympathetic control, decreases hypertrophy, and prevents CHF post-MI In patients, reduces ventricular arrhythmias, improves autonomic and hemodynamic function during exercise, reduces exercise HR, improves HR recovery post exercise, reduces cholinesterase activity, and inhibits chronotropic response during exercise
Donepezil		A cholinesterase inhibitor used to treat dementia, crosses the blood-brain barrier	Prevents LV dysfunction, neurohumoral activation and CHF in rats In a rat model of CHF due to MI vs. untreated rats, those given donepezil had a smaller biventricular weight (and max. rate of rise LV pressure. End-diastolic LV pressure improved). Norepinephrine and BNP and HR variability improved
Nitroglycerin			May have direct NO-mediated effects on vagal activity, but this is offset by the reflex sympathetic activation Vs. placebo, transdermal nitroglycerin had no effect on HR variability parameters or baroreflex sensitivity
Omega-3 fatty acids			May improve parasympathetic activation, enhance baroreceptor control, and improve HR variability in the elderly. Substantiation for benefit in CHF is speculative. Slows sinus rate via an uncertain mechanism

6.5.2 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors, which improve outcomes in CHF (see Chap. 36 for details), are associated with improvement in parasympathetic activation [73–76]. Improvements in measures of heart rate variability may be secondary to improvement in CHF in general or to inhibition of sympathetic activation. However, any causal relationship between ACE inhibitors and vagus activation remains speculative at best. Like ACE inhibitors, angiotensin receptor blockers appear to modulate and improve PNS activity [77–79]. Similar to ACE inhibitors, however, it is likely that SNS withdrawal and PNS activation are not a direct effect but, rather, are reflex mediated due to an improvement in hemodynamics.

6.5.3 Nitroglycerin

Nitroglycerin may have direct NO-mediated effects on vagal activity [80]. This, however, may be offset by the reflex sympathetic activation that occurs with peripheral vasodilatation. Compared with placebo, transdermal nitroglycerin had no effect on heart rate variability parameters or baroreflex sensitivity.

6.5.4 Omega-3 Fatty Acids

Omega-3 fatty acids may improve parasympathetic activation, enhance baroreceptor control [81], and improve heart rate variability in the elderly [82], but substantiation for this and any benefit in CHF patients remain highly speculative. Omega-3 fatty acids may slow sinus rate slightly, though the mechanism is uncertain. See Chap. 27 for details.

6.5.5 Nicotinic Agonists

Repeated exposure of ganglionic neurons to nicotinic agonists to prevent loss of parasympathetic control of CHF has been tested [83]. Despite decreased ganglionic function leading to reduced parasympathetic control of CHF, repeated exposure to nicotinic agonists during CHF development resulted in preserved or even supernormal effects of parasympathetic stimulation.

6.5.6 *Acetylcholinesterase Inhibitors*

Pyridostigmine bromide is an acetylcholinesterase inhibitor that does not cross the blood-brain barrier and works in the peripheral synaptic cleft. It prolongs the effect of acetylcholine. In healthy animals and humans, it appears to stimulate the parasympathetic nerves. Pyridostigmine has been evaluated in a rat model of CHF [84]. In conscious rats, pyridostigmine bromide reduces the basal heart rate, increases vagal tone, and reduces sympathetic control of the heart. In rats, pyridostigmine appears to decrease the hypertrophy seen in CHF, reduces the expression of collagen in non-infarcted myocardium, and prevents the development of systolic CHF after myocardial infarction. In patients, cholinergic stimulation by pyridostigmine appears to reduce ventricular arrhythmias and improve autonomic and hemodynamic function during dynamic exercise. Pyridostigmine can reduce the exercise heart rate by up to 60 % without changing the resting heart rate.

In a prospective, randomized, double-blind, placebo-controlled, crossover trial of 20 patients with stable CHF (mean age 55 years, mean ejection fraction 24 %), pyridostigmine (30 mg) improved heart rate recovery after maximal exercise at 1 min but not at 3 min. Ingested pyridostigmine 30 mg or a matching placebo on separate days did not affect peak heart rate, oxygen uptake, or respiratory exchange ratio or change plasma norepinephrine or brain natriuretic peptide concentrations [85].

In another study, CHF patients participated in a double-blind, crossover protocol (placebo or pyridostigmine 30 mg orally TID for 2 days). In those with frequent ventricular ectopy, pyridostigmine reduced ventricular ectopy by 65 %. For a heart rate variability group, pyridostigmine slowed heart rate and improved heart rate variability. The authors suggested that long-term trials of pyridostigmine in CHF patients should be conducted [86]. In a study of patients with chronic CHF submitted to three maximal cardiopulmonary exercise tests on different days, oral pyridostigmine (45 mg TID for 24 h) reduced cholinesterase activity by 30 %, inhibited chronotropic response throughout exercise up to 60 % of maximal effort, and improved heart rate reserve (and heart rate recovery in the first minute after exercise), whereas peak heart rate was similar to placebo [87].

Donepezil, a cholinesterase inhibitor used to treat Alzheimer's dementia, crosses the blood-brain barrier. Donepezil has been shown to prevent LV dysfunction and neurohumoral activation and CHF in rats.

Donepezil was tested in a rat model of CHF due to healed myocardial infarction. Compared to untreated rats, those given donepezil had a smaller biventricular weight (and maximal rate of rise in LV pressure and end-diastolic LV pressure was improved). Neurohumoral factors (norepinephrine and BNP) were improved with donepezil as was heart rate variability [88].

6.5.7 *Muscarinic Agonists and Antagonists*

Carbachol, a muscarinic agonist, can prevent beta-adrenergic receptor-stimulated apoptosis in cardiac myocytes, suggesting that muscarinic activation could affect the rate of disease progression in CHF [89].

Pirenzepine, a selective muscarinic receptor antagonist, works as an anticholinergic drug but at lower doses can have a cholinergic affect that augments vagal activity in CHF.

Scopolamine likewise blocks muscarinic receptors but, at lower doses, can enhance parasympathetic activity. Scopolamine is relatively nonselective, but it can affect heart rate variability [90]. In 21 patients with moderate to severe CHF, scopolamine increased time and frequency domain parameters of heart rate variability. However, scopolamine has not been tested clinically with regard to outcomes in patients with CHF [90].

Twelve patients with NYHA Functional Class II–IV CHF and coronary artery disease (mean LV ejection fraction 26.7 %) were randomly assigned to a placebo or transdermal scopolamine patch. There was a small, but significant, increase in all time domain HRV variables with scopolamine. There was improvement in HR variability parameters [91].

In a double-blind, randomized, placebo-controlled, crossover study, 16 patients with chronic, stable CHF and ischemic cardiomyopathy (mean LV ejection fraction 28 %; NYHA Functional Class II–III) and eight age-matched healthy controls received scopolamine (500 μg/72 h) or a placebo patch. Scopolamine reduced average heart rate and increased time domain measures of heart rate variability. While exercise performance did not improve, heart rate at submaximal exercise was reduced by scopolamine [92]. In another report, low doses of transdermal scopolamine enhanced tonic and reflex cardiac vagal activity in patients in the acute phase of MI as measured by an increase in baroreflex sensitivity, heart rate variability, and respiratory sinus arrhythmia [93].

6.6 Standard Drugs for Heart Failure

Although various drugs that are utilized to attempt to improve outcomes in CHF patients (diuretics, statins [94, 95], aldosterone blockers [96–98], vasodilators, beta-blockers, ivabradine, and antiarrhythmic drugs) may affect sympathetic vagal balance, it is certainly possible that any positive association between these drugs and outcomes may be by other mechanisms. Even exercise training may affect vagal tone and improve outcomes in patients with CHF [99]. Recent data from the SHIFT [50] and BEAUTIFUL [48, 49] trials that evaluate the use of ivabradine in CHF patients indicate that heart rate slowing independent of autonomic interactions may also have some benefit with regard to select outcomes.

6.7 Can Anticholinergic Drugs Adversely Affect Heart Failure Patients?

Presently, little data substantiate any harm caused by an anticholinergic drug in patients with CHF. In part, this could be due to the fact that parasympathetic activation is already limited in these patients. However, this has not been evaluated carefully. Disopyramide, an antiarrhythmic drug with substantial anticholinergic properties, has a strong negative inotropic effect, but the mechanism of this effect has not been well tested. Nevertheless, the relationship between any anticholinergic response, i.e., increase in heart rate, has not necessarily been linked to worsening in CHF. To date, although not well tested, there are no clear-cut observational data indicating that antimuscarinic drug therapy for overactive bladder can precipitate CHF.

6.8 Concluding Remarks

Deranged autonomic nervous system activity plays an instrumental role in the pathophysiology of CHF. Increased activity of the sympathetic nervous system and decreased activity of the PNS contribute to disease progression. Early in the development of CHF, impaired parasympathetic activity may have a deleterious role in CHF progression.

Emerging evidence suggests that interventions that augment PNS activity can exert several beneficial effects directly and independently but in part by opposing the sympathetic nervous system. Direct measurement of PNS activity is difficult, and thus surrogate markers are often used to assess its status. Much interest is currently focused upon determining means to restore PNS activity, with devices or medications, to improve patient functionality and to reduce the morbidity and mortality of patients living with CHF.

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Chapter 7
Risk for Sudden Cardiac Death in Heart Failure: Underlying Mechanisms and Therapeutic Modalities

Philip B. Adamson, Emilio Vanoli, and Eduardo Gronda

Abstract Sudden cardiac death remains a major challenge to modern cardiology with multiple potential mechanisms that contribute to lethal arrhythmogenesis. Effective prevention strategies include suppression of lethal arrhythmias by preventing autonomic mediated adverse electrical remodeling using beta-adrenergic blockers, coupled with prevention of angiotensin- and aldosterone-dependent structural remodeling and fibrosis. Neurohormonal blockade significantly reduces the relative risk for sudden death, but must be coupled with lethal arrhythmia termination strategies using implantable cardioverter defibrillators in patients with depressed left ventricular function. This synergy between medical and device therapies is the basis for effective primary prevention strategies in heart failure patients. Heart failure pathophysiology is complex, but the fundamental mechanisms of disease progression and electrical remodeling leading to high risk for sudden death are similar. As a result, therapies targeting reversal of heart failure disease progression many times impact adverse electrical remodeling, thus lowering risk for lethal arrhythmias. This chapter reviews the fundamental autonomic, neural, structural, and hormonal mechanisms involved in sudden death risk for patients with chronic heart failure. Therapeutic strategies for prevention of sudden death using medications and implanted devices are reviewed along with the mention of promising emerging technologies that may

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impact sudden death rates. It is clear that heart failure disease management requires expertise in medical and device management of the syndrome. Training programs are evolving to meet the need for specially trained individuals who can fully integrate the skill sets required to provide appropriate medication and device expertise.

Keywords Heart failure • Electrophysiology • Death, sudden • Autonomic nervous system • Renin-angiotensin-aldosterone system • Implantable cardioverter defibrillator

7.1 Introduction

Sudden cardiac death is the leading cause of mortality in the Western world, cited as causative in over 500,000 deaths in the United States yearly. While definitions differ between clinical trials, sudden cardiac death is usually adjudicated as death within minutes to hours from the onset of symptoms in a patient who otherwise was clinically stable [1–3]. Definitional issues complicate comparisons across clinical trials since many differ about which deaths are adjudicated as "sudden." A notable example comes from the European trial Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS classified unwitnessed deaths that occurred during sleep as "unknown cause" rather than "sudden," whereas other trials consider overnight deaths as "sudden" [4, 5]. Further complicating epidemiologic assessment is that "sudden cardiac death" is many times listed as primary cause of mortality on death certificates without substantiation from autopsy data [6–10].

The cardiology community's fascination and frustration with sudden death began in the 1970s and was eventually considered "the most important challenge facing modern cardiology" [11]. Despite significant breakthroughs in medical and device therapies, which have substantially changed the risk characteristics, the syndrome of sudden cardiac death still remains an important challenge facing modern cardiology [12, 13]. This chapter will focus on the underlying mechanisms of arrhythmic death and focus on therapeutic modalities available for prevention and treatment.

7.2 Epidemiology of Sudden Cardiac Death in Cardiovascular Disease

Clinical epidemiology describing sudden death is fraught with significant challenges, but most still believe that the majority of true sudden cardiac deaths result from ventricular tachyarrhythmias, while bradyarrhythmias, great vessel rupture, and pulmonary embolism account for other etiologies of sudden cardiovascular collapse [14–24]. Well over 90 % of patients who develop ventricular fibrillation outside the hospital die. In many cases, survivors have neurologic deficits [25, 26]. For every minute a malignant ventricular tachyarrhythmia persists, the chance of survival is reduced by 10 %, so that 10 min after cardiovascular collapse, there is

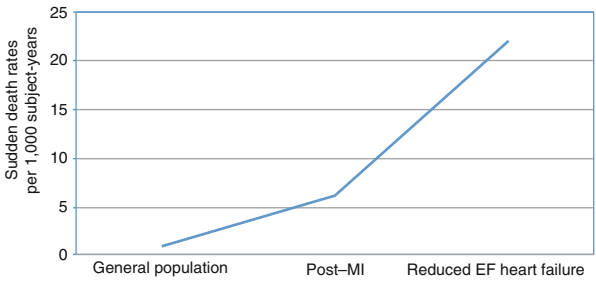

Fig. 7.1 Sudden death rates in the general population, post-myocardial infarction (MI) and in patients with reduced ejection fraction [6]

virtually no chance of survival [25]. The intensely immediate need for defibrillatory shock helps explain the poor prognosis when patients experience out-of-the-hospital cardiac arrest. This is true even in areas with well-developed first-responder systems.

The time aspect of sudden death, accentuated by the fact that the event is generally not preceded by warning symptoms [27], has led to the obvious need to identify risk groups in order to preempt the onset or rapidly treat ventricular tachyarrhythmias. Identification of high-risk groups allows both pharmacologic suppression of ventricular arrhythmias and termination of potentially lethal arrhythmias early after initiation using implanted devices [28–30]. These complementary approaches can be applied in either "primary" or "secondary" sudden death prevention strategies. Primary prevention of sudden death is provided for patients without an arrhythmia history, but who are at high risk for lethal events because of the presence of structural heart disease. Secondary strategies are offered for patients who have survived potentially lethal ventricular arrhythmias. While these approaches seem distinct, they are different only in timing during the complex pathophysiology underlying electrophysiologic adverse remodeling associated with chronic cardiovascular disease as it progresses to heart failure.

This concept is supported by the incidence of out-of-the-hospital sudden cardiac arrest, which is estimated to be 0.8/1,000 subject-years in individuals without clinically recognized heart disease. In patients with overt coronary artery disease, sudden death incidence is 13.6/1,000 subject-years in subjects with prior MI and 21.9/1,000 subject-years in subjects with symptomatic heart failure [6] (Fig. 7.1). Patients with heart failure, then, represent a high-risk group in which both pharmacologic and device therapies may provide significant opportunities for primary prevention of sudden death.

7.3 Mechanisms of Sudden Death in Heart Failure

Ventricular arrhythmias arise from a complex environment that involves adverse remodeling of myocardial electrophysiology coupled with waxing and waning of neural and hormonal signals that arise in response to altered strain on the damaged

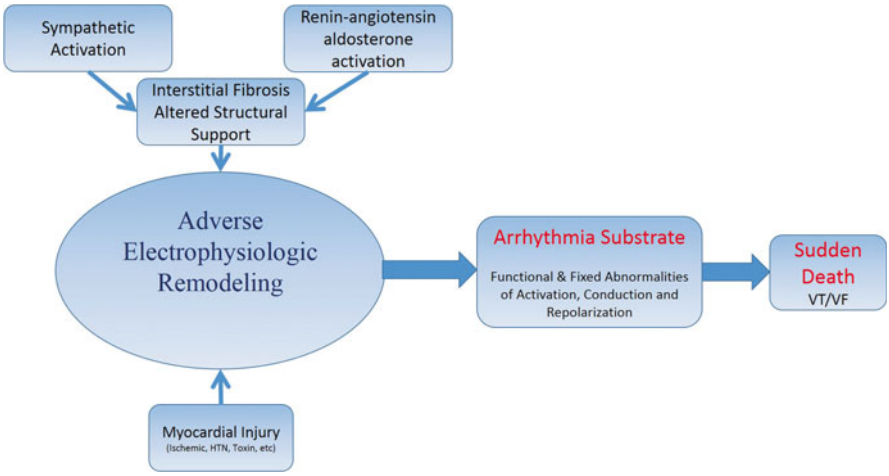

Fig. 7.2 Progression of the arrhythmogenic substrate responsible for the development of ventricular tachycardia (VT) and ventricular fibrillation (VF) associated with sudden cardiac death in heart failure patients

myocardium (Chaps. 46 and 52). Abnormalities in renal function due to poor perfusion in patients with heart failure may also contribute directly to progression in an arrhythmogenic substrate. Broader understanding of the link between the pathologic changes leading to progressive pump failure and adverse electrical remodeling will open new options for therapeutic intervention.

Cardiac electrophysiologic adverse remodeling is the consequence of structural heart disease, many times resulting from myocardial ischemia or infarction [31–37] (Fig. 7.2), but is clearly seen in patients with dilated cardiomyopathy or hypertrophic cardiomyopathy [38] (Chap. 16). The scope of this chapter is to review the primary mechanisms and therapeutic opportunities to prevent sudden death in patients with heart failure, but it is important to consider that sudden death can occur at any point in the progression from normal to the end stage of heart disease associated with clinical heart failure (Fig. 7.1).

Animal models have provided unique insight to this progression from normal to end-stage heart failure in the same subjects. Certain pathophysiologic themes emerge during this progression which point to the importance of autonomic responses to injury and associations between myocardial substrates conducive for reentrant or triggered arrhythmias. As this pathophysiology progresses, so does the risk for lethal arrhythmias. Even in animal models of sudden death, innate abnormalities of cardiac autonomic control can be seen prior to the onset of cardiovascular disease. Specifically, animals which develop ventricular fibrillation (VF) in response to coronary artery occlusion at the time of myocardial infarction (MI) are characterized by weak vagal reflexes and evidence for elevated sympathetic control [39–42]. Myocardial damage worsens this imbalance, which is associated with the development of specific alterations in regional activation and heterogeneity of repolariza-

tion. Individuals at high sudden death risk seem to progress rapidly to "arrhythmogenic heart failure" as left ventricular dysfunction develops due to progressive ischemic heart disease [42]. Neural and hormonal responses to left ventricular dysfunction result in multiple abnormalities that increase the likelihood of lethal arrhythmia development.

Clinical corroboration of the concepts observed in animal modeling is suggested by the findings that patients who died suddenly without prodromal symptoms, otherwise "normal," usually have autopsy evidence for significant obstructive coronary artery disease usually with a very recent thrombotic event (35–37). This would suggest that the first "symptom" of acute coronary occlusion in these individuals is a lethal arrhythmia. Further evidence is provided by the few patients who survive unexpected cardiac arrest without a prior history of cardiovascular disease, which characterizes them with significant cardiac autonomic control system dysfunction resulting in imbalances favoring strong sympathetic input with relatively weak vagal control [43].

Following myocardial infarction, autonomic imbalances favoring the sympathetic nervous system coupled with depressed vagal reflex activation to a blood pressure increase, i.e., a depressed "baroreflex sensitivity test," are specifically effective in identifying high-risk experimental animals and in patients with left ventricular dysfunction [39–42]. Relevant to this clinical information is the fact that, experimentally, vagal augmentation by electrical stimulation of the cervical sympathovagal trunk significantly reduces the incidence of ventricular fibrillation when applied to high-risk animals [44]. In contrast, vagal inhibition by atropine [45] or sympathetic activation by ephedrine [46] also enhances arrhythmic risk and mortality in otherwise low-risk subjects. Patients with conditions such as myocardial infarction or heart failure, which are characterized by an autonomic milieu consisting of parasympathetic withdrawal, or inherently weak cardiac vagal control, coupled with sympathetic activation, are at increased relative risk for lethal arrhythmias [47, 48]. Thus, patients have an increasing risk for sudden death as their heart disease progresses from coronary occlusion to heart failure (Fig. 7.1). In this regard, patients with heart failure represent one of the highest-risk groups that are routinely under physician's care (Chaps. 5 and 6).

7.3.1 Mechanisms of Ventricular Arrhythmias in Heart Failure: Electrophysiologic Adverse Remodeling

Cardiac electrophysiology in heart failure patients is the result of complex interactions between local events, such as myocardial ischemia, fibrosis, and replacement of the normal myocardial syncytium coupled with functional modifications by cardiac control systems primarily arising from the autonomic nervous and renin-angiotensin-aldosterone systems (Chap. 35). Adverse tissue and architectural remodeling, characteristic of chronic heart failure, is not homogeneous, which has direct consequences on cardiac electrical properties. In addition to cardiac structural changes, remodeling of cardiac ion channel densities, structure, or function,

coupled with alterations in cell-to-cell communication, significantly alters both activation and repolarization. This process, called "electrical remodeling," represents the upstream process by which an arrhythmogenic substrate provides risk for lethal tachyarrhythmias (Fig. 7.2) [49–54] (Chap. 47).

7.3.2 Alterations in Activation and Risk for Sudden Death

Cardiac cell activation and conduction of the action potential through the myocardial syncytium depend on the availability of appropriate sodium current and cell-to-cell communication through the proper density and distribution of gap junctions [55–58]. Adverse remodeling associated with chronic cardiovascular disease and heart failure can alter activation and conduction by influencing sodium channel (I_{Na}) densities especially in areas of myocardial ischemia or infarction. I_{Na} function is also altered in heart failure by changes in cytoskeletal support of the channel [53, 58–63]. Conduction abnormalities can arise from altered I_{Na} or by functional abnormalities imposed by intracellular fibrosis or changes in cell size.

These aspects of electrical remodeling can result in a "fixed" arrhythmogenic substrate when changes in the ventricular myocardium permanently alter electrophysiologic characteristics in the area of change. Examples of fixed electrophysiologic abnormalities include fractionated activation across a "mottled" infarct created by surviving tissue interspersed among necrotic or fibrotic tissue [64–70]. Activation fronts encountering areas of patchy fibrosis or fatty necrosis either alter conduction impedance or allow conduction through the zone by way of surviving tissue that forms conduction channels that traverse the area of patchy necrosis. Impulses conducting through channels can exit from the zone of patchy conduction to encounter excitable tissue and give rise to triggers for reentrant arrhythmias. This combination of delayed activation, unidirectional block, and discontinuous conduction is thought to be the macroscopic mechanisms responsible for reentrant tachyarrhythmias.

Additional influences on activation electrophysiology include changes in anisotropy or cell-to-cell communication arising from altered gap junctions producing delayed conduction in the affected areas. Myocardial ischemia or left ventricular hypertrophy results in the downregulation of connexin 43 (Cx43), as well as a redistribution of this protein to the lateral aspects of the myocyte [71–74]. The stimuli for gap junction remodeling are not completely understood, but likely rely on neural and hormonal control of expression and distribution kinetics.

Activation alterations produce fractionated wave fronts that are detectable in heart failure patients at high sudden death risk [68, 69]. The mechanisms involved in establishing fixed changes in activation involve stimulation of fibrosis and fatty necrosis by angiotensin II, aldosterone, and ß-adrenergic receptor activation (Table 7.1). Therefore, neurohormonal intervention is a critical means to prevent permanent changes in the myocardium that produce a fixed substrate for arrhythmias. It is unclear

Table 7.1 Hypothesized effect of neurohormonal intervention to prevent the development of an arrhythmogenic substrate or suppress arrhythmia triggers in cardiovascular disease (see text for detailed references)

Drug class	Action	Antiarrhythmic effect	SCD reduction
ACE inhibitors	Antifibrotic	Prevent fixed substrate	Minimal effect in chronic heart failure
Aldosterone antagonism	Antifibrotic	Prevent fixed substrate	↓ 34 % heart failure
Beta-blockade	Antiadrenergic, antifibrotic, reduction in hypertrophy, antiapoptotic	Prevent fixed substrate and suppress functional triggers	↓ 41 % heart failure
Bisoprolol			
Metoprolol succinate			
Carvedilol			

if continued neurohormonal antagonism results in reversal of the electrophysiologic substrate for lethal arrhythmias once that substrate is established. What is clear, however, is that altered activation and conduction, especially when coupled with repolarization heterogeneity, are key components of the high-risk substrate [75, 76].

7.3.3 Alterations in Repolarization and Risk for Sudden Death

Prolonged repolarization is characteristic of ischemic heart disease and heart failure pathophysiology resulting in lengthening of the myocardial monophasic action potential [77–92]. Typically, changes in ventricular function, tissue, and electrical remodeling in heart failure are heterogeneous, which is especially true for repolarization abnormalities [78–89]. Repolarization heterogeneity can produce severe repolarization dispersion which is found in subjects at high risk for lethal arrhythmias [78]. Interestingly, lower-risk individuals seem to have much less repolarization heterogeneity compared to their high-risk counterparts. Why some individuals develop severe repolarization heterogeneity is complex, but likely relates to control system responses to injury, such as the degree of sympathetic activation following myocardial infarction. Abnormal repolarization can be detected in humans and animals at high sudden death risk in a variety of ways, including microvolt T-wave alternans [79, 80], increased QT interval dispersion, or heterogeneous ventricular repolarization by high-density mapping [78].

Prolongation of action potential duration may have an adaptive purpose. When the repolarization phase of cardiac tissue prolongs, it increases the likelihood that a reentrant wave front may encounter refractory tissue, which would serve to terminate the circuit. With this effect, repolarization prolongation has the potential to be antiarrhythmic, but the prolongation must be global and homogeneous for the effect to prevent an unstable ventricular electrophysiologic environment. These conditions are seldom encountered when adverse ventricular remodeling occurs.

Prolonged repolarization in heart failure arises because of changes in expression of functional ion channels responsible for the plateau and rapid repolarization of the monophasic action potential [83–93]. Repolarization abnormalities that contribute to the arrhythmogenic substrate arise from both acute changes in autonomic control [90] and from ion channel remodeling in the presence of left ventricular hypertrophy or stretch. Most consistently, the downregulation of the transient outward potassium channel, I_{to}, which contributes to the plateau phase of the monophasic action potential, is encountered in cells from most etiologies of heart failure. Other potassium channel abnormalities that occur in heart failure include reduced delayed rectifier (I_K) current density, coupled with faster deactivation kinetics and slow activation properties, which result in prolongation of the rapid repolarization phase of the monophasic action potential. Left ventricular hypertrophy results in a significant downregulation of the inward rectifying potassium channel, I_{Ks}, which becomes the predominant channel responsible for myocyte repolarization in states of sympathetic activation. Along with changes associated with hypertrophy, cytoskeletal support protein remodeling also influences potassium channel function [93]. When regional tissue remodeling is present, with areas of compensatory hypertrophy, the resulting heterogeneous repolarization kinetics increase the risk for spontaneous ventricular tachyarrhythmias (Chaps. 46 and 47).

Global prolongation of ventricular repolarization in patients with heart failure arises from multiple mechanisms [76], which include potassium channel dysfunction, as well as abnormalities in calcium homeostasis [94–100]. It must be recognized that calcium handling is a key component that gives rise to decreased force of contraction, but abnormalities in calcium kinetics also have direct electrophysiologic ramifications [94]. Cells from failing ventricles exhibit a decrease in calcium transient amplitude and its rate of decay. Heterogeneity of calcium transient amplitude and delay when comparing endocardial, mid-myocardial, and epicardial regions, as well as global changes associated with regional heterogeneity and ischemia in the failing heart, very likely contribute to ventricular electrophysiologic instability [96]. Further alterations in the sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), phospholamban, and the sodium-calcium exchanger proteins are described in the failing ventricle and can alter the intracellular calcium concentration [97]. This is associated with ryanodine receptor defects, which when combined with other alterations in calcium homeostasis increases the risk for calcium-dependent afterdepolarizations (Chap. 4). Afterdepolarizations are key elements that form the basis for triggered arrhythmias and sustained polymorphic ventricular tachycardia.

Heterogeneous ventricular repolarization kinetics that result in regional and global prolongation are induced by both acute and chronic changes in neural and hormonal control of the heart. Therefore, substrate changes resulting in fixed repolarization abnormalities can potentially be prevented by neurohormonal intervention, such as aldosterone antagonism or beta-blockade, when applied early in the adverse remodeling process. Chronic neurohormonal intervention also provides benefit by preventing functional or momentary abnormalities in repolarization induced by acute neural activation in response to further injury or physiologic needs.

7.3.4 Hormonal Activation and Sudden Death Risk

The development of permanent (fixed) electrophysiologic substrates can be prevented by early use of neurohormonal interventions including angiotensin-converting enzyme (ACE) inhibitors [101], aldosterone antagonism [102], or antiadrenergic intervention with beta-blockers [103–108] (Table 7.1). Although the direct mechanisms involved in neurohormonal induced electrical remodeling are not fully characterized, general conclusions can be drawn from clinical trial observations. For example, ACE inhibitor therapy reduces mortality primarily by preventing pump failure deaths presumably by inhibiting progressive architectural changes leading to inefficient left ventricular function [109–115]. However, if applied following myocardial infarction (without the requirement for heart failure), ACE inhibitors seem to reduce the incidence of sudden death by as much as 20 % demonstrated by meta-analysis techniques [101].

One can speculate that ACE inhibitor intervention may be effective in reducing sudden death early after myocardial injury by inhibiting angiotensin II-induced interstitial fibrosis leading to fractionated activation characteristic of arrhythmogenic substrates [112, 116]. Aldosterone stimulates proliferation of cardiac fibroblasts resulting in increased interstitial collagen formation which may influence arrhythmogenic substrate development over time. Other effects of angiotensin-aldosterone activation, such as promotion of inflammation with the resulting increase in oxygen free radicals and destabilization of atherosclerotic plaques, may also increase the risk for ventricular electrical instability. In addition to the direct effects on myocardial structure, angiotensin II facilitates adrenergic effects on ventricular electrophysiology by reducing norepinephrine reuptake, increasing the amount of norepinephrine released with each nerve firing, and increasing the firing rate of sympathetic neurons [117–119] (Chap. 36).

Control system interactions operant in the heart failure milieu make it clear that the precise mechanisms involved in the development of lethal arrhythmias are complex and multifactorial. This illustrates that effective sudden prevention strategies must account for multiple potential mechanisms requiring the combination of multiple medications and device therapies.

7.3.5 Sympathetic Activation and Sudden Death *(Chap. 5)*

Sympathetic adrenergic activation in heart failure represents a combination of inherent control system characteristics present before heart disease develops coupled with how individual systems respond to ventricular injury [42]. Sympathetic activation is almost always accompanied by parasympathetic withdrawal, which should be considered when examining how autonomic alterations in heart failure lead to lethal arrhythmias.

In addition to functional changes in global sympathetic outflow to the heart, neural remodeling in the neuroeffector junction can be arrhythmogenic. Sympathetic

hypersensitivity in areas of myocardial necrosis alters local cardiac electrophysiology increasing regional repolarization dispersion and increases risk for lethal arrhythmias [122, 123]. Myocardial injury can produce regional differences in nerve growth factors, which can stimulate sympathetic nerve "sprouting" and regionally increase relative sympathetic effect. This phenomenon further destabilizes ventricular electrophysiology and leads to increased risk for sudden death [120, 121].

Neural adverse remodeling relates to several factors, but the neural regeneration process after myocardial injury is mainly directed by growth factors, among which nerve growth factor (NGF) appears to be very important. Experimental data in conscious dogs documented that NGF infusion in the left stellate ganglion induces significant nerve sprouting (evaluated by analysis of the tyrosine hydroxylase (TH) and growth-associated protein 43 (GAP43 markers), leading to excessive expression of cardiac sympathetic innervation. This was directly associated with increased risk for sudden cardiac death [124–126].

Further elaboration of the impact of NGF in ischemic myocardium demonstrated that the factor is produced by cardiac myocytes and specific receptors for this neurotrophin (TrkA, tyrosine protein kinase receptor) are present in the myocyte membrane. NGF may have a beneficial role as it favors neoangiogenesis, which may provide some level of protection to ischemic myocardium [124]. These observations suggest that the process of cardiac nerve regeneration following myocardial injury may be an adaptive response designed to sustain failing cardiac contractility through sympathetic augmentation and angiogenesis, but at the maladaptive cost of higher risk of life-threatening arrhythmias.

The impact of adverse neural remodeling on cardiac electrophysiology is mediated through the development of anatomically fixed arrhythmogenic substrates that permanently disrupt orderly myocardial activation and repolarization characteristics of the heart. In addition, "functional" abnormalities, which are temporary and depend on local conditions such as acute sympathetic activation, myocardial ischemia, or inflammation, are directly mediated particularly through sympathetic remodeling. Functional abnormalities may include changes in local repolarization due to regional increases in sympathetic activation, for example, or may include activation fractionation from conduction delay induced by acute alteration in autonomic tone. Factors such as acute myocardial ischemia or infarction, electrolyte imbalances, or medications can also alter ion channel function resulting in high risk for functional electrophysiologic abnormalities that may lead to sudden death. Functional abnormalities tend to be difficult to predict and may occur shortly before the initiation of a sustained ventricular arrhythmia.

7.3.6 Cardiorenal Interactions and Risk for Lethal Arrhythmias

The presence of coexisting conditions has a substantial effect on the outcome of heart failure patients, and specifically kidney disease is associated with one of the highest risks of adverse outcomes driven both by heart failure progression and by

lethal arrhythmia [126, 127]. This adverse interaction seems to relate to decreased renal perfusion as cardiac output drops in heart failure patients. Normally, the "renal fraction" is 20 % of cardiac output, but this percentage declines with worsening heart failure. This further enhances renal sympathetic efferent nerve activity that results in marked increases in renal norepinephrine spillover and a sympathetically mediated increase in plasma renin activity [128].

The kidney is robustly innervated by the sympathetic system and acts both as an afferent signaling source and as a conduit for increased sympathetic efferent activation [129], providing an important prognostic tool in evaluating and monitoring heart failure patients. Increased renal norepinephrine spillover predicts reduced survival in heart failure patients.

Activation of renal sensory nerves in patients with heart failure contributes to disease progression and triggers proarrhythmic cardiac substrate enhancing arrhythmia susceptibility [129]. This clearly impacts chronic kidney disease patient survival as lethal arrhythmias are a more frequent cause of death among this group even with moderate (stage 3) chronic kidney disease [131].

Worsening renal function in patients with heart failure is associated with more frequent lethal arrhythmias [129, 130]. A post hoc analysis of the MADIT II database suggests that an estimated glomerular filtration rate below 35 ml/min/1.73 m^2 in ICD (implantable cardioverter defibrillator) patients was associated with a trend toward unfavorable outcome compared to the control group [131]. The reason ICDs were less effective in the low-GFR group seems related to the defibrillation threshold that progressively increases along with renal function decline. These factors lead to increased risk for arrhythmias [131]; at the same time defibrillation threshold makes ICD therapy less effective. Changes in myocardial tissue in the presence of renal dysfunction seem to be directly related to renal dysfunction which adversely impacts the arrhythmic substrate.

Other abnormalities, including electrolyte imbalances that may occur in the context of more intensive diuretic administration, are closely coupled with increased sympathetic activity. Adverse tissue remodeling in the presence of chronic kidney disease was evaluated in one study using cardiac magnetic resonance tomography in 24 hemodialysis patients. This data found abnormal patterns of late gadolinium myocardial tissue enhancement in 79 % of analyzed cases. Late enhancement was present in three distinctive patterns: a diffuse pattern was present in seven cases, an infarct-related pattern in six cases, a non-infarct related in seven cases, while the absence of structural remodeling was seen in only five cases [132]. The data suggest that a significant increase of myocardial interstitial fibrosis burden was induced by chronic renal failure. The study outlined some of the specific changes that take place in myocardial structure in patients with chronic kidney disease, which lead to proarrhythmic increase of defibrillation threshold.

In summary, neural and hormonal responses to heart failure result in permanent and functional alterations in myocardial activation and repolarization. The impact of neural and hormonal activation is rapid and continuous, which increases the risk for electrical "accidents" leading to sudden death. Understanding these mechanisms has led to very effective means to prevent sudden death, as well as the progression of myocardial dysfunction and heart failure.

7.4 Therapeutic Interventions: Drug Therapy

Further support for neurohormonal activation as a key mechanism leading to adverse tissue and electrical remodeling comes from clinical trials using specific drug therapies, such as beta-blockers [103, 106–108], ACE inhibitors, and aldosterone receptor antagonists [102, 133] (Table 7.1). Each of these interventions targets a specific component of the body's response to heart failure and represents effective interventions to suppress lethal arrhythmias. ACE inhibitor therapy is known to reduce sudden death risk in patients with Stage A and B heart failure, which includes patients with coronary vascular disease or asymptomatic left ventricular dysfunction. However, angiotensin intervention with ACE inhibitors or angiotensin receptor blockers has more inconsistent effects on sudden death risk after heart failure develops. Beta-blocker therapy and aldosterone antagonism, however, consistently reduce the relative risk for sudden death in patients after myocardial infarction and in those with heart failure.

Pharmacologic interventions focus on functional or structural events that eventually lead to the development of lethal arrhythmias. Consequently, sudden death prevention in patients with chronic heart failure involves two basic mechanisms. Suppressing lethal ventricular tachyarrhythmias can be accomplished by preventing the fixed or functional electrophysiologic substrate conducive for arrhythmogenesis and suppressing electrophysiologic triggers responsible for initiating a reentrant circuit. Since the substrate for triggered activity and reentry is in large part dependent on neurohormonal activation in response to injury, it is not surprising that the most effective pharmacologic means to prevent lethal arrhythmias in patients with heart failure is with beta-blocker therapy coupled with angiotensin-converting enzyme inhibition and aldosterone antagonism (Chap. 53).

Such a concept was specifically tested in the CIBIS III trial in which bisoprolol titration occurred *before* ACE inhibitor therapy was started. This approach resulted in significantly lower sudden death mortality when compared to the standard guideline approach prescribing initial renin-angiotensin-aldosterone inhibition first before beta-blocker therapy [134].

Historically, the evolving understanding of functional and anatomic adverse remodeling of cardiac autonomic control has led to major therapeutic breakthroughs. After several years of study, it became apparent that beta-blockers were not contraindicated in heart failure patients, but actually a first-line therapy. Cardiac parasympathetic withdrawal occurs as heart failure progresses suggested by weakening of the baroreceptor reflex and low measurements of heart rate variability in patients with advanced heart disease. These observations led to the concept that direct vagal nerve or baroreceptor electrical stimulation may benefit patients with heart failure. Central integration of peripheral afferent signals in patients with heart failure may be altered by spinal cord electrical stimulation to attenuate the adverse changes in efferent neural output. These electrical stimulation therapies are the subjects of ongoing clinical trials in patients with heart failure [135, 136] (Chap. 6) (Table 7.2).

Table 7.2 Novel implantable electronic devices currently under development

Device	Action	Proposed cardiac effect in heart failure	SCD reduction
Direct vagal nerve stimulation	Parasympathetic augmentation	Reverses adverse remodeling, prevents triggers for ventricular arrhythmias	Preclinical evidence for prevention. No clinical evidence
Direct baroreceptor stimulation	Parasympathetic augmentation, sympathetic inhibition, central effect	Reverses adverse remodeling, prevents triggers for ventricular arrhythmias	Unknown
Spinal cord stimulation	Alter central autonomic processing	Unknown	Preclinical evidence for prevention
Renal nerve denervation through ablation	Decrease sympathetic activity, unquantified central effect	Antiadrenergic with reversal of adverse remodeling	Unknown

7.4.1 Lethal Arrhythmia Termination

It is apparent, then, that lethal arrhythmias occur when a fixed arrhythmogenic substrate develops or if functional electrophysiologic changes are significant enough to trigger reentry. These substrates are highly dependent on neural and hormonal influences, which can change over time depending upon the current cardiovascular milieu. It is well known that the ever changing cardiac electrophysiologic substrate is always at some risk for the development of lethal arrhythmias even in the presence of adequate neurohormonal antagonism. This point is illustrated by the mode of death in patients randomized to active therapy in the major beta-blocker trials. Consistently, the relative mortality risk was decreased in the MERIT-HF, CIBIS-II/III, and US Carvedilol trials, but patients on active therapy still died suddenly over 50 % of the time.

Abrupt control system changes that occur during sleep may serve to destabilize the cardiac electrical system in at-risk patients, which coupled with the possibility that they may be in the pharmacodynamic trough phase of their beta-blocker effect, may increase the risk for nocturnal sudden death. In particular, cardiac sympathetic discharges that occur during REM sleep are coupled with a loss of the normal nocturnal vagal surge early after myocardial infarction and more so in patients with heart failure [141]. This leads to a cardiac autonomic environment conducive for triggered and reentrant arrhythmias.

Since sudden death rates remain high with a significant number occurring at times when no responder would be available, patients at risk for sudden death, specifically patients with heart failure, may have long-term benefit from an ICD capable of delivering electrical therapy for lethal arrhythmias immediately upon detection. The strategy of lethal arrhythmia termination using ICD therapy is complementary to that of neurohormonal intervention and now is proven to augment reductions in cardiovascular mortality in patients with heart failure.

7.4.2 *Lethal Arrhythmia Termination Using Implantable Cardioverter Defibrillators* (*Chap. 52*)

The potential value of automatic detection of lethal arrhythmias with immediate delivery of electrical defibrillation using an ICD led to intense efforts to identify patients at high enough risk for sudden death to justify ICD use. Patients with left ventricular dysfunction, defined as a left ventricular ejection fraction ≤35 % due to any cause, are known to benefit from ICD use by reduction in mortality [137–141]. Importantly, patients enrolled in clinical trials were first treated with guideline-recommended medical therapies, along with revascularization interventions when needed. Adequate time was allowed for LVEF recovery before ICD implantation was tested. Additionally, patients with end-stage renal disease were excluded from ICD clinical trials and would not be expected to experience mortality reduction with ICD use.

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was the first primary prevention trial to include patients with nonischemic left ventricular dysfunction (LVEF <35 %). This trial was unique in that it sought to determine which of the three strategies were superior for sudden death prevention: (1) the effects of maximal neurohormonal intervention (beta-blockers, ACE inhibitors, and aldosterone antagonists) alone, (2) maximal medical therapy with arrhythmia suppression using amiodarone, and (3) maximal medical therapy coupled with arrhythmia termination using an ICD [141]. Total mortality reduction was seen only in the ICD arm, with amiodarone performing similarly to maximal medical therapy alone. Therefore, the primary outcome of the SCD-HeFT trial established that patients with nonischemic dilated cardiomyopathy, as well as those with ischemic heart disease, resulting in an LVEF <35 % had long-term mortality reduction by combining arrhythmia suppression using maximal medical therapy with lethal arrhythmia termination using an ICD.

7.5 Concluding Remarks

Sudden death prevention in patients with chronic heart failure due to low ejection fraction is accomplished by utilizing pharmacologic therapies that target specific parts of heart failure pathophysiology. Particularly, beta-adrenergic blockade and aldosterone antagonism clearly reduce sudden death, but angiotensin intervention very likely has beneficial effects by modifying the evolving electrophysiologic substrate leading to high risk for lethal arrhythmias. Guideline-directed medical therapies are very effective in both reducing sudden death risks and improving ventricular systolic performance.

Implantable cardioverter defibrillator use complements neurohormonal intervention with further reductions in overall mortality in this high-risk population. General recommendations suggest that patients with persistently low ejection fractions (≤35 %), despite maximal medical therapy, would be appropriate candidates for ICD use. Patients with end-stage renal disease or a high chance of dying in the next

12 months due to noncardiac causes were not studied in clinical trials validating ICD applications due to an expected lack of long-term benefit.

The synergism between device and neurohormonal intervention is evolving to include implantable electronic stimulating devices that augment parasympathetic activity through direct vagal nerve stimulation or increase baroreflex activation through electrical stimulation. This melding of devices and the underlying pathophysiology of heart failure is currently in clinical trial evaluation and promises to be the next frontier of improving survival for patients with heart failure.

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Chapter 8
Pharmacological Management of Heart Failure and Device Therapy in Heart Failure

Jens Jakob Thune and Finn Gustafsson

Abstract Pharmacological management of heart failure focuses on alleviation of symptoms and improvement of long-term outcome. For chronic heart failure with reduced ejection fraction, medical therapy is based on five drug classes which have been shown to reduce mortality, ACE inhibitors, angiotensin II-AT_1 receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and the combination of the vasodilators hydralazine and isosorbide dinitrate, while symptoms of fluid retention and congestion are managed with loop diuretics. For patients with acute heart failure, medical therapy is supportive and consists of inotropes, vasopressors, and diuretics. Device therapy in the form of cardiac resynchronization therapy may be used to alleviate symptoms and prolong life in patients with symptomatic heart failure, reduced ejection fraction, and left bundle branch block. For patients with very low cardiac output and severe symptoms despite optimal medical therapy, mechanical circulatory support may be an option as a bridge to recovery or heart transplantation or as last resort therapy.

Keywords Heart failure • Ejection fraction • Treatment for HF • Cardiac resynchronization therapy • Device therapy • NYHA functional classification • ACE inhibitors • ARBs • MRAs • Beta-adrenergic blockers

8.1 Introduction

The pharmacological management of patients with heart failure is predominantly based on the clinical presentation of the patient. Clinically, heart failure is classified as either acute or chronic heart failure, and chronic heart failure is further classified into heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), with an arbitrary cutoff left ventricular ejection fraction around 40–45 % [1, 2] (Chap. 1). The majority of evidence-based therapies are found in the treatment of patients with chronic heart failure with reduced ejection

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fraction. For chronic heart failure with preserved ejection fraction and acute heart failure, no treatment has yet been shown in randomized clinical trials to improve long-term outcome, and the treatment of these patients remains purely focused on alleviation of symptoms. The primary object of this chapter will thus be to present the treatments used for chronic heart failure with reduced ejection fraction.

The step from understanding the pathophysiology of heart failure (see Chap. 3) to predicting which treatments effectively change the course of the disease has proven difficult. Several theoretically beneficial therapies have failed to improve patient outcome despite being based on a solid rationale and backed by thorough basic research and animal models. Consequently, the management of heart failure is based on empirical evidence of improved patient outcome from large randomized clinical trials rather than theoretical considerations of mechanisms of drug action.

Patient selection for the large randomized clinical trials has been based on a low left ventricular ejection fraction and severity of symptoms. For grading of symptoms, the New York Heart Association (NYHA) functional classification is used. Patients in NYHA class I are asymptomatic with no limitations of physical activity; patients in NYHA class II are symptomatic with undue breathlessness at normal levels of activity; patients in class III have shortness of breath at less than normal levels of activity; and patients in class IV are unable to carry out any physical activity without discomfort and may have symptoms even at rest. As almost all major clinical trials have used the NYHA functional classification as inclusion criteria, it has become an integral part of assessing and communicating patient status, and it forms the basis of when to initiate the different drug classes available. However, with increasing evidence of beneficial effects of aggressive drug treatment even in patients with a low symptomatic burden (NYHA class II), the most important distinction currently is between patients who are asymptomatic, where only a few drugs are recommended, and patients who are symptomatic, where additional drugs become indicated and device therapy may be an option for some (Chap. 1).

8.2 Chronic Heart Failure with Reduced Ejection Fraction

Five classes of drugs have been shown to reduce long-term mortality for patients with HFrEF. These are angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-AT_1 receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, and the combination of the vasodilators hydralazine and nitrate. In addition, the heart rate-lowering drugs ivabradine and digoxin reduce the risk of being hospitalized for worsening heart failure. Diuretics, in particular loop diuretics, do not improve long-term outcome but are essential in the management of fluid retention and volume overload (Chaps. 5, 36, 38, 40, 50 and 52).

In addition to pharmacological options, a number of medical devices is available to improve patient outcome. These include implantable defibrillators, cardiac resynchronization devices for patients with chronic heart failure with reduced ejection fraction and left bundle branch block, and mechanical circulatory support devices for patients with very severe heart failure (Chap. 7).

8.3 Classes of Drugs Used in Heart Failure with Examples

1. ACE inhibitors: captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril
2. Angiotensin II-AT_1 receptor blockers: candesartan, losartan, valsartan
3. Beta-adrenoceptor blockers: bisoprolol, carvedilol, metoprolol, nebivolol
4. Mineralocorticoid receptor antagonists: eplerenone, spironolactone
5. Diuretics: bendroflumethiazide, bumetanide, furosemide, hydrochlorothiazide, metolazone
6. Vasodilators: hydralazine, nitrate, nitroprusside
7. Inodilators: dobutamine, levosimendan, milrinone
8. Cardiac glycosides: digitoxin and digoxin
9. Other drugs: α-adrenergic agonists, dopamine, ivabradine, nesiritide

Table 8.1 summarizes the mechanism of action of each drug class.

8.3.1 ACE Inhibitors and Angiotensin II-AT_1 Receptor Blockers

ACE inhibitors (ACEi) reduce mortality and the risk of hospitalization for heart failure at all degrees of heart failure [3]. ACEi are therefore a key element of drug therapy for chronic heart failure and should be initiated in all patients. ACE inhibitors block the conversion of angiotensin I to angiotensin II by ACE, whereas the angiotensin II-AT_1 receptor blockers (ARBs) exert their effect by blocking the angiotensin II type 1 receptor. ACEi and ARBs thus share the same mechanism of

Table 8.1 Classes of drugs used in heart failure with mechanism of action and effect on pre- and afterload

Drug class	Main mechanism of action	Preload	Afterload
ACEi	Reduced conversion of angiotensin I to angiotensin II	↓↓	↓↓
ARB	Inhibition of angiotensin II AT-1 receptors	↓↓	↓↓
Beta-blockers	Inhibition of adrenergic beta-receptors	–	↓
MRA	Inhibition of mineralocorticoid receptors	↓	–
Ivabradine/digoxin	Reduction in heart rate	–	–
Diuretics	Natriuresis	↓↓	↓
Hydralazine	Arterial vasodilatation	–	↓↓↓
Nitrates	Venous vasodilation	↓↓↓	↓
Inodilators	Increased intracellular Ca^{2+} concentration or increased Ca^{2+} sensitivity	↓	↓↓↓
α-adrenergic agonists	Stimulation of α-adrenergic receptors	↑	↑↑↑

Arrows indicate effect size ranging from one (minor effect) to three (major effect) with arrows pointing down indicating a decrease in loading condition and arrows pointing upward an increase. An hyphen indicates no relevant effect

action, which is to reduce the effect of angiotensin II. Both ACEi and ARBs are thought to have a class effect with no difference in clinical benefit for different drugs within each group. The evidence for clinical benefit in heart failure is stronger for ACEi than for ARBs, and ACEi are the preferred drugs, while ARBs are referred to those patients who are allergic to ACEi or suffer from unwanted side effects, especially cough (Chap. 36).

ACEi reduce blood pressure by lowering both arterial and venous smooth muscle tone. The benefit of ACEi in heart failure is independent of their blood pressure-lowering effect. In addition to its direct effect on vascular tone, ACEi reduce aldosterone secretion from the adrenal cortex and reduce the release of antidiuretic hormone from the pituitary gland, both of which are favorable effects in patients with chronic heart failure. ACEi also affects renal blood flow by decreasing vascular tone in the renal arterioles which leads to increased renal blood flow, although glomerular filtration is reduced because of a relatively larger effect on the postglomerular efferent arterioles than the preglomerular afferent arterioles.

Treatment with ACEi is initiated at low doses and titrated to target doses established through clinical trials (captopril 50 mg three times/day, enalapril 10 mg twice/day, lisinopril 20–40 mg/day, ramipril 5 mg twice/day, or trandolapril 4 mg/day). Because there is no negative inotropic effect, ACEi may be initiated even while the patient still has signs and symptoms of congestion. During titration, regular control of renal function and potassium levels are required because of the renal effects of ACEi. In the inpatient setting, titration is done over days, whereas stable outpatients may be titrated over weeks.

The most common side effects of ACEi are related to symptoms of low blood pressure. In addition, some patients may experience hyperkalemia due to reduced levels of aldosterone, and in patients with hypovolemia, where renal perfusion is more dependent on angiotensin II activation, ACEi may cause functional renal insufficiency. Between 5 and 20 % of patients on ACE inhibitors develop a dry cough, because of blockage of bradykinin degradation, and these patients are then switched to an ARB [4].

8.3.2 Beta-Adrenergic Blockers

Together with ACEi, blockade of the adrenergic beta-receptors is the key element of medical therapy at all stages of chronic heart failure with reduced ejection fraction. Initially thought to be detrimental due to its negative inotropic and chronotropic effects, beta-blockade has consistently been shown to markedly reduce mortality and morbidity in patients with heart failure [5]. There is no substantial evidence proving that one beta-blocker is superior to another, but target doses and effect on mortality have been most clearly demonstrated for carvedilol, bisoprolol, and sustained release metoprolol, which are therefore most commonly used in clinical practice.

Beta-blockers exert their effect by inhibiting the beta-type adrenergic receptors. This attenuates the effect of catecholamines on heart rate, cardiac contractility, and

oxygen consumption, as well as vascular muscle tone. In addition to their effect on the heart, beta-blockers inhibit renin release by the kidneys. How these multiple mechanisms translate into long-term improved cardiac function and reduced morbidity and mortality is not fully understood, and beyond the scope of this chapter, but is most likely an effect of protecting the failing heart from the detrimental effect of a chronic increase in catecholamine levels. Some studies suggest that beta-blockade suppresses cardiac myocyte apoptosis. The main clinical effect stems from blockade of the β1-receptor, while the clinical benefit of blocking the β2- and β3-receptors is less clear. Available beta-blockers differ in their selectivity for the β1-receptor, but this does not translate into differences in clinical effect.

Beta-blockers, like ACE inhibitors, are initiated at a low dose and titrated to target doses derived from clinical trials. In contrast to ACE inhibitors, beta-blockers have a negative inotropic effect and should therefore not be started while the patient has signs and symptoms of congestion. Often, the patient will be slightly more symptomatic during the first couple of days after initiation; uptitration of beta-blocker dose is therefore done more slowly than ACE inhibition in order to avoid causing a decompensation episode.

Usually, an ACEi is titrated first, and the beta-blocker is added sequentially in the outpatient setting. Sustained metoprolol can be initiated at 25 mg/day (12.5 mg/day in NYHA class IV) and titrated slowly (monthly) to a maximum dosage of 200 mg/day. Carvedilol is begun at 3.125 mg twice/day and titrated every 2 weeks to a maximum dose of 25–50 mg twice/day. Bisoprolol is begun at a dose of 1.25 mg/day and titrated to 10 mg/day. Side effects of beta-blockers are plentiful but mostly benign and usually taper off within a week of treatment onset or dose titration. Most common side effects are symptoms of hypotension and low heart rate such as dizziness, tiredness, and headache.

8.3.3 Mineralocorticoid Receptor Antagonists (MRAs)

The mineralocorticoid aldosterone is an important contributor to the pathophysiology of heart failure. Aldosterone exerts a variety of detrimental effects in patients with chronic heart failure. Initially thought to be secreted almost exclusively by the adrenal gland, causing renal retention of sodium in exchange of potassium, aldosterone-producing cells and aldosterone receptors are also found in several other organs, including the heart, where aldosterone acts locally to promote extracellular fibrosis. The main trigger for aldosterone release is angiotensin II, but even though ACE inhibition initially lowers aldosterone levels, they rise again to high levels during chronic ACE inhibition.

MRAs improve survival and reduce rehospitalization by one third for patients with symptomatic chronic heart failure with reduced ejection fraction (NYHA class II–IV) [6, 7]. The administration of MRAs inhibits the detrimental effects of increased levels of aldosterone in heart failure patients. Thus, MRAs cause natriuresis, a decrease in intravascular water volume and decreased blood pressure. In the

heart, evidence suggests that MRAs reduce interstitial fibrosis. Furthermore, MRAs reduce the risk of sudden death in heart failure likely by reducing the incidence of ventricular arrhythmias related to hypokalemia owing to the potassium-sparing effect of MRA.

The two currently available MRAs are spironolactone and eplerenone, with no documented differences in clinical effect. However, because eplerenone has much lower affinity for progesterone and androgen receptors, it does not cause gynecomastia and breast tenderness. The main side effect of both MRAs is intrinsic to the blockade of aldosterone in that they cause hyperkalemia. Therefore, MRAs should not be initiated in patients with K^+ above 5.0 or estimated glomerular filtration rate below 30 ml/min/1.73 m [2], and renal function and potassium levels should be monitored regularly during treatment.

8.3.4 Ivabradine/Digoxin

In patients with sinus rhythm, heart rate is determined by the rate of depolarization of the sinus node. A major determinant of the rate of depolarization is the "funny" (I_f) current, which is caused by sodium and potassium ions crossing the so-called f-channels in the sinus node cells. Ivabradine is a pure inhibitor of the funny current and causes a decrease in heart rate without the negative inotropic and blood pressure-lowering effects of beta-blockers. For patients in sinus rhythm who have an elevated resting heart rate (>75 BPM) despite having been titrated to their maximally tolerated beta-blocker dose, ivabradine reduces the risk of being hospitalized for worsening heart failure and the risk of death [8]. The rationale for using ivabradine in heart failure patients is that the lowering of heart rate provides more time for diastole, facilitating better filling of the ventricles and increased coronary perfusion, which occurs during diastole (Chaps. 1 and 52). Despite the fact that ivabradine has been tested on top of treatment with beta-blockers, its most common use is in patients who are intolerant of beta-blockers because of their negative inotropic and blood pressure-lowering effect.

Digoxin is a glycoside, which may be used for lowering heart rate in patients who are in atrial fibrillation, where ivabradine does not work. Digoxin slows conduction in the atrioventricular (av) node, by augmenting parasympathetic tone, which leads to a lower heart rate, longer diastole, and hence improved left ventricular filling. In addition, digoxin exerts some positive inotropic effect by inhibiting the Na/K pump, which in turn promotes Na/Ca exchange and causes an increase in intracellular calcium levels that improves contractile force. Digoxin has a narrow therapeutic window; side effects of elevated serum levels of digoxin are gastrointestinal and neurological disturbances, while digoxin intoxication may cause ventricular arrhythmias and death. While digoxin for patients in sinus rhythm has been shown to reduce the risk of hospitalization for worsening heart failure, this was before the introduction of beta-blockade as standard therapy, and digoxin is now rarely used in patients in sinus rhythm [9].

8.3.5 Diuretics

For patients with chronic heart failure, a main cause of symptoms is fluid retention and volume overload. In patients with signs and symptom of fluid retention, diuretic therapy with loop diuretics has a quick and marked effect on symptoms. Hence, diuretic therapy is essential in these patients, and loop diuretics are among the most fundamental drugs for providing symptomatic relief, although they do not affect long-term mortality and morbidity. In particular, loop diuretics are paramount in the symptomatic treatment of patients with acute decompensated heart. In these patients, loop diuretics are often administered intravenously to improve bioavailability (because intestinal absorption of oral agents may be limited by bowel wall edema) and maximize effect. In the acute phase, large doses of loop diuretics may be necessary. Conversely, once an episode of decompensation is well treated, the need for loop diuretics is reduced, and most stable patients require only a small oral dose daily (e.g., furosemide 40–80 mg/day). The diuretic effect of furosemide lasts 6 h, after which the kidneys are highly sodium avid, and diuretic efficacy will be lost if the patient is not maintained on a low-sodium diet as well.

Thiazides play a minor role in the treatment of heart failure. Some patients with only very mild peripheral edema may be treated sufficiently with thiazide diuretics, but this is rare. Adding a thiazide on top of loop diuretics produces a synergistic response since the drugs block sodium reabsorption at different sites in the renal tubule, and thiazides prevent compensatory distal tubular reabsorption of sodium. In patients who do not respond adequately to loop diuretics, the addition of the thiazide-like diuretic metolazone produces a powerful diuretic response even in patients with reduced renal function (as opposed to regular thiazides). Because of its strong diuretic effect, metolazone should mainly be used in inpatients or occasionally outpatients who are followed very closely.

Diuretics are indicated for patients with symptomatic heart failure even after they have been rendered free of edema. Diuretics are generally necessary indefinitely. Serum electrolytes should be monitored closely because of the concern for increased risk of arrhythmic death in patients with heart failure taking non-potassium-sparing diuretics.

8.3.6 Hydralazine/Isosorbide Dinitrate

The combination of the arterial vasodilator hydralazine (75 mg three times/day) and the venous dilator isosorbide dinitrate (40 mg three times/day) reduces mortality in African-Americans who are in NYHA class III or IV despite standard medical therapy. Outside of African-Americans, the combination of hydralazine and isosorbide dinitrate is used as an alternative to ACE inhibition for patients with symptomatic heart failure who have contraindications to ACE inhibition due to either impaired renal function or intolerable side effects.

Organic nitrates such a nitroglycerin are vasodilators (particularly of systemic veins) thereby reducing preload. Nitrates have a role in the management of acute pulmonary edema and heart failure in a setting of hypertension or angina. Contraindications include concurrent sildenafil use and severe aortic stenosis.

Nitroprusside is a potent intravenous drug that causes arterial vasodilation. It may be warranted if further vasodilation and afterload reduction are necessary. Side effects include thiocyanate toxicity, especially in patients with hepatic or renal dysfunction, and coronary steal phenomenon in patients with ischemic heart disease (see also Chap. 40).

8.4 Device Therapy for Heart Failure

8.4.1 Cardiac Resynchronization Therapy (CRT)

In patients with a wide left bundle branch block, ventricular depolarization occurs in the lateral wall substantially later than at the septal wall. Hence, contraction of the lateral wall occurs later than contraction of the septal wall causing a dyssynchronous contraction pattern instead of the normal homogenous synchronous contraction. Dyssynchronous contraction in heart failure leads to inefficient left ventricular pumping, waste of myocardial energy, and in some cases contraction of parts of the left ventricle even after the aortic valve is closed as well as increased functional mitral regurgitation.

Cardiac resynchronization therapy (CRT) is the restoration of simultaneous contraction of the left ventricle by the insertion of a pacemaker electrode in the coronary sinus to pace from the left side of the heart in addition to the standard electrode placed in the right ventricle. An implantable pacemaker can then activate the two electrodes so the septal and lateral walls are activated simultaneously, and homogenous, synchronous contraction of the left ventricle is restored.

Cardiac resynchronization therapy reduces both mortality and morbidity in the majority of patients with symptomatic heart failure with reduced ejection fraction and left bundle branch block [10, 11]. In addition, a large proportion of patients have less dilatation of the left ventricle and improved left ventricular ejection fraction. About a quarter of patients do not experience an improvement in functional capacity, and several methods to identify nonresponders before the insertion of a CRT device have been tried. However, the only consistent predictor of benefit of CRT remains the wide left bundle branch block. Consequently, there is no place for inserting a CRT device in patients without a left bundle branch block even if echocardiography shows signs of dyssynchronous contraction. A CRT device may have the capacity to function as an implantable cardioverter defibrillator (ICD, see below) in which case the device is termed a CRT-D device as opposed to a CRT-P device which does not have an ICD function.

In order to obtain full effect of the CRT device, patients must be paced in the ventricles more than 85 % of the time. For patients in sinus rhythm, this is not a problem, but patients with atrial fibrillation and a high resting heart rate may not be

paced enough. In these patients, pharmacological lowering of the heart rate may be enough to obtain sufficient ventricular pacing, but in some patients, ablation of the His-bundle and induction of full atrioventricular block is necessary.

The main side effect of CRT is the risk of procedure-related complications during device implantation and the risk of device infection and lead displacement. The risk of complications is generally higher with CRT devices than with conventional pacemakers because of the extra wire to the left coronary sinus and the long procedure time.

8.4.2 Implantable Cardioverter Defibrillators (ICDs)

Patients with heart failure have an increased risk of sudden cardiac death caused by ventricular arrhythmia. Hence, the implantation of an ICD lowers the risk of death for patients with symptomatic heart failure and reduced ejection fraction. The risk of sudden cardiac death is highest for patients with reduced ejection fraction due to ischemic heart disease, and the evidence of benefit of ICD implantation is strongest for this group. It is necessary to implant an ICD into 14 patients on average in order to save the life of 1 patient over a 46 months period [12]. An ICD may be combined with a CRT device for patients with a wide left bundle branch block (CRT-D)

8.4.3 Heart Transplantation and Mechanical Circulatory Support

Patients with very severe heart failure with symptoms at rest and very low exercise capacity (maximum oxygen uptake of less than 12–14 ml/min/kg) may be considered for heart transplantation. However, some patients with chronic heart failure are too ill to survive the wait for a donor heart. These patients are potential candidates for mechanical circulatory support with a left ventricular assist device (bridge to transplant). Left ventricular assist devices work by pumping blood from the left ventricle via a mechanical pump to the ascending aorta, bypassing the aortic valve, which is therefore closed. The left ventricular assist devices are able to deliver a cardiac output that is adequate for maintaining organ function and allowing the patient to become ambulant. Peri-implantation mortality is around 8 % with the main long-term complication being pump thrombosis and bleeding problems due to the oral anticoagulation needed to prevent pump thrombosis and emboli. The first generation of left ventricular assist devices were pulsatile with limited durability due to mechanical wear and tear, but second- and third-generation devices, which are non-pulsatile and produce a constant flow, are much more durable. Because of the enhanced durability, left ventricular assist devices are now also offered to patients who are symptomatic enough to qualify for heart transplantation but not suitable candidates because of contraindications such as age, renal dysfunction, or high pulmonary resistance (destination therapy) [13].

8.4.4 Treatment Principles of Chronic Heart Failure with Reduced Systolic Function

The pharmacological treatment of chronic heart failure with reduced ejection fraction roughly follows the outline in Table 8.2. All patients should receive an ACEi/ARB and a beta-blocker unless intolerant. Usually ACEi/ARB is initiated first because this can be done in patients who still have signs of decompensation with beta-blocker added thereafter. However, in stable patients, the order of initiation of ACEi/ARB and beta-blockers is not important. Medical therapy is often initiated in the setting of an acute decompensation episode, and these patients will therefore be treated with loop diuretics as well. Diuretic treatment is for symptomatic relief rather than prognostic improvement but remains essential in the patient with fluid overload. Later, some patients might not need loop diuretics or only a low oral maintenance dose. However, diuretics should not be withdrawn during titration of beta-blocker. If a patient is still symptomatic after titration of ACEi/ARB and beta-blocker, a mineralocorticoid antagonist is then added.

Patients who remain symptomatic following the titration of the three disease-modifying drug classes might obtain symptomatic relief and reduced risk of decompensation with the addition of ivabradine to lower heart rate. For patients with chronic atrial fibrillation, there is no effect of ivabradine, and digoxin may be used to lower heart rate instead. In African-Americans, hydralazine/isosorbide dinitrate should be considered.

Following titration of medicine, an assessment of systolic function, functional capacity, and the presence of a left bundle branch block should be done. Patients who continue to have low left ventricular ejection fraction (equal to or less than 35 %) should be offered an ICD to prevent sudden cardiac death, and those patients who also have left bundle branch block should receive a combined ICD and CRT device (CRT-D).

Table 8.2 Schematic overview of pharmacological management and devices in heart failure with reduced systolic function

Drugs/drug class	NYHA I	NYHA II	NYHA III	NYHA IV
ACEi/ARB	■	■	■	■
Beta-blockers	■	■	■	■
MRAs		■	■	■
Ivabradine/digoxin		▒	▒	▒
Apresolin/NTG		▒	▒	▒
CRT-P/D		▒	▒	▒
ICD		▒	▒	▒
LVAD/HTX			▒	▒
Diuretics		▒	▒	▒

■ Should be used
▒ Should be considered

LVAD/HTX: left ventricular assist device/heart transplantation

8.4.5 Heart Failure with Preserved Ejection Fraction

Despite several large clinical trials, no medical therapy has been shown to affect the clinical course of heart failure with preserved left ventricular ejection fraction. This disease entity is characterized by impaired filling of the left ventricle (diastolic dysfunction), which results in elevated ventricular filling pressures at rest or during exercise and, in some patients, reduced cardiac output. The diagnosis is not easy, and clinically, the group of patients diagnosed with heart failure with preserved ejection fraction likely represents a broad spectrum of diseases. In addition, it is likely that several of these patients have symptoms from other organ systems (e.g., lungs or musculoskeletal) which are erroneously attributed to heart failure.

Because of a lack of disease-modifying therapies, treatment is purely symptomatic. Symptoms are often aggravated by hypertension or supraventricular arrhythmias, so strong blood pressure control and control of heart rate are indicated. Fluid retention and congestion are treated with loop diuretics.

8.5 Acute Heart Failure

The term acute heart failure encompasses several distinct entities. Acute heart failure with low blood pressure might be a presentation of new onset systolic heart failure (most often seen as a complication to an acute myocardial infarction), known chronic heart failure with acute decompensation, or first presentation of a hitherto unrecognized nonischemic cardiomyopathy. Another group consists of patients with congestion, pulmonary edema, and normal or high blood pressure. Consequently, treatment of acute heart failure depends on the clinical presentation. A common and useful method to evaluate the patients with acute heart failure is to assess perfusion state (warm/cold) and congestion (wet/dry) and categorize the patient according to Fig. 8.1 [14].

Patients in group A (warm and dry) are warm and well perfused with no signs of significant congestion. These patients may be considered stable and do not have acute heart failure. Efforts should be aimed at maintaining stable volume status and preventing disease progression.

Group B patients (warm and wet) have decompensated chronic heart failure and show signs of congestion at rest but have adequate perfusion to maintain critical organ function. Congestion should be treated with intravenous loop diuretics to reduce volume overload and intravenous or oral nitrates to reduce afterload and alleviate pulmonary congestion. Patients who present with an episode of decompensation have usually gained several kilos weight, because of water retention, in the days or weeks leading up to the acute episode. Thus, monitoring weight is an important aspect of treatment, and the aim of diuretic therapy during an episode of decompensation is to reduce weight by approximately 1 kg/day. One important caveat of loop diuretics is that if decompensation occurs, the effect of oral loop

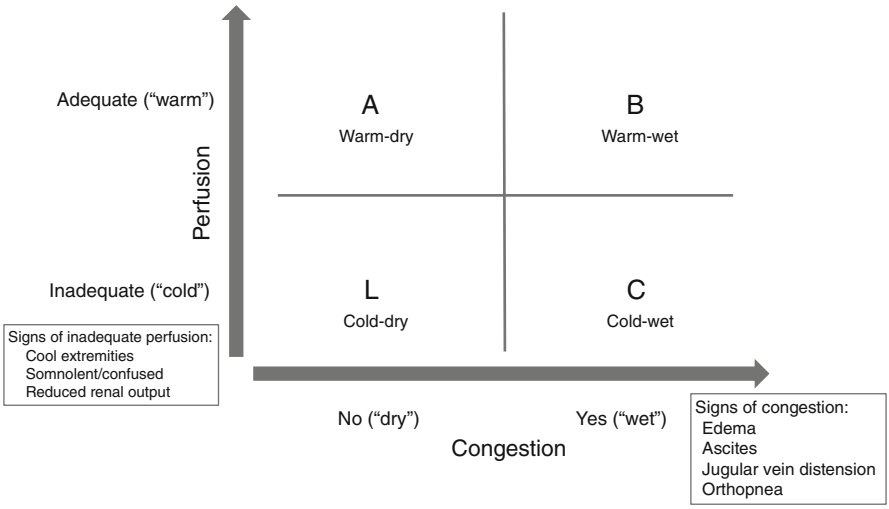

Fig. 8.1 Classification of clinical presentation of patients with acute heart failure according to signs and symptom of congestion and reduced perfusion of peripheral organs (Adapted with permission from reference [14])

diuretics is reduced due to diminished bioavailability. Hence, it is often necessary to convert to intravenous administration of loop diuretics during an episode of decompensation.

Group C patients (cold and wet) have signs of both hypoperfusion and congestion. These patients are in cardiogenic shock. The patient will have low blood pressure and appear cold and clammy due to peripheral vasoconstriction. Blood lactate levels will be elevated because of insufficient supply of oxygen. The prognosis for patients in cardiogenic shock is very poor with short-term mortality above 50 % for patients with cardiogenic shock complicating acute myocardial infarction; no intervention, pharmacological or mechanical, has been shown to improve long-term outcome.

The immediate goal of treatment is to restore an adequate organ perfusion pressure (commonly expressed as the need for patients to be “warmed up” before they can be “dried out”). This is done by intravenous administration of a catecholamine, either dopamine or noradrenaline, with a target mean arterial blood pressure above 65 mmHg. Norepinephrine almost exclusively affects arterial tone, whereas dopamine at intermediate doses (2–10 μg/kg/min) also increases cardiac contractility and heart rate. At higher doses (10–20 μg/kg/min), dopamine results in increased afterload through alpha-adrenergic stimulation, which may be detrimental in heart failure. Once adequate blood pressure has been obtained, patients may be treated with diuretics to relieve congestion.

If there are signs of organ dysfunction (e.g., pulmonary edema, decreased renal output, and increasing lactate levels) despite a mean arterial blood pressure above 65 mmHg, the next step is to increase cardiac output. Pharmacologically, this is

done by the use of an intravenous inotrope (as a bridge to definitive treatment such as revascularization or cardiac transplantation) such as:

- *Dobutamine* exerts its effect through a direct stimulation of adrenergic β1-receptors, which leads to increased cytosolic Ca^{2+} and causes an increased myocardial contractility and reduced afterload. Side effects include hypotension, ventricular arrhythmias, and worsening of ischemic heart disease by increasing myocardial oxygen demand.
- *Milrinone* is an inhibitor of phosphodiesterase-3 and prevents the breakdown of cyclic AMP. This augments the effect of β1-stimulation and produces a similar response as dobutamine (i.e., vasodilation) with increased myocardial contractility and reduced afterload.
- *Levosimendan* enhances myocardial contractility by sensitizing myocyte proteins to Ca^{2+}-ions and causes afterload reduction by reducing smooth vascular tone.

None of the inotropes have been shown to improve long-term outcome, but they may bridge the patient to a definite therapy such as LVAD or cardiac transplantation or, in some cases, improvement of patient status, for instance, by allowing diuresis and relief of volume overload, in term permitting introduction or reinstitution of life saving oral heart failure medications as discussed above.

Group L patients (cold and dry) have low cardiac output and poor tissue perfusion but are not congested. This is a rare presentation of heart failure. Occasionally, these are patients who have been over-treated with diuretics and they may benefit from volume replacement. The goal of therapy is to initiate and titrate chronic heart failure treatment with an ACE inhibitor, beta-blocker, and mineralocorticoid antagonist. Digoxin may lead to improvement in some patients. Patients may respond transiently to inotropes but long-term use has produced adverse effects.

8.6 Concluding Remarks

The morbidity and mortality of heart failure with reduced ejection fraction has decreased substantially due to the introduction of evidence-based treatment. The three main drug classes responsible for this effect are ACEi/ARBs, beta-blockers, and MRAs. Additional drugs may be indicated in selected patient groups, and for some patients, device-based CRT improves symptoms and prolongs life.

In contrast to heart failure with reduced ejection fraction, no specific therapy has been shown to improve prognosis for patients with preserved ejection fraction or patients with acute heart failure. The treatment of these patient groups therefore remains focused on symptom relief and treatment of possible underlying disease (e.g., hypertension or ischemic heart disease). Finally, for some patients with very severe and debilitating disease, mechanical circulatory support and/or heart transplantation may be an option.

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Chapter 9
Exercise in Heart Failure: Effectiveness Versus Safety

Stuart D. Russell

Abstract Exercise training in patients with heart failure has been shown to improve exercise tolerance and quality of life and reduce symptoms of heart failure. Recently, the first large-scale trial evaluating the effects of exercise training in heart failure, the Heart Failure – A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, was presented. Although there was no improvement in the primary endpoint of all-cause mortality and hospitalization, there was a mortality benefit demonstrated for patients with clinical signs of increased mortality and for those that actually performed exercise training of at least 3 metabolic equivalent (MET) hours per week. This chapter reviews the results of this trial and the safety of exercise training for patients with chronic heart failure.

Keywords Exercise training • Heart failure • Oxygen consumption • Exercise physiology

9.1 Introduction

Heart failure is the number one discharge diagnosis from most hospitals in the United States today. Currently, an estimated 5.1 million Americans over the age of 20 have heart failure. The American Heart Association estimates that over eight million people will suffer from heart failure by the year 2030 [1]. Unfortunately, despite advances in the therapy of these patients with medications and devices, there is still high morbidity and mortality related to this disease.

For years, bed rest and small amounts of exercise for patients with heart failure were emphasized. Treatment guidelines in the 1980s included bed rest as a principle therapy for patients with heart failure [2, 3]. During this period, many studies demonstrated the safety and efficacy of exercise training in post-myocardial infarction

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Table 9.1 Results of randomized, controlled trials of exercise training

Reference	# trained	Change in peak VO_2	Change in QOL	Morbidity and mortality
Belardinelli [8]	36	15 %		No difference
Belardinelli [15]	50	2.9 ml/kg/min	Improved	Improved
McKelvie [17]	90	104 ml/min	No	No difference
HF-ACTION [19]	1,159	0.6 ml/kg/min	Improved	No difference except high risk
Belardinelli [20]	63	14.7 %	Improved	Improved

VO_2 oxygen consumption, *QOL* quality of life

patients, and that work was quickly transferred to heart failure patients [4]. In the early 1990s, a number of investigators began to examine the effects of exercise therapy for patients with heart failure. Early studies of exercise training using predominantly aerobic methods demonstrated an improvement in peak oxygen consumption and exercise time [5–18].

As shown in Table 9.1, five trials have evaluated the effects of exercise training on morbidity and mortality in patients with heart failure. The largest of these was the Heart Failure – A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, which randomized 2,331 medically stable outpatients with an ejection fraction less than 40 % to either exercise training or usual care at 82 centers within the United States, Canada, and France, with a median follow-up of 30 months [19]. The primary endpoint of the trial was a composite of all-cause mortality or hospitalization, and secondary endpoints included all-cause mortality, composite endpoints of cardiovascular mortality or cardiovascular hospitalization, and cardiovascular mortality or heart failure hospitalization. Although there was no statistically significant difference in the primary endpoint, there were clinically significant trends towards reduction in the secondary endpoints of mortality and heart failure hospitalizations, among others. In prespecified supplementary analyses adjusting for highly prognostic baseline characteristics, the reduction in all-cause mortality or hospitalization (the primary endpoint) was statistically significant, as were the reductions in the secondary endpoints. Based on the results of this trial, in the spring of 2014, the Centers for Medicare and Medicaid Services decided to reimburse payments for phase II cardiac rehabilitation in these patients. This landmark trial has changed both the understanding of clinical outcomes and the safety of exercise training in these patients. The aims of this chapter will be to review both the efficacy and safety of exercise training for patients with heart failure.

9.2 Cardiac Physiology During Exercise in Heart Failure

Higginbotham, Sullivan, and Cobb performed a number of exercise tests with invasive monitoring while measuring both oxygen consumption (VO_2) and ejection fraction in both normal patients and those with heart failure [21–23]. At baseline, heart failure patients have an increased resting heart rate, but a reduction in heart rate at

peak exercise [21]. These studies were performed prior to heart failure patients being treated with beta-adrenergic blockers, and one can assume that this chronotropic incompetence should be more pronounced in the current era. Heart failure patients were also found to have a reduction in stroke volume at both rest and peak exercise. Of interest, the central arteriovenous (A-V) oxygen difference was increased at rest and increased to a similar level at peak exercise to the A-V oxygen difference in normal controls. However, it is not clear that these central cardiac changes are solely responsible for the exercise limitations of these patients. Various interventions such as inotropes and vasodilators that improve cardiac output and leg blood flow do not improve exercise tolerance [24–26].

Due to these findings, the peripheral muscle response to exercise has also been evaluated. Leg blood flow is reduced due to low cardiac output but also increased leg vascular resistance and abnormal arteriolar constriction [21, 22, 27]. There are also many intrinsic skeletal muscle changes that limit exercise. These include reduced skeletal muscle capillary density, change in skeletal muscle fiber type with a shift from oxidative type I fiber to glycolytic type II muscle fiber, a reduction in oxidative enzymes in the Krebs cycle, a decrease in mitochondrial size and number, an increase in inflammatory markers, and a reduction in muscle mass and strength [27]. One could certainly hypothesize that some of these adaptations that occur could be improved by exercise training. Figure 9.1 outlines the multiple hypothesized and proven benefits of exercise training [28]. In addition to reversing some of the detrimental effects outlined above, exercise also decreases the production of neurohormones, reduces inflammation, and improves endothelial function. However, until the HF-ACTION trial, the effects of exercise training in a large number of patients had never been evaluated.

9.3 Outcomes with Exercise

The HF-ACTION trial was the first large trial designed to evaluate the survival benefit of exercise training in patients with heart failure. The initial trial design was to randomize 3,000 patients to either exercise training or usual care [29]. At the onset of the trial, there was an emphasis placed on ensuring that patients were on excellent medical therapy and 94 % of the patients were on an ACE inhibitor or angiotensin receptor blocker, 94 % were on a beta-blocker, 45 % were on an aldosterone antagonist, and about 40 % had an implantable cardioverter-defibrillator. From a symptom standpoint, the patients were about two thirds New York Heart Association functional class II and 33 % class III. Only 23 patients in the trial had NYHA class IV symptoms at baseline and would caution one that the effects of exercise training in this population are less well understood.

Patients were randomized to either phase II cardiac rehabilitation with 36 monitored sessions or usual care. They were then given either a cycle ergometer or a treadmill to continue exercising as an outpatient. Patients were also given a heart rate monitor to assess the quantity of exercise that patients were performing at home after

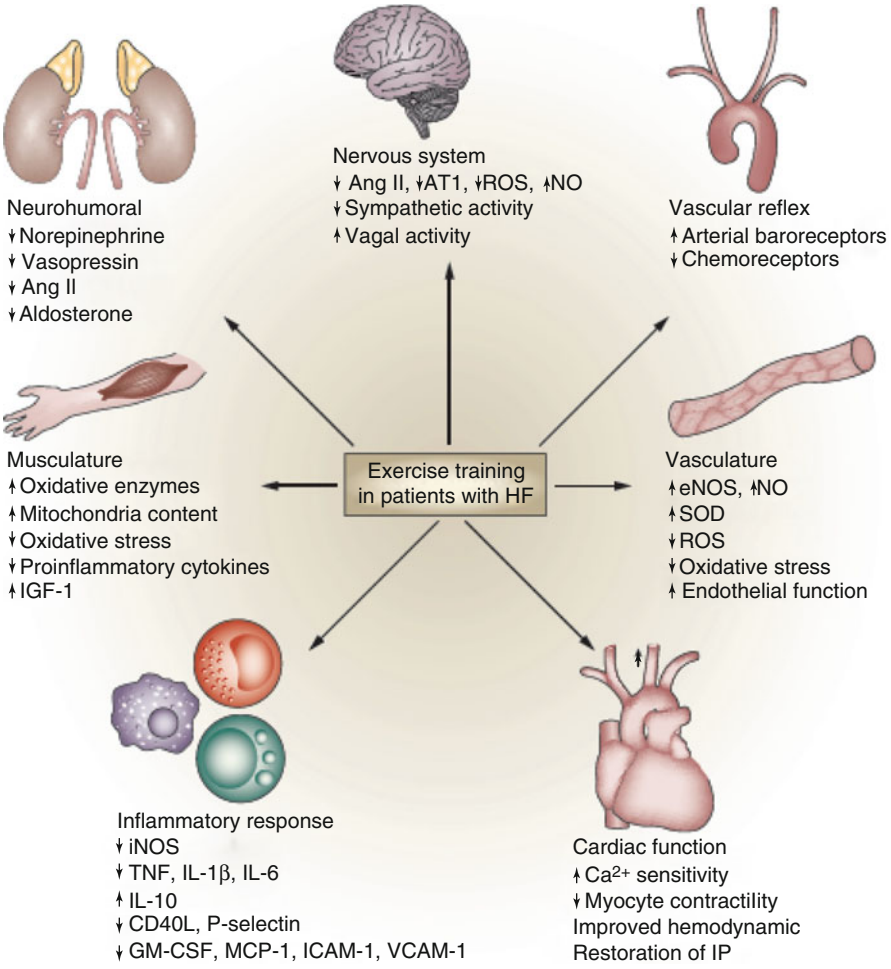

Fig. 9.1 Exercise training has been shown to have benefit on multiple pathways in patients with heart failure. *Abbreviations*: *Ang II* angiotensin II, *AT1* angiotensin II type 1 receptor, *CD40L* CD40 ligand, *eNOS* endothelial nitric oxide synthase, *GM-CSR* granulocyte-macrophage colony-stimulating factor, *HF* heart failure, *ICAM-1* intercellular adhesion molecule 1, *IGF-1* insulin-like growth factor 1, *IL* interleukin, *iNOS* inducible nitric oxide synthase, *IP* ischemic preconditioning, *MCP-1* macrophage chemoattractant protein 1, *NO* nitric oxide, *ROS* reactive oxygen species, *SOC* superoxide dismutase, *TNF* tumor necrosis factor, *VCAM-1* vascular cell adhesion molecule 1 (Adapted with permission from reference [28])

the 36 sessions were completed. Prior to beginning the trial, each patient performed a symptom-limited metabolic stress test to evaluate for safety of exercise, to rule out ischemia, to determine the initial heart rate training goal, and to determine the peak oxygen consumption. For the patients that were randomized to exercise, after they completed their monitored sessions, they were then given either a treadmill or a cycle ergometer with encouragement to continue to exercise at home.

To monitor how much exercise they did, they were also given a heart rate monitor that was downloaded to follow the amount of exercise that they were completing. The initial prescription during the cardiac rehab phase was for walking, treadmill, or stationary cycling for 15–30 min at a heart rate of 60 % of their heart rate reserve assuming that heart rate was below the ventilatory threshold of the patient. The duration was increased to 30 min and then to a total of 40 min over time. One should note that there was no strength component to the exercise prescription, and the training consisted solely of aerobic training. After 18 sessions, the patients began home-based exercise as well. At the conclusion of all 36 sessions, patients were given a goal of exercising 40 min five times a week at a heart rate of 60–70 % of their heart rate reserve.

Of the 1,159 patients randomized to exercise training, only 736 actually completed all 36 sessions of exercise. For the exercise training patients during the first 3 months, the median time of exercise was 76 min per week when the goal was 90. Exercise time increased to 95 min per week by 6 months but then dropped off to 74 min per week at year 1 when the training goal was actually 120 min a week. Although the patients were encouraged to exercise to the goal time, like most humans, the drive to continue to exercise decreased over time.

9.3.1 Morbidity and Mortality

The primary outcome of the trial was a composite of all-cause mortality and hospitalization, and there was no significant difference between the two arms. Similarly, there were no differences in the usual secondary endpoints including cardiac deaths and cardiac or heart failure hospitalizations.

Despite the negative initial findings, two important groups were found to benefit with exercise training. As part of the initial trial design, four patient characteristics were determined to be prognostic predictors of mortality or hospitalization including exercise time, Beck depression score, history of atrial arrhythmias, and ejection fraction. When the outcomes were adjusted for these variables, exercise training was found to have a significant reduction in the endpoint of cardiovascular mortality or heart failure hospitalization. The second group found to benefit from exercise training was those that actually did exercise. Secondary analysis of the HF-ACTION trial examined the relationship between actual volume of exercise and outcomes [20]. Even moderate amounts of exercise were associated with a reduction in mortality and hospitalizations. Once patients exercised at least 3 metabolic equivalent (MET) hours per week, the benefit of exercise was realized. Metabolic equivalent hours were determined based on the baseline exercise test that the patients performed. For example, if their peak exercise MET level was 5 and they were prescribed to exercise at 60–70 % of peak exercise, they would be exercising between 3 and 3.5 METs per h. The total volume of exercise per week would then be calculated to determine the total number of MET hours the patient performed each week.

Belardinelli et al. [30] have also demonstrated both the efficacy of exercise training and the importance of persistent exercise to achieve those benefits. They recently

reported the results of their 10-year exercise training trial that had previously demonstrated a reduction in mortality and heart failure hospitalizations at 5 years [15]. The exercise protocol used was similar with patients exercising at 60 % of peak VO_2 (for 40 min a session). One important difference is that patients continued to perform supervised exercise throughout the entire exercise period. This resulted in 88 % adherence to exercise training throughout the entire 10-year period. The trial was smaller with only 123 patients, but even with smaller numbers, there was a statistically significant 36 % reduction in readmissions and a 32 % reduction in mortality. Quite clearly, the benefits of exercise are clear. The difficulty is finding ways to continue to motivate patients to exercise over time. Further studies are required to find novel, less expensive ways to promote continued exercise training.

When evaluating the efficacy of exercise training, it is important to note that virtually no patients with NYHA functional class IV heart failure symptoms have been studied in randomized exercise training protocols. Although the HF-ACTION trial found that patients with markers of a worse prognosis benefitted with exercise training, one must remember that at baseline they still had NYHA class II or III heart failure symptoms and the mortality benefit has only been demonstrated in that population of patients.

9.3.2 Functional Capacity

In addition to survival, improvements in quality of life and functional capacity are also important measurements when considering the benefits of a therapy. In the HF-ACTION trial, the effects of exercise training on 6-min walk distance and peak VO_2 were evaluated. At both 3 and 12 months after the initiation of training, there were significant improvements in both measurements with the exception of 6-min walk distance at a year. However, although statistically significant, the actual improvements were minimal when compared to the amount of improvement in other trials. Exercise patients only increased their 6-min walk distance by 20 m at 3 months and that dropped to 13 m at a year. Similarly, peak VO_2 increased by 0.6 ml/kg/min at 3 months and was sustained. This contrasts to the Belardinelli study in which the exercise patients increased their oxygen consumption by about 2.5 ml/kg/min, a training effect that was sustained for the entire length of the 10-year trial [30]. Similarly, for the HF-ACTION trial, those who actually performed exercise had a significant increase in peak VO_2 of about 0.9 ml/kg/min [20]. These changes are similar to the effects of cardiac resynchronization therapy for patients with NYHA class III and IV heart failure [31].

9.3.3 Quality of Life

Similar to improvements in exercise capacity, exercise training is associated with an improvement in quality of life. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to evaluate the effects of exercise training on quality of life in the

Table 9.2 Benefits of exercise training

Improved survival
Reduced overall and heart failure hospitalizations
Increased exercise capacity
Improved quality of life

HF-ACTION trial [32]. Exercise training was associated with an early improvement in quality of life by 3 months that was sustained over time. Belardinelli looked at changes in Minnesota Living with Heart Failure score and similarly found an increase at year 1 [30].

Similar to the effects of exercise on overall outcomes, there is a clear relationship between the volume of exercise and improvement in exercise capacity and quality of life. This emphasizes the importance of actually adhering to the prescribed therapy.

9.4 Safety of Exercise Training

Despite the demonstration of benefit of exercise training in patients with heart failure outlined in Table 9.2, there still remains a concern about the safety of exercise in this patient population. Additionally, there is little data about the effects of exercise training in patients with NYHA class IV heart failure. Before prescribing exercise for these and all patients, it is important to appropriately evaluate the patients to determine the safety of exercise for them. Patients should be evaluated by an exercise test to evaluate for exercise-induced ischemia and exercise-induced arrhythmias and to help determine a safe exercise training heart rate range for the individual patient. In the HF-ACTION trial, all patients underwent a symptom-limited metabolic gas exchange exercise test on a treadmill using the modified Naughton protocol [33]. This test was performed to exclude patients with noncardiac limitations to exercise and those with ischemia. Additionally, the heart rate training range was made at 60–70 % of the heart rate reserve assuming as long as that target rate was below the ventilatory threshold.

The HF-ACTION trial evaluated a number of safety endpoints between the two arms. They found no difference in the incidence of serious adverse events such as progressive heart failure, unstable angina, arrhythmias, or neurologic events [19]. They also examined the incidence of hospitalization and death rate in the first 3 h after exercise and did see a small increase in hospitalizations with 37 (3.2 %) in the exercise arm compared to 22 (1.9 %) in the control arm. There was no difference in death after exercise between the two arms, a finding confirmed by the Belardinelli trial [30]. Although there was no increase in the incidence of ICD (implantable cardioverter-defibrillator) firing after exercise, the investigators did examine predictors for ICD firing during the trial [34]. Of 1,053 patients that had a defibrillator prior to enrollment in the trial, 20 % of the patients in the exercise arm and 22 % of those in the control arm experienced a shock. Risk factors for ICD firing included

those with a previous history of ventricular or atrial arrhythmias or those with exercise-induced dysrhythmias. Additionally, those with a lower diastolic blood pressure and nonwhite race also were associated with an increased incidence of firing. This increase incidence of arrhythmias emphasizes the importance of determining the safety of exercise training for the individual patient before embarking on an exercise training regimen.

9.4.1 Exercise in NYHA Class IV Patients

There have been no studies of large numbers of patients with NYHA class IV symptoms, and the safety of exercising these patients has also not been evaluated. For another sick group of patients, those with pulmonary hypertension, Grunig et al. [35] evaluated the effects of exercise training in patients with World Health Organization (WHO) functional classes I–IV. Only 18 patients with WHO class IV symptoms were included. They had significant improvements in 6-min walk distance and quality of life. Additionally, there were no signals of any safety issues in this group. Although one can't directly extrapolate these findings to heart failure patients, it is reassuring to see that other patient groups with advanced disease still do benefit from exercise training, at least in terms of their functional capacity.

9.4.2 Exercise Prescription

Prior to initiating an exercise program, all patients should have a comprehensive evaluation of both their heart failure therapy and their current physical state. Patients that are volume overloaded should be diuresed. One should also rule out ischemia for those with an ischemic etiology or those without a prior assessment of their functional capacity. One should also strongly consider performing metabolic gas exchange during the exercise test as was done in the HF-ACTION test. In addition to evaluating exercise-induced ischemia, many studies have shown that both peak oxygen consumption and the slope of ventilation to carbon dioxide production are helping for evaluating prognosis [36–42]. One can also rule out pulmonary limitations to exercise and develop a baseline to measure potential functional capacity improvements using this test. Additionally, patients with exercise-induced ventricular tachycardia or hypotension should have this evaluated and treated prior to starting their exercise regimen.

Based on the safety of exercise shown in the HF-ACTION trial, one should use a similar intensity of exercise when making an exercise prescription. Patients were started at 60 % of their heart rate reserve and then increased to 70 % over time. Once the training heart rate is established, allow a 10-beat per minute range around that target heart rate (if training heart rate is 130, set a goal heart rate range of 125–135 beats per minute). Because of the chronotropic incompetence and use of beta-blockers

in patients with heart failure, many patients will have a very small heart rate reserve, and therefore their target heart rate will not be much above their resting heart rate. One can also set the exercise training target of to a value of 11–14 on the Borg Rating of Perceived Exertion scale [43]. This rate is usually below the ventilatory threshold and corresponds with a level of exertion that will provide a training effect.

Initiating exercise training at a cardiac rehabilitation facility is ideal for patients with heart failure so that their initial exercise episodes can be monitored. However, many people cannot easily attend a cardiac rehabilitation facility due to time or location constraints. Those patients can still be given an exercise prescription and their exercise can be performed at home, outdoors, a local mall, or other large store. For those that have difficulty checking their heart rate, a good rule of thumb is to exercise at a rate where they can carry on a conversation without long pauses because of breathlessness or to a rate of perceived exertion. One should caution that even for these patients, it is still reasonable to evaluate for ischemia and exercise-induced arrhythmias prior to initiating this program.

Finally, once the exercise intensity, duration, and frequency are established, there are some practical matters for patients to remember. First, a slow warm-up from rest is important. This has been shown to reduce the risk of musculoskeletal injury and possibly reduce the risk of ischemia and arrhythmias [44]. This should last between 5 and 10 min and consist of stretching exercise followed by a slow buildup in aerobic activity to the prescribed level. Similarly, after exercise, patients should undergo a cooldown period of lower exercise intensity followed again by stretching exercises prior to stopping the exercise period. At first, patients may have a 10-min warm-up, 5-min exercise period, and a 10-min cooldown period. Over time, they should slowly build up their exercise period to a goal of 40 min per session.

9.4.3 Areas for Future Research

Although patients may be quite motivated to exercise at first, over time the frequency, intensity, and duration of exercise may be reduced. All studies of exercise training have shown that the benefit is sustained only in those patients who continue to exercise persistently. Table 9.3 outlines some motivational hints that might help to maintain motivation over time. Further studies evaluating new technologies to track exercise and provide motivation such as smart phone applications should also be performed.

Unfortunately, the HF-ACTION trial did not include any patients with heart failure with a preserved ejection fraction (HFpEF), and the understanding of clinical outcomes of exercise training in these patients is still limited. Five trials have evaluated the effects of exercise training in a total of 166 patients with HFpEF [45–49]. Exercise training has been shown to improve peak VO_2, 6-min walk distance, and quality of life. At this time, no one has evaluated the impact of exercise on hospitalizations or mortality in patients with HFpEF, although there have been no reports of deaths related to exercise training.

Table 9.3 Tips for maintaining an exercise regimen

Remind yourself of the benefits of routine exercise
Set short- and long-term goals
Exercise with others
Make exercise more entertaining (bring music, different location)

9.5 Concluding Remarks

Exercise training has been demonstrated to be safe and beneficial for patients with heart failure. Patients should be evaluated with exercise testing prior to initiating an exercise prescription to ensure that patients can safely exercise without ischemia or arrhythmias. For those that actually exercise and maintain exercise activity, a reduction in heart failure hospitalizations and mortality may be expected. Finally, there is a clear relationship between the volume of exercise and experienced benefits and routine; persistent encouragement of patients to exercise and to continue their exercise behavior should be performed.

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Chapter 10
Cardiac Muscle and the Troponins

Elizabeth A. Hausner

Abstract The cardiac troponins (cTns) are structural proteins of the cardiac myocyte contractile apparatus. When measured in circulating blood, the cardiac troponins are sensitive and specific indicators of cardiac myocyte necrosis. The elevation of cardiac troponins without necrosis remains controversial. Understanding of the troponins now includes recognition of the role of posttranslational modifications of troponin T and troponin I in the modulation of cardiac muscle contraction and overall physiology. The assays currently available for detection of troponins in the circulation are immunologically based, using antibodies to a number of epitopes of troponin I and T. Posttranslational modifications, proteolysis, and single nucleotide polymorphisms may affect the ability of the assay antibodies to recognize epitopes on the circulating troponins. The focus of this chapter is an overview of the biology of the cTns, their role in cardiac muscle contraction, and the detection of cardiac troponins with commercially available assays.

Keywords Cardiac troponin • Troponin • Troponin I • Troponin T • Cardiac biomarker • Biomarkers of myocardial damage

10.1 Introduction

The cardiac troponins (cTns) are a complex of three protein subunits, troponin C (TnC, the Ca^{2+}-binding subunit), troponin I (TnI, the inhibitory subunit), and troponin T (TnT, the tropomyosin-binding subunit). The complex as a whole provides physiologic modulation of calcium sensitivity and cardiac myocyte contraction.

Disclaimer The views and opinions expressed are those of the author and do not reflect the positions of the Food and Drug Administration.

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Circulating cardiac troponins are the gold standard clinical chemistry test for diagnosing myocardial infarction as recommended by the European and American Cardiology Societies in 2000 and again in 2007 and 2012 [1–3].

Although an elevated cTn is sensitive and specific for cardiac myonecrosis, it is not specific for myocardial infarction (MI) (i.e., cellular injury related to myocardial ischemia) [4]. Cardiac troponin can also be elevated in other conditions such as heart failure, pulmonary embolus, hypertrophic cardiomyopathy, hypertension with or without left ventricular hypertrophy, renal failure, severe anemia, strenuous exercise, and sepsis [3]. In general, cTn elevation, regardless of the etiology, conveys a worse prognosis.

The focus of the chapter is an overview of the biology of the cardiac troponins (cTns) and their role in cardiac muscle contraction. In addition, this chapter also discusses the evolution of cTn assays and factors that may affect detection.

10.2 Comparison of Cardiac and Skeletal Muscle

Muscle is classified into three categories: smooth (nonstriated), striated skeletal, and striated cardiac muscle. Striated cardiac muscle can be further categorized into atrial muscle, ventricular muscle, and specialized muscle of the cardiac conduction system. The specialized muscles of the conduction system have few contractile fibers and, therefore, limited contractility. The contraction of the heart muscle is influenced by numerous factors, including the intrinsic properties of the different cardiac muscle types, the isoforms, and the variations and modifications in any and all of the muscle proteins [5].

The skeletal and cardiac muscle have similarities of structure, function, and microscopic appearance. Both skeletal and cardiac muscle cells have myofibrils, arranged in parallel fashion. The cardiac muscle fibers have extensively branching networks, whereas the skeletal muscle fibers primarily run in parallel throughout the length of the muscle. Both muscle types have interdigitating thick and thin filaments arranged in the repeating unit of the sarcomere. Striated skeletal muscle is multinucleate, while cardiac muscle cells are mononucleate. Both muscle types contain sarcoplasm (cytoplasm), sarcoplasmic reticulum, and a T-tubule system formed by invaginations of the sarcolemma.

Because the heart muscle beats continuously, there is a constant demand for energy. The cytoplasm surrounding the cardiac myofibrils contains a high density of mitochondria, comprising 25 % of the cellular volume. Unlike skeletal muscle, the heart contracts involuntarily in a rhythmic fashion and cannot draw upon different types and groups of muscle fibers to meet metabolic demands. Cardiac muscle contraction is brief, and relaxation must occur after each contraction.

Other unique properties of cardiac muscle include automaticity and intercalated disks. Automaticity is the ability of cardiac myocytes to beat spontaneously even when denervated. Intercalated disks are a connection and communication system containing three intercellular adhesion structures: fascia adherens junctions,

desmosomes, and gap junctions. The intercalated discs allow for the rapid transmission of the action potential. This rapid communication system facilitates coordinated contraction of the heart, permits diffusion of ions and small molecules, and allows for coupling of electrical and metabolic activity [6, 7].

10.3 The Sarcomere

The sarcomere, illustrated in Fig. 10.1, is the functional unit of striated muscle. These units are arranged in series, creating the myofibrils. The striated microscopic appearance is due to the alternating A bands (thick filaments) and I bands (thin filaments). Thick filaments are composed of two myosin heavy chains (MHC) complexed with two molecules each of myosin light chains (MLC-1, essential light

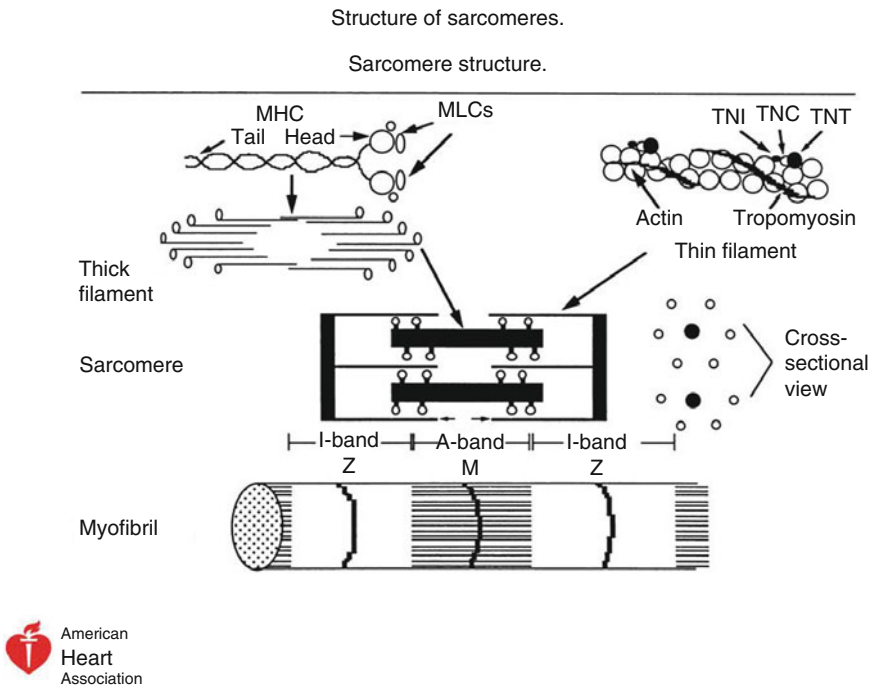


Fig. 10.1 The schematic illustrates the main structural components of a striated muscle cell sarcomere. Thin filaments (I bands) are composed of actin monomers and tropomyosin. The thick filaments (A bands) are composed of two myosin chains complexed with myosin light chains. The striated microscopic appearance of the sarcomere is due to alternating A bands and I bands. The Z lines, forming the lateral boundaries of the sarcomere, are comprised primarily of α-actinin and other proteins. The M-band in the middle of the sarcomere is formed of cross-connecting elements of the cytoskeleton. Myosin filaments are cross-linked by myomesin (This figure which originally appeared in Marian and Roberts [8] is used here with permission)

chain, and MLC-2, regulatory light chain). Thin filaments are composed of Tm and actin. The actin monomers polymerize into a double-helical structure longitudinally oriented around myosin. The tropomyosin molecule is arranged end to end to form a continuous strand along the actin filament. The cardiac troponin complex is bound via tropomyosin to every seven actin monomers in a 7:1:1:1 actin-tropomyosin-troponin ratio [9]. Tropomyosin binds to seven actin monomers in the thin filament and overlaps adjacent Tm molecules. The Z lines are the lateral boundaries of the sarcomere, comprised of a backbone of layers of α-actinin and other associated proteins, that facilitate interactions of actin filaments, titin molecules, and other elements. The T-tubule system communicates with the sarcoplasmic reticulum, assists in transmitting the action potential across the cell, and interdigitates with the Z lines. Costameres link the Z band to the sarcolemma [10]. The M-band, located in the middle of the sarcomere, is formed of cross-connecting elements of the cytoskeleton. The myosin filaments interact with the M-band protein, myomesin [11]. A three-filament model of muscle contraction has been proposed that includes the giant protein titin in addition to the thin and thick filaments. Titin, sometimes referred to as the third filament system, spans half the sarcomere from the Z-disk to the M-band as a springlike filament and is thought to provide the elastic properties of the sarcomere, among other possible functions [12].

10.4 Biology of the Cardiac Troponins

The cTns are a complex of three protein subunits, troponin C (TnC, the calcium-binding subunit), troponin I (TnI, the inhibitory subunit), and troponin T (TnT, the tropomyosin-binding subunit), arranged in a 1:1:1 stoichiometric ratio. This complex plays a role in the physiologic modulation of calcium sensitivity and cardiac myocyte contraction.

As structural components of the cardiac myocyte, cTns are well conserved across species, making them a “translational biomarker” in both veterinary and human medicine and a useful indicator of drug-related cardiac damage in biomedical research. Different isoforms, alternative splicing, mutations, and posttranslational modifications to the troponins have been associated with the function and health of the heart as well as various pathologic conditions such as cardiomyopathies (Chap. 1).

Troponin C Cardiac TnC is an 18 kDa EF-hand calcium-binding protein with two lobular domains, each of which has two Ca^{2+}-binding sites. Each of the four EF-hands has two α-helices between which is a Ca^{2+}-binding loop. There is an additional α-helix at the N-terminal (N-helix). The N-terminal binding sites control the regulatory function of the subunit. The same isoform of TnC is expressed in cardiac and slow skeletal muscle (ssTnC) and is not specific for the heart (c/ssTnC). Nonconservative amino acid substitutions in the first EF-hand of c/ss TnC impede calcium binding [13–15, 16, 18].

Troponin I Cardiac TnI, a 24 kDa protein, was named for its inhibition of actin-activated myosin ATPase activity [22]. In humans, cardiac troponin I is produced from the TNNI3 gene on chromosome 19. When intracellular Ca^{2+} is low, the inhibitory region of cTnI binds to actin, inhibiting muscle contraction. Binding of Ca^{2+} to TnC increases as the intracellular concentration of Ca^{2+} increases. This induces a conformational change that increases the affinity of TnC for cTnI. Conformational changes to cTnI allow the molecule to alternate binding between TnC and actin in response to intracellular calcium concentrations [19]. Both cTnI and ssTnI are detectable throughout fetal development, but the skeletal isoform is predominant during that time period. There is a transition to expression of cTnI in the heart during the first nine postnatal months. Some data suggest that this isoform shift from fetal to adult may have functional implications for the heart. Hearts with congenital malformations may have a different time frame of isoform transition [20, 21].

Cardiac TnI has six distinct functional regions including: (1) an N-terminal extension, $cTnI_{(1–30)}$, unique to the cardiac isoform, containing phosphorylation sites Ser-23 and Ser-24; (2) the N-terminal, $cTnI_{(34–71)}$, a region that provides contact with troponin C; (3) $cTnI_{(80–136)}$ that binds to C-terminal regions of cTnT; (4) the overlapping inhibitory region, $cTnI_{(128–147)}$, that binds cTnC and actin-tropomyosin; (5) switch or triggering region, $cTnI_{(147–163)}$; and (6) the C-terminal domain that binds actin-tropomyosin, $cTnI_{164\text{-}210}$ [17]. Residues 42–136 are sometimes referred to as part of the IT arm [18].

In addition to regulating the actin-myosin interaction, regions of the cTnI subunits as well as specific modifications to those regions have been shown to have additional regulatory control over cardiac function. The inhibitory region of cTnI contains Thr-143, a major phosphorylation site, which may affect velocity of shortening and is also implicated in the posttranslational modifications of cardiac troponins associated with hypertrophy and subsequent heart failure [22]. The phosphorylation sites in the NH_2-terminal extension are targets for a number of protein kinases (PK), including protein kinase A (PKA). Under ß-adrenergic stimulation, the phosphorylation of Ser-23/Ser-24 decreases the Ca^{2+} affinity of the cTn complex and increases the rate of myocardial relaxation [23, 24]. Protein kinase C may phosphorylate cTnI at Ser-23/Ser-24, Ser-43/Ser-45, and Thr-144. Phosphorylation at Thr-144 appears to depress cooperative activation of the thin filament [25]. The process of dephosphorylation is little understood at this time. The N-terminal extension of cTnI may be removed, posttranslationally, due to hemodynamic stress or ß-adrenergic deficiency. This truncation removes the Ser 23/Ser-24 phosphorylation sites; however, the core structure of cTnI remains functional. Genetically modified mice with this alteration are viable through adulthood. The truncation of the N-terminal seems to increase the rate of relaxation of the ventricular muscle, increasing tolerance to decreased preload, an effect similar to phosphorylation of Ser 23/Ser-24 [24, 26–28].

Troponin T Cardiac TnT, a 37 kDa protein, the largest of the three subunits, has diverse intermolecular interactions. Cardiac TnT binds to cTnI and cTnC to form the overall troponin complex and also binds to tropomyosin (Tm) and actin. In

humans, three TnT genes have been described. These separate genes encode the isoforms found in slow skeletal muscle, fast skeletal muscle, and cardiac (cTnT) muscle. Each isoform is subject to alternative RNA splicing, producing multiple tissue-specific isoforms [19, 29]. The cardiac-specific TnT is encoded by the TNNT2 gene, located on chromosome 1. A number of isoforms have been identified, four of which have been described for the human heart. Cardiac TnT_1 and TnT_2 are expressed primarily in the fetal heart. Cardiac TnT_3 is the primary isoform in the healthy adult heart, and $cTnT_4$ is expressed in the fetal heart and is reexpressed in the adult failing heart. Although most of cTnT is highly conserved, there is a unique, hypervariable N-terminal region (residues 1–69) which is variable across isoforms [16, 19, 30].

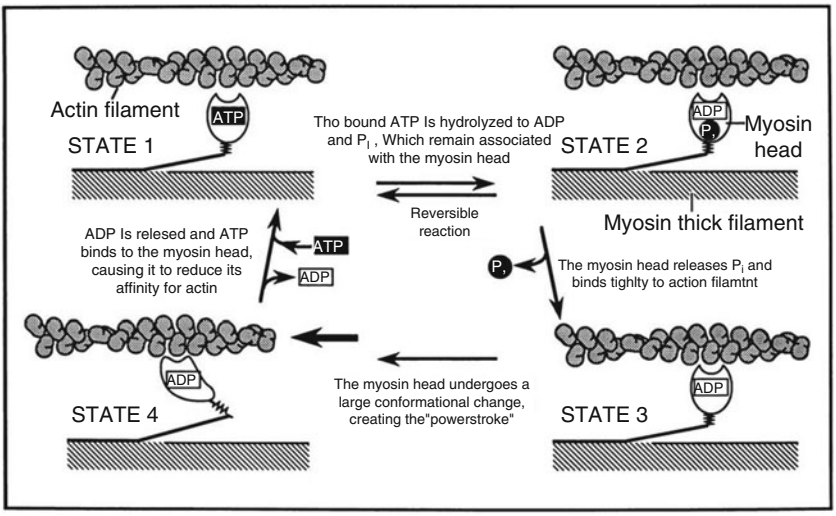
Similar to cTnI, the N-terminal region of cTnT contains several phosphorylation sites, primarily Ser-2, Thr-294, Thr-204, Thr-213, and Ser-208. The role of cTnT phosphorylation and cardiac function is unclear, but data suggest that phosphorylation of cTnT decreases the binding affinity of cTnT for Tm and reduces the ability of troponin to expose blocked myosin binding sites. The net result is a decrease in Ca^{2+}-dependent actomyosin ATPase activity [31]. A number of mutations associated with hypertrophic and dilated cardiomyopathies have been identified in human cTnT [32].

10.5 Cardiac Muscle Contraction

The sliding filament theory of muscle contraction was proposed in 1954 by Huxley and Hanson, years before it was recognized that calcium and the cardiac troponin complex played a key role in this process. The sliding of the interdigitated thin and thick filaments causes a shortening of the distance between the Z lines, as observed by microscopy. Later work demonstrated that contraction involves a cycle of myosin "reaching forward" to bind to actin and form the crossbridge, contraction, release of actin, and then the forward movement of the hinged globular region of the myosin S1 segment to begin the cycle again, as shown in Fig. 10.2.

Hydrolysis of ATP provides the energy for myosin to pull the actin filaments. The myosin crossbridges rotate toward the center of the sarcomere in what is referred to as the "power stroke." Subsequently, an ATP molecule binds to the myosin head, breaking the crossbridge and allowing myosin to reattach to the actin at a site further along the actin filament. After decades of rigorous scientific examination, the sliding filament model still stands, albeit refined by new data. A plethora of new proteins and lipids have been demonstrated to be involved in contraction, restoration of relaxation, and maintenance of structural integrity under conditions of consistent deformation (contraction-relaxation).

The cycle of a heartbeat is the process that leads to and includes contraction, ejection, subsequent relaxation, and filling of the cardiac chambers with blood. The cardiac cycle begins with an action potential and membrane depolarization.



American Heart Association

Fig. 10.2 Cardiac muscle contraction through one cycle of cardiac contraction and relaxation (This figure which originally appeared in Marian and Roberts [8] is used here with permission). In State 1, ATP is bound to the globular head of myosin. The myosin ATPase hydrolyzes ATP, generating ADP and Pi (State 2). The Pi is released and the globular head binds to the actin filament (State 3). Flexion of the hinge region of myosin displaces the globular head over the actin filament, causing the power stroke and muscle contraction (cardiac systole (State 3 to State 4)). ADP is released, with ATP again taken into the binding site on the globular head, releasing myosin from actin (return to State 1)

The concentration of intracellular Ca^{2+} rises, followed by Ca^{2+} binding to cTnC, changes in the thin filament, and force generation of crossbridges. The cycling of muscle fibers between contraction and relaxation must occur within the heartbeat and be adaptable to a wide range of heart rates and contractility. It has been proposed that the rise of intracellular Ca^{2+} and the Ca^{2+}-induced troponin switch occurs within approximately 20 ms, the first 20–30 % of the isovolumetric pressure rise. This suggests that the rate of myocardial contraction is limited by processes other than Ca^{2+}-regulated troponin switching [33] (Chap. 4).

In diastole, the N-terminal tail of cTnT, the inhibitory peptide of cTnI, and an actin-binding region of cTnI hold Tm in a blocking position that prevents the development of crossbridges (steric blocking model) [34]. The electrical events of the action potential and membrane depolarization are linked to the mechanical result of cardiac contraction. This excitation-contraction coupling begins with the release of calcium from the sarcoplasmic reticulum. Calcium enters the cytoplasm primarily via the L-type channels and triggers the release of more calcium from the sarco-

plasmic reticulum via the ryanodine receptor (i.e., Ca^{2+}-induced Ca^{2+} release). The increased level of cytosolic Ca^{2+} interacts with the regulatory N-domain of cTnC. The Ca^{2+} binding to cTnC induces exposure of a hydrophobic patch that draws the switch peptide region of cTnI to cTnC. The movement of the switch peptide toward the hydrophobic area of cTnC drags the adjoining inhibitory region of cTnI, causing release of the thin filament and an actin-binding site. The calcium-binding signal also induces release of the cTnT to tropomyosin interaction [5, 35]. The C-terminus of cTnI is carried along with this motion. The sequence is sometimes referred to as the "drag and release" mechanism [17]. This conformational change in the troponins allows actin crossbridge formation and sarcomeric shortening or contraction.

Return to the diastolic conformation of the cardiac troponin complex is an energy-requiring process that involves dissociation of calcium from cTnC, reversion of the conformation of the different subunits, and reduction of crossbridge formation. Four pathways modulate the removal of Ca^{2+} from the cytosol during the active process of relaxation, including the sarcoplasmic reticulum Ca^{2+} ATPase, sarcolemmal Na^{+}/Ca^{2+} exchanger, mitochondrial Ca^{2+} uniporter, and sarcolemmal Ca^{2+} ATPase [35]. Factors such as phosphorylation of the subunits, mutations, and isoform switching of the troponin subunits as well as the assay system used (e.g., isolated subunit versus troponin complex, reconstituted into thin filament or cardiac myocyte) can alter the kinetics of Ca^{2+} association and dissociation with cTnC [23]. Liu evaluated the effect of cTnI and cTnT modifications associated with cardiac disease on the rates of calcium association and dissociation both in isolated troponin complex and when these modifications were reconstituted into the thin filament [36]. Effects on the kinetics of Ca^{2+} association and dissociation from the reconstituted thin filament were observed when almost no effects were detected in the isolated cTn complex. The majority of disease-related protein modifications did not alter the Ca^{2+}-binding properties of the isolated troponin complex. However, when reconstituted into the thin filament, the mutations associated with dilated cardiomyopathy decreased the Ca^{2+} sensitivity of the thin filament. The mutations associated with restrictive and hypertrophic cardiomyopathy, as well as the ischemia-induced truncation of cTnI, increased the Ca^{2+} sensitivity of the thin filament. The various protein modifications altered the steady-state Ca^{2+} binding to TnC by influencing both the Ca^{2+} association and dissociation rates on the thin filament.

10.6 Increases in Circulating Cardiac Troponins

The circulating forms of cTns (i.e., those proteins identified in the systemic circulation after a myocardial infarction) include cTnT, cTnI, the cTnI-TnC complex, and a ternary complex of cTnT-cTnI-TnC [37, 47]. Most cTns are present in the myocyte as part of the structural elements. An estimated 3–8 % of the total cellular troponin is free in the cytoplasmic pool. It is hypothesized that free troponin in the

cytoplasmic pool contributes to initial increases in circulating cTn following myocardial injury. Subsequent increases are thought to be due to degradation of structural proteins [38]. The probability of proteins the size of the troponins leaking from a viable cell is uncertain. The leakage from viable cells of fragments detectable by assays is possible but raises additional questions.

There are six proposed mechanisms for cTn release: (1) myocyte necrosis, (2) apoptosis, (3) normal myocyte cell turnover, (4) cellular release of proteolytic troponin degradation products, (5) increased cellular wall permeability, and (6) formation and release of membranous blebs. Cardiac myocyte death can be further categorized to include pathways of extrinsic death receptor pathway, intrinsic apoptosis, necrosis, necroptosis, and possibly others [39, 40]. How the mechanism of damage influences the form in which the troponins are released is not completely characterized.

Some baseline level of circulating cTns might be expected due to normal maintenance and turnover of cardiac myocytes. Replacement of cTns includes the synthesis, assembly, and degradation of the individual components of the cardiac sarcomere. The mechanism by which the individual components of this multiprotein complex are removed and replaced while maintaining the functionality of the contractile unit is incompletely understood. In rats, the rate of incorporation of radiolabeled amino acids into the troponin complex in situ demonstrated that cTnI and cTnT had similar half-lives (i.e., similar turnover rate) of 3.2 and 3.5 days, respectively. These half-lives were significantly different from cTnC's half-life of 5.3 days [41].

It is generally accepted that circulating cTn is highly susceptible to phosphorylation and proteolysis. Regardless of the mechanism by which troponins are released into circulation, some sections of the complex and fragments are more susceptible than others to degradation and modification. Modifications may include acetylation, protein sequence variants such as mutants, alternatively spliced isoforms, amino acid polymorphisms, and protein complexes. Each of these posttranslational modifications may have variable effects on the ability of a given antibody to detect cTnI [42]. Degradation of cTnT after release into the circulation is not as well understood. At least in hemodialysis patients, circulating cTnT molecules are degraded into smaller fragments that may be detectable by assays [43]. The process and overall kinetics of clearance are incompletely understood.

10.7 Assays

In 1987, Cummins et al. [58] described a radioimmunoassay for cardiac troponin I. Two years later, Katus et al. [59] announced an enzyme-linked immunosorbent assay (ELISA) for cardiac troponin T. Currently, there is one commercially available cTnT assay and numerous commercially available cTnI assays.

In this chapter, assays will be discussed in terms of sensitivity, specificity, and factors that may influence detection. The diagnostic interpretation of cardiac troponin increases and the clinical application are discussed in the next Chapter.

The oldest category of commercial assays, no longer in use, was less sensitive in detecting increases in cTn, compared to newer assays. A 10 % coefficient of variation was achieved at approximately 1 μg/l, and, therefore, pathologic elevations were detected almost exclusively. The current assays have third- and fourth-generation antibodies and incorporate newer technology to increase the analytical sensitivity. Assays currently available are informally referred to as high-sensitive, ultrasensitive, or sensitive-contemporary assays. These assays reliably detect to greater than the 99th percentile value but only quantitate cTn in a fraction of clinically healthy individuals. The IFCC recommends describing an assay as "high sensitivity" only if the cTn is measurable in more than 50 % of healthy subjects (and preferably in more than 95 %) below the 99th percentile of the assay and above the assay's limit of detection. The total imprecision (coefficient of variation) at the 99th percentile should be ≤10 % [45, 46]. Conrad and Jarolim suggest reserving the term "ultrasensitive" for assays capable of quantitating cTn at levels less than the lowest cTn concentrations seen in healthy individuals [46].

The use of antibodies to a variety of troponin epitopes has several significant consequences. First, the available assays have different sensitivities to detect circulating troponins. Second, results generated with one assay may not be comparable to results produced with another assay in another facility, making analysis or meta-analysis of results difficult. The interaction of the assay antibodies with the targeted epitope of the cTn fragment may be influenced by the posttranslational or post-release modification of the measured molecule. That is, the epitope in the circulating troponin species may be masked, destroyed, or otherwise unavailable for antibody recognition. Posttranslational modifications, complexes with other proteins (e.g., using heparin for anticoagulation), heterophile or human anti-mouse antibodies, and cTnI autoantibodies may affect the immunochemical measurement of cTnI. The chelating agent EDTA has been demonstrated to split the calcium-dependent I-T-C and I-C troponin complexes, affecting measured concentrations in assays that preferentially measure these forms [19].

When a serum sample is analyzed for circulating cTns, it is unlikely that a single chemical entity is detected. Several investigators have demonstrated progressive cTn degradation following acute myocardial infarction, contributing to a profile of cardiac troponin fragments and modified fragments and variants, some of which provide the necessary epitope for recognition by the assay antibody. This profile may vary among patient populations, and fragments may not necessarily be detected in a 1:1 ratio [37, 47, 48]. In addition to degradants and posttranslational modifications, natural variants, such as single nucleotide polymorphisms (SNPs), can also impair the ability of the commercial antibodies to recognize the targeted epitopes. Investigators have used the UniProt database to identify the SNPs in the TNNI3 and TNNT2 genes that might involve antibody-binding domains of either cTnI or cTnT. The number of polymorphisms identified in TNNI3 and TNNT2 are 19 and 4, respectively. The investigators also noted that 12 out of 17 commercial cTnI

assays and the cTnT immunoassay contained antibodies targeting SNP-containing domains. Although two of the SNPs are considered to be clinically silent thus far, the majority of these SNPs are associated with inherited cardiac disorders. Due to incomplete penetrance and variable clinical expression of the disorders, carriers of the identified SNPs may experience myocardial infarctions before they exhibit signs of cardiomyopathy. In this patient population, cTn values may be false negative because of their variant forms [49]. Mutations in cTnI and cTnT subunits have been shown to be associated with dilated, hypertrophic, and restrictive cardiomyopathies. Mutations in cTnC have also been associated with dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) [50].

Other isoforms of troponins may cross-react with the antibodies in the cTnT assay, leading to a false-positive result. Several recent publications describe persistent elevations in circulating cTnT without concomitant elevations in circulating cTnI in patients with various neuromuscular disorders. This finding is suggestive of re-expression of isoforms in diseased skeletal muscle and release into circulation [52–54].

Although there are standardized clinical chemistry measurands (e.g., glucose), there is no standardization of the troponin I assays for reasons that include the heterogeneity of the analyte(s) as described above. The IFCC Working Group on Standardization of Troponin I has described the challenges for achieving metrological traceability for troponin I assays [55]. The current recommendations include the ability of each assay to accurately and reliably report troponin values in the upper reference limit of a one-tailed 99th percentile of a reference population. The 99th percentile was chosen as the cut point of normality by a consensus that an acceptable false-positive rate would be approximately 1 % [4]. Clearly, the reference population is a significant factor in determining the diagnostic criteria for any given assay. There is no universal or consensus definition on what characteristics constitute a reference population or how many individuals are needed. Both the age and sex of the reference population as well as the baseline characteristics in general have been suggested to affect the values obtained and, therefore, the upper reference limit (URL) for the cut point. Three contemporary sensitive assays were used to measure cTnI in 2,404 individuals and a subgroup with more stringent inclusion criteria of 908 individuals. One assay showed significantly higher values in men than in women. Age dependency was not demonstrated in this study although others have suggested that increasing age of the population may correlate with higher 99th percentile values [45, 56, 57].

10.8 Concluding Remarks

The cardiac troponins are structural proteins in the contractile apparatus of the cardiac myocyte. The role of posttranslational modification has been recognized to affect both the function of the troponins and the overall regulation of cardiac muscle contraction. The cardiac troponins in the systemic circulation are sensitive and specific biomarkers for myocardial necrosis. Currently available assays

for the cardiac troponins are based upon antibody recognition of different epitopes of the cardiac troponin molecules. Posttranslational modification, proteolysis, and single nucleotide polymorphisms of the troponins may affect the ability of the antibodies to access or recognize the critical epitopes. This may have implications for the diagnostic accuracy of troponins in some situations or patient populations. Considerations for the clinical use of troponins and the role in diagnostic criteria are discussed in the following Chapter.

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Chapter 11
Circulating Cardiac Troponins as Specific Biomarkers of Myocardial Damage: Clinical Considerations

Karen A. Hicks

Abstract Cardiac troponin (cTn) is one of the most widely used biomarkers in clinical care and biomedical research. Compared to the MB fraction of creatine kinase (CK-MB), cTn is the preferred biomarker for detecting myocardial necrosis because of its high myocardial tissue specificity and high clinical sensitivity. Although an elevated cTn value reflects injury leading to myocardial necrosis, the underlying mechanism may be difficult to ascertain. Such mechanisms may be ischemic, nonischemic, or analytical in origin and can only be determined by considering the clinical context in which the measurement is made.

The chapter discusses a general approach to the clinical interpretation of cTn elevation and how an acute myocardial infarction may be differentiated from other etiologies.

Keywords Cardiac troponin • Troponin • Troponin I • Troponin T • Cardiac biomarker • Myocardial infarction • Myocardial damage • Circulating troponins

11.1 Introduction

Myocardial injury is detected when biomarkers such as cardiac troponin (cTn) and the MB fraction of creatine kinase (CK-MB) are elevated in the systemic circulation [1–3]. Since 2000, cardiovascular professional organizations have recognized cTn (I or T) as the preferred biomarker for detecting myocardial necrosis because of its nearly absolute myocardial tissue specificity and high clinical sensitivity [1–3].

Disclaimer This chapter reflects the views of the author and should not be construed to represent FDA's views or policies.

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According to the Joint European Society of Cardiology (ESC) and the American College of Cardiology (ACC) Committee for the Redefinition of Myocardial Infarction (MI) in 2000 and the Joint ESC/ACC Foundation/American Heart Association (AHA) and World Heart Federation (WHF) Task Forces for the Universal Definition of MI in 2007 and 2012, an increased value for cTn is defined as a measurement exceeding the 99th percentile of a normal reference population [1–3]. Reference values for each assay should be determined in each laboratory with appropriate quality control, and optimal precision, the coefficient of variation (CV) at the 99th percentile, is defined as ≤10 % for each assay [1–3]. The 2012 Third Universal Definition of MI recommends reporting cTn values in nanograms (ng) per liter (ng/L) or picograms (pg) per milliliter (pg/mL) instead of ng/ml or μg/ml, which underscores the evolution in the sensitivity of cTn assays [3].

Although an elevated cTn value is sensitive and specific for cardiac myonecrosis, it is not specific for myocardial infarction (MI) (i.e., injury related to myocardial ischemia) [4]. A diagnosis of MI must always take into consideration the clinical scenario, electrocardiographic and physical examination findings, laboratory and imaging results, temporal changes in cardiac biomarkers, and pretest likelihood that the elevated cTn value represents a MI. Cardiac troponin values can also be elevated as a result of myocardial injury in other conditions such as heart failure, pulmonary embolus, hypertrophic cardiomyopathy, hypertension with or without left ventricular hypertrophy, renal failure, severe anemia, strenuous exercise, and sepsis [3]. In general, cTn elevation, regardless of the etiology, conveys a worse clinical prognosis [4].

The focus of this chapter is on key clinical considerations in the interpretation of cTn values and areas requiring further study. For a full discussion on the biology of the cTns, their role in cardiac muscle contraction, and cTn assays as well as the factors that may affect detection, see Chap. 10.

11.2 Definition of MI

Prior to discussing a general approach to interpreting elevated cTn values, it is essential to have a working knowledge of how a MI is defined.

The definition of MI has evolved since 1979 when the Joint International Society and Federation of Cardiology/World Health Organization recommended using at least two of the following criteria to establish the clinical diagnosis: (1) history, (2) electrocardiographic changes, and (3) serum enzymes [5].

In the early 1990s, the development of cTnI and cTnT assays transformed how cardiac injury was detected. In 2000, the Joint ESC/ACC Committee recognized that cardiac necrosis is the result of prolonged ischemia and defined MI as a constellation of clinical, pathological, biochemical, electrocardiographic, and imaging characteristics [1].

In 2007, the Joint ESC/ACCF/AHA/WHF Task Force defined acute MI (AMI) as "evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia" [2]. A key update to the 2000 definition included the detection of a rise

and/or fall of cardiac biomarkers (preferably troponin), requiring serial collection of these biomarkers. The Task Force recommended collecting cardiac biomarkers on the first assessment, 6–9 h later, and if the earlier measurements were normal but the clinical suspicion for MI was high, between 12 and 24 h. The 2007 definition also classified MIs into five types: Type 1 is a spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection; Type 2 is secondary to ischemia due to either increased oxygen demand or decreased supply; Type 3 is sudden unexpected cardiac death; Type 4a is related to PCI; Type 4b is related to stent thrombosis; and Type 5 is related to CABG. The five types of MI are described in greater detail in Chap. 19.

In 2012, the Joint ESC/ACCF/AHA/WHF Task Force made important updates to the 2007 definition including changes in troponin thresholds for the diagnosis of MI types 4a and 5 and the introduction of a new category of MI (type 4c) for restenosis [3]. The timing of CABG-related MI was also changed from "within 72 h" to "within 48 h" of the procedure. The Task Force recommended collecting blood samples for the measurement of cTn on the first assessment and 3–6 h later. Further samples were required if there were additional ischemic events or if the timing of the index symptoms was unclear. Table 11.1 summarizes the changes in the definition of MI from 2000 to 2012 and how the MI types are defined.

The 2012 MI categories are similar to those from 2007, but the threshold for a Type 4a, PCI-related MI, increased from >3 × 99th percentile of the upper reference limit (URL) to >5 × 99th percentile, and the threshold for a Type 5 CABG-related MI increased from >5 × 99th percentile URL to >10 × 99th percentile URL. These thresholds are arbitrary. The Third Universal Definition of MI also defined a Type 4c MI due to restenosis as ≥50 % stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values exceeding the 99th percentile URL and no other significant obstructive coronary artery disease of greater severity following either (i) an initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50 %) [3].

The definition of periprocedural MI (PPMI) remains controversial. Further study is needed to determine whether PPMIs (and particular thresholds) contribute to the prediction of death or MI (as do Type 1 MIs) when considered with pre-procedure risk estimates, atherosclerotic burden, and procedural complexity [4]. In 2013, the Society for Cardiovascular Angiography and Interventions (SCAI) published a definition for "clinically relevant" MI after both PCI and CABG procedures that uses higher thresholds than the 2012 Universal Definition of MI and CK-MB instead of cTn as the preferred biomarker [6]. In patients with normal baseline CK-MB and without ACS, SCAI recommends defining a clinically relevant PPMI as a peak CK-MB measured within 48 h of the procedure ≥10× the local laboratory ULN or in the absence of CK-MB measurements, a cTn (I or T) ≥70× ULN (or by CK-MB ≥5× ULN or cTn ≥35× ULN plus the development of new pathological Q waves in ≥2 contiguous leads or new persistent left bundle branch block [LBBB]) [6].

In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling, SCAI recommends defining a clinically relevant PPMI as absolute increments in CK-MB (or cTn) equal to those levels recommended above, compared to the most recent pre-procedure level.

Table 11.1 Definitions of myocardial infarction

Definition	Criteria for acute myocardial infarction	Types	Reinfarction
Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (2000) [1]	*Biochemical markers for detecting myocardial necrosis*: The following are biochemical indicators for detecting myocardial necrosis: 1. Maximal concentration of troponin T or I exceeding the decision limit (99th percentile of the values for a reference control group), on at least one occasion during the first 24 h after the index clinical event 2. Maximal value of CK-MB (preferably CK-MB mass) exceeding the 99th percentile of the values for a reference control group on two successive samples or maximal value exceeding twice the upper limit of normal (ULN) for the specific institution on one occasion during the first hours after the index clinical event Values for CK-MB values should rise and fall; values that remain elevated without change are almost never due to MI. In the absence of availability of a troponin or CK-MB assay, total CK (greater than two times the upper reference limit) or the B fraction of CK may be employed, but these last two biomarkers are considerably less satisfactory than CK-MB		

2007 Universal Definition of myocardial infarction [2]	The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions anyone of the following criteria meets the diagnosis for myocardial infarction: 1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following: (a) Symptoms of ischemia (b) ECG changes indicative of new ischemia [new ST-T changes or new LBBB (LBBB)] (c) Development of pathological Q waves in the ECG (d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality 2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood	*Type 1*: spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection *Type 2*: MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension *Type 3*: sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood	$\geq$ 20 % increase of the value in the second cardiac biomarker sample 3–6 h following the immediate measurement at the time of the suspected clinical signs or symptoms

(continued)

Table 11.1 (continued)

Definition	Criteria for acute myocardial infarction	Types	Reinfarction
	3. For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3×99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized 4. For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 5×99th percentile URL plus: (a) Either new pathological Q waves or new LBBB (b) Angiographically documented new graft or native coronary artery occlusion (c) Imaging evidence of new loss of viable myocardium Have been designated as defining CABG-related myocardial infarction 5. Pathological findings of an acute myocardial infarction	*Type 4a*: myocardial infarction associated with PCI If cTn values are elevated prior to PCI and are not stable (or falling) for at least two samples 6 h apart, there are insufficient biomarker criteria to diagnose a periprocedural MI (PPMI) If the baseline cTn values are elevated and are stable or falling, then a rise of ≥20 % (as with reinfarction) together with the features of the electrocardiogram or imaging can be applied *Type 4b*: myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy *Type 5*: myocardial infarction associated with CABG If a cTn assay is not available, CK-MB, as measured by mass assay, is considered the best alternative	

2012 Third Universal Definition of myocardial infarction [3]	The term acute myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI: 1. Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile URL and with at least one of the following: (a) Symptoms of ischemia (b) New or presumed new significant ST segment-T wave (ST-T) changes or new LBBB (c) Development of pathological Q waves in the ECG (d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (e) Identification of an intracoronary thrombus by angiography or autopsy 2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased	Same MI types as the 2007 Universal Definition of Myocardial Infarction with the addition of Type 4c MI *Type 1: spontaneous myocardial infarction*. Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD *Type 2: myocardial infarction secondary to an ischemic imbalance*. In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH *Type 3: myocardial infarction resulting in death when biomarker values are unavailable*. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained before cardiac biomarkers could rise or in rare cases cardiac biomarkers were not collected	≥20 % increase of the value in the second cardiac biomarker sample 3–6 h following the immediate measurement at the time of the suspected clinical signs or symptoms

(continued)

Table 11.1 (continued)

Definition	Criteria for acute myocardial infarction	Types	Reinfarction
	3. PCI-related MI is arbitrarily defined by elevation of cTn values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values ≥20 % if the baseline values are elevated and are stable or falling. In addition, either: (a) Symptoms suggestive of myocardial ischemia, or (b) New ischemic ECG changes, or (c) Angiographic findings consistent with a procedural complication, or (d) Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required 4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL	*Type 4a: myocardial infarction related to PCI.* Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 × 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values ≥20 % if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required *Type 4b: myocardial infarction related to stent thrombosis.* Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL	

	5. CABG related MI is arbitrarily defined by elevation of cardiac biomarker values (>10×99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (a) New pathological Q waves or new LBBB, or (b) Angiographic documented new graft or new native coronary artery occlusion, or (c) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality	*Type 4c: myocardial infarction related to restenosis.* ≥50 % stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values > 99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50 %) *Type 5: myocardial infarction related to CABG.* Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10×99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality If a cTn assay is not available, the best alternative is CK-MB (measured by mass assay)	

AMI acute myocardial infarction, *CABG* coronary artery bypass graft surgery, *CAD* coronary artery disease, *CK* creatine kinase, *CK-MB* creatine kinase-MB isoform, *cTn* cardiac troponin, *ECG* electrocardiographic, *LBBB* left bundle branch block, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *ULN* upper limit of normal, *URL* upper reference limit

In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling, SCAI recommends defining a clinically relevant PPMI as absolute increases in CK-MB (or cTn) equal to the levels recommended above in addition to new ST segment elevation or depression and signs consistent with a clinically relevant MI (e.g., heart failure, hypotension).

How to define a PPMI and what thresholds to use remain highly controversial and will likely be a focus of future definitions. Given the variability in reference ranges for current troponin assays, White suggests that it may not be possible to define a particular threshold that could be applied to all [7].

11.3 Timing of Troponin Elevation

Serial cTn measurements may be helpful in determining whether the kinetics of cTn change are more consistent with acute coronary syndrome (ACS) or other etiologies such as acute decompensated heart failure (ADHF).

11.3.1 Timing of Troponin Elevation in MI

In the setting of an AMI, elevations in cTn values can be detected in the blood within 2–4 h following the onset of ischemic symptoms but in some cases may not be detected for up to 8–12 h [8]. Although cTn and creatine kinase-MB (CK-MB) share a similar time frame for elevation, the increases in cTn values may persist longer and remain elevated for up to 14 days, as shown in Fig. 11.1 [8]. Serial levels are useful in differentiating whether the process is acute, subacute, or chronic and whether the event is distinct from a prior event (e.g., reinfarction, PPMI).

In the setting of reperfusion, cTn and CK-MB in ST elevation MI (STEMI) patients are detected sooner, have higher peak values, and decline more rapidly, resulting in a smaller infarct, compared to STEMI patients without reperfusion.

11.3.2 Timing of Troponin Elevation in Other Disease Processes

Troponin and/or CK-MB values that remain elevated without change at an appropriate sampling interval (e.g., baseline, 6–9 h, and again at 12–24 h) are not usually a result of a MI and suggest other disease processes (e.g., heart failure, renal failure) [4].

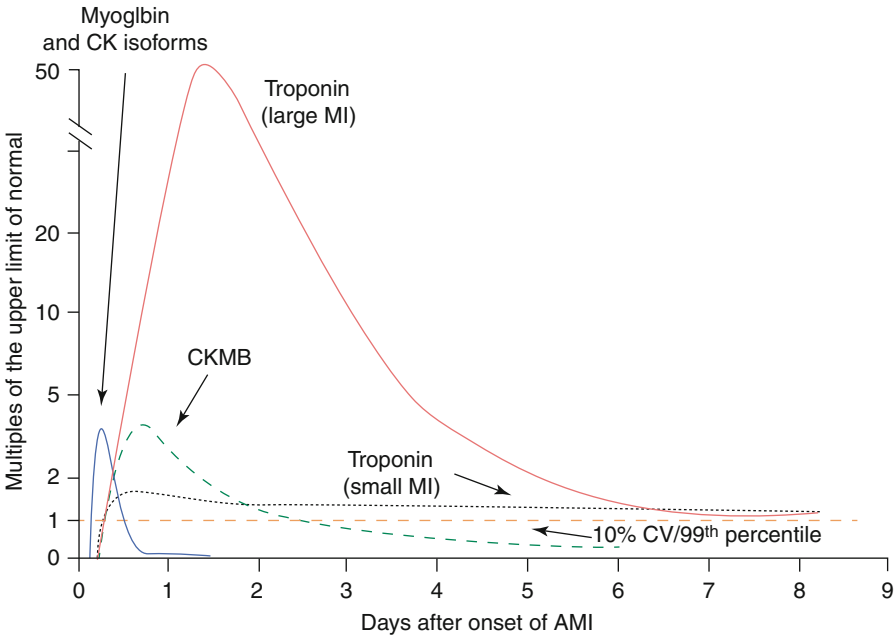

Fig. 11.1 Timing of release of various biomarkers after acute myocardial infarction. The biomarkers are plotted showing multiples of the cutoff for acute myocardial infarction (AMI) over time. The *dashed horizontal line* shows the upper limit of normal (ULN; defined as the 99th percentile from a normal reference population without myocardial necrosis; the coefficient of variation of the assay should be 10 % or less). The earliest rising biomarkers are myoglobin and CK isoforms (leftmost curve). CK-MB (*dashed curve*) rises to a peak of two to five times the ULN and typically returns to the normal range within 2–3 days after AMI. The cardiac-specific troponins show small elevations above the ULN in small infarctions (e.g., as is typically the case in STEMI). The troponin levels may stay elevated above the ULN for 7 days or more after AMI. *CK* creatine kinase, *CK-MB* MB fraction of creatine kinase, *CV* coefficient of variation, *MI* myocardial infarction, *NSTEMI* non-ST elevation myocardial infarction, *UA/NSTEMI* unstable angina/non-ST elevation myocardial infarction (Text is reproduced with permission from reference [8]. The Figure is originally from Shapiro and Jaffe [17]. Reproduced here with the permission of Mayo Foundation for Medical Education and Research. All rights reserved)

11.4 General Approach to Interpretation of Troponin Elevations

One conceptual model for the clinical distribution of elevated troponin is displayed in Fig. 11.2. Troponin elevations can result from ischemic and nonischemic conditions [4]. In the setting of ischemia, cTn elevation can be due to a MI-related ACS (Type I), a non-ACS condition, or sudden cardiac death (Type 3). Myocardial infarctions occurring in non-ACS conditions can be classified into coronary (e.g., Types 2, 4, and 5 MIs) and noncoronary (hypoxia, global ischemia, hypoperfusion, and cardiothoracic surgery) etiologies [4] (Chaps. 19 and 23).

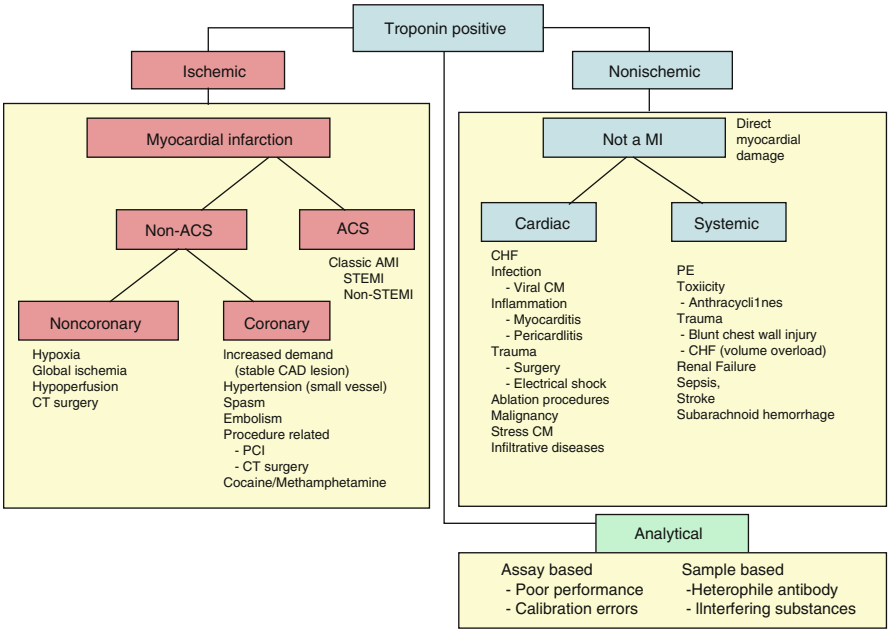

Fig. 11.2 Conceptual model for clinical distribution of elevated troponin. *ACS* acute coronary syndrome, *AMI* acute myocardial infarction, *CAD* coronary artery disease, *CHF* congestive heart failure, *CM* cardiomyopathy, *CT* cardiothoracic, *PCI* percutaneous coronary intervention, *PE* pulmonary embolism, *STEMI* ST segment elevation myocardial infarction (Adapted with permission from reference [4])

In nonischemic conditions, troponin elevation can occur as a result of direct myocardial damage that is not related to a MI. Nonischemic conditions can be classified into cardiac and systemic etiologies. Cardiac etiologies include heart failure (HF), infection (viral cardiomyopathy), inflammation (myocarditis, pericarditis), trauma (surgery, electrical shock), ablation procedures, malignancy, stress cardiomyopathy (CM), and infiltrative diseases. Systemic etiologies include pulmonary embolus, toxicity (anthracyclines), trauma (blunt chest wall injury, HF from volume overload), renal failure, sepsis, stroke, and subarachnoid hemorrhage [4].

In addition to ischemic and nonischemic conditions, troponin elevations can occur as a result of analytical factors. Such factors can be further classified as assay based (poor performance, calibration errors) or sample based (heterophile antibody or other interfering substances) [4].

Although an elevated troponin likely represents myocardial necrosis, the etiology of this finding can only be determined by considering the clinical context in which the measurement is made. Not all troponin elevations are due to a MI, and not all MIs from an ischemic origin result from ACS events. Regardless of the etiology, an elevated troponin conveys a worse clinical prognosis.

In some cases, troponin elevations can be multifactorial. For example, a patient can experience a myocardial infarction and a pulmonary embolus or a myocardial infarction and a stroke at the same time. Therefore, careful consideration of the

patient's clinical scenario, serial 12-lead electrocardiograms, and laboratory and imaging results are required to make the correct diagnosis.

The next sections examine some common causes of elevated troponin in clinical practice.

11.4.1 Troponins in ACS

Cardiac troponins are widely used to detect ischemic cardiac injury in patients with ACS. ACS includes ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (Chaps. 19 and 23). By convention, STEMIs and NSTEMIs are cardiac biomarker positive (elevated troponins), and unstable angina is cardiac biomarker negative (normal troponin values). Recently, some have questioned whether a category for unstable angina should still exist, given the high sensitivity of the current assays and the identification of more events, previously categorized as unstable angina, as myocardial infarctions [9].

Since unrecognized ACS could result in a fatal outcome, it is important to first exclude this diagnosis when a patient has a high pretest probability for ACS because it could alter patient management. The pretest probability for ACS can be determined by the patient's clinical presentation, risk factors, history of coronary artery disease and/or prior revascularization, electrocardiographic changes, and new wall motion abnormalities.

ACS patients with elevated troponins are most likely to benefit from an aggressive treatment strategy to include antiplatelet therapy, coronary angiography, and revascularization [4]. In contrast, patients with elevated troponin and a low pretest probability of ACS are unlikely to benefit from such a strategy. Instead, the main goal is to identify and treat the underlying cause of the elevated troponin (e.g., pulmonary embolism, heart failure).

Both patients with and without elevated troponin, but with a high pretest probability of ACS, should be considered for early invasive management. In general, patients can be categorized as either (1) high risk, prompting an early invasive strategy, or (2) low risk, leading to either an early conservative or invasive strategy [4]. Global risk, as estimated from clinical risk scores (TIMI, GRACE, or PURSUIT) or as determined from a combination of high-risk features (recurrent angina/ischemia at rest or at a low workload, heart failure, hemodynamic instability, worsening mitral regurgitation, high-risk stress test, sustained ventricular tachycardia, diabetes mellitus, prior CABG, PCI within 6 months, or left ventricular ejection fraction <0.40), can also be used to select the best treatment strategy.

11.4.2 Troponins in Nonischemic Clinical Conditions

Although the knowledge of cTns is based largely on studies in the ACS population, the tissue specificity of cTns has led to a new understanding of numerous pathological conditions in other disease processes such as heart failure, pulmonary embolism,

renal failure, hypertrophic cardiomyopathy, hypertension with or without left ventricular hypertrophy, severe anemia, strenuous exercise, sepsis, and chemotherapy-associated cardiac toxicity. The next sections discuss the use of cTn in some common clinical conditions. For an excellent summary of practical clinical considerations in the interpretation of troponin elevations, the reader is referred to the American College of Cardiology Foundation 2012 Expert Consensus Document [4].

11.4.2.1 Heart Failure

Depending on the thresholds used, troponin values are frequently abnormal in patients hospitalized for acute HF [10]. In the Acute Decompensated Heart Failure National Registry (ADHERE), approximately 75 % of patients hospitalized for acute decompensated HF (ADHF) had elevated cTn values (cTnI >0.4 ng/ml or cTnT >0.01 μg/l) [11]. When higher thresholds were considered, only 6.2 % of ADHF patients had elevated troponins (cTnI ≥1.0 ng/ml or cTnT ≥0.1 μg/l) [11]. In both acute and chronic HF, patients with elevated troponins have a higher risk of death or rehospitalization for HF than those without elevated troponins [4, 10].

Proposed mechanisms underlying cTn release are speculative and include increased wall stress, epicardial coronary artery disease, neurohormonal activation, inflammatory cytokines, oxidative stress, and altered calcium handling [10]. In any HF patient, cTn release may be multifactorial.

In some cases, it may be difficult to determine whether a patient is experiencing heart failure as a result of an AMI or as a primary heart failure event (ADHF). In patients with initially elevated troponins on hospital admission, repeat cTn assessment within 6–12 h is recommended to help determine whether the kinetics of the cTn changes and clinical course are more consistent with ACS or ADHF [10]. Given the increased sensitivity of newer cTn assays, repeat assessments could be made sooner (e.g., within 3–6 h).

In the ambulatory setting, chronic HF patients with persistently elevated cTn values should undergo an evaluation for ischemic heart disease, if not already conducted, and may benefit from more aggressive medical therapy [10].

Currently, the National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines state that using cTn testing in HF patients to identify those at increased risk outside the ACS setting is a Class IIb recommendation only [12]. These guidelines also state that routine biomarker testing in HF patients for risk stratification only is not indicated (Class III recommendation) [12].

11.4.2.2 Pulmonary Embolism

Pulmonary embolism is a common disease and can be fatal. Mortality within the first 2 weeks of the index event ranges from 2 % to 15 % [13].

Therefore, prompt diagnosis and risk stratification in the acute phase are necessary to optimize treatment.

In pulmonary embolism, venous thromboemboli in the pulmonary circulation cause an acute increase in pulmonary artery pressure and right ventricular afterload. The right ventricle dilates and becomes hypokinetic, leading to failure. In cases of extensive embolism, cardiac output decreases, and myocardial ischemia, syncope, hypotension, shock, and death can result [13].

A 2007 meta-analysis of 20 studies showed that 10–77 % (median 39 %) of subjects had troponin values that exceeded the normal cut point for the respective assay [4, 14]. Troponin release in pulmonary embolism is multifactorial and can occur from right ventricular dysfunction, tachycardia ("demand ischemia"), hypotension, and hypovolemia [13]. Patients with right ventricular dysfunction are more likely to demonstrate elevated troponin values, but troponin elevation can also be seen in patients without right ventricular dysfunction [4, 13]. The meta-analysis also showed that elevated troponin T or I levels in the setting of pulmonary embolism were associated with 30-day all-cause mortality (odds ratio [OR]: 5.24; 95 % confidence interval [CI], 3.28–8.38) [14].

In patients with massive pulmonary emboli and hemodynamic compromise with or without increased troponin values, thrombolytic therapy (intravenous alteplase, streptokinase, or urokinase) should be considered unless patients have contraindications to such therapy. Patients with massive centrally located thrombus may also benefit from surgical pulmonary embolectomy [4, 13].

11.4.2.3 Chronic Kidney Disease

In dialysis-dependent patients with end-stage renal disease (ESRD) or those with moderate to severe renal impairment and residual renal function, the pathophysiology of troponin release remains unclear [4]. In a 2005 meta-analysis, the rate of cTnT and cTnI values exceeding the normal cut point ranged from 12 % to 66 % and 0.4 % to 38 %, respectively [15]. In this meta-analysis, elevated cTnT (>0.1 ng/mL) was significantly associated with all-cause mortality (relative risk [RR]: 2.64; 95 % CI, 2.17–3.20) and cardiac death (RR: 2.55; 95 % CI, 1.93–3.37) [15]. In the 12 studies using troponin I, different assays and cut points were used, and pooling was problematic, but elevated cTnI was also associated with an increase in all-cause mortality (RR: 1.74; 95 % CI, 1.27–2.38).

ESRD patients more frequently have chronically elevated troponin levels. To distinguish a chronically elevated troponin level from an elevated troponin in the setting of ACS, the NACB Laboratory Medicine Practice Guidelines recommend using a ≥20 % increase in cTn in the 6–9 h after the index event to define AMI [16].

11.5 Areas Requiring Further Study

Although the 2007 and 2012 Universal Definitions of MI recommended the use of sex-specific cTn values, many of the conventional assays do not have sufficient sensitivity to detect differences by sex in the normal reference range and instead

rely on a single diagnostic threshold that may lead to underdiagnosis of MI in women. A high-sensitivity cTnI assay is being studied in the ongoing High-STEACS (High-Sensitivity Troponin in the Evolution of Patients with Acute Coronary Syndrome) trial. This trial uses a diagnostic threshold for MI of 16 ng/L in women and 34 ng/L in men, compared to the conventional cTn assay which uses a threshold of 50 ng/L for both sexes. This 26,000 patient study will contribute to an understanding of whether sex-specific cTn thresholds will result in better clinical outcomes.

In addition to sex-specific cTn thresholds, determination of thresholds to define PPMI in the PCI and CABG settings will need to be addressed in future updates to current definitions.

11.6 Concluding Remarks

Cardiac troponin (cTn) is one of the most widely used biomarkers in science and is both sensitive and specific for myocardial necrosis. Since 2000, cTn (I or T) has been recognized as the preferred biomarker for detecting myocardial necrosis. Although an elevated cTn is sensitive and specific for cardiac myonecrosis, it is not specific for MI (i.e., injury related to myocardial ischemia). A diagnosis of MI must always take into consideration the pretest probability of ACS as defined by risk factors, symptoms, laboratory and imaging results, and electrocardiographic changes. In the setting of an elevated cTn, ACS and other conditions that could be fatal if not recognized early (e.g., pulmonary embolus) should be excluded first so that these conditions can be appropriately managed.

Elevations of cTn due to myocardial injury can also be found in other conditions such as heart failure, pulmonary embolus, and renal failure. In general, cTn elevation, regardless of the etiology, conveys a worse clinical prognosis.

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Chapter 12
Natriuretic Peptides and Biomarkers in the Diagnosis of Heart Failure

Nicholas Phreaner, Kevin Shah, and Alan Maisel

Abstract Heart failure is common and difficult to diagnosis by history and physical exam alone. Natriuretic peptides (NPs) are synthesized and released in the setting of volume overload and ventricular wall stretch. They have an important physiologic role and are elevated in the setting of heart failure. B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are useful in both diagnosis and prognosis of heart failure. NPs should not be used in isolation and there are caveats to their interpretation. In the future, new biomarkers may be used in conjunction with NPs to aid in the treatment, prognosis, and diagnosis of heart failure. This chapter discusses the physiology of NPs, the role of BNP and NT-proBNP in the diagnosis of heart failure, the caveats to NP interpretation, and the emerging biomarkers in heart failure.

Keywords Heart failure • Diagnosis • Prognosis • Biomarkers • B-type natriuretic peptide • N-terminal pro-B-type natriuretic peptide

12.1 Introduction

Heart failure (HF) is a common diagnosis and a frequent cause for medical evaluation in clinic and emergency department (ED) settings. In 2010, the prevalence of heart failure in adult Americans was estimated at 5.1 million and is expected to increase by 25 % by the year 2030 [1, 2]. The diagnosis of HF is challenging due to the nonspecific presenting symptoms and the multiple comorbidities associated with HF. In addition, the prompt recognition of HF is vital to ensure appropriate management to reduce morbidity and mortality associated with this condition.

Over the last decade, natriuretic peptides have changed the way HF is diagnosed and have become important tools for the diagnosis and risk stratification of patients with heart failure in all heart failure guidelines. Biomarkers such as B-type natriuretic

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peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are frequently used in the evaluation of symptoms such as acute dyspnea, particularly in the absence of classic HF symptoms. Included within the composite of clinical judgment and consideration of comorbid conditions, the appropriate interpretation of natriuretic peptides is now crucial for the diagnosis of heart failure.

In this chapter, we discuss the physiology of natriuretic peptides and their use in the diagnosis of heart failure. In addition, we discuss the role of other biomarkers such as troponin, copeptin, mid-region pro-atrial natriuretic peptide (MR-proANP), mid-region pro-adrenomedullin (MR-proADM), ST2, galectin-3, growth differentiation factor 15 (GDF-15), procalcitonin, and matrix metalloproteinases (MMPs).

12.2 Physiology of Natriuretic Peptides

Natriuretic peptides (NPs) constitute a family of peptides with shared structure and function. The NP family consists of atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide (CNP). Common to all NPs are a conserved amino acid loop structure and natriuretic, diuretic, and vasorelaxant activity. NPs are secreted from the myocardium in response to increased intravascular volume and help regulate fluid homeostasis. Each NP is encoded by a unique gene and differs in their tissue-specific distribution and regulation of synthesis and release.

Atrial natriuretic peptide (ANP) was first isolated in 1984 after a discovery that an atrial extract produced potent natriuresis and vasodilation. As the name suggests, ANP is primarily synthesized in the atria. Minor triggers such as exercise can release previously synthesized ANP. CNP is primarily derived from vascular endothelium but can also be found in the central nervous system and kidneys [3]. Currently, the clinical utility of CNP in heart failure is limited.

BNP was discovered 4 years after ANP and has become the predominant NP used clinically. BNP was first isolated in porcine brain resulting in the original name: brain natriuretic peptide. However, we now know that BNP is primarily synthesized in cardiac ventricular myocytes, and the term B-type natriuretic peptide is now preferred. Unlike ANP, BNP is not stored to a large degree in the cardiac myocardium but rather is synthesized in response to ventricular wall stretch, dilation, or increased pressure from increased intravascular volume [4]. BNP is first synthesized as a preprohormone that is processed into the 108-amino-acid (aa) peptide, proBNP. ProBNP is further cleaved into the functionally inert 76 aa NT-proBNP and the biologically active 32 aa BNP (Fig. 12.1). NT-proBNP has a longer half-life compared to BNP (1–2 h vs 20 min). Due to the longer half-life, NT-proBNP is higher and fluctuates less than BNP when measured in the serum.

In peripheral organs, biologically active NPs bind to natriuretic peptide receptors (NPR-A, NPR-B, and NPR-C) to initiate a cGMP-dependent signaling cascade. NPR-C and neutral endopeptidase (NEP) work to clear NPs. The physiologic action of ANP and BNP is to counteract the renin-angiotensin-aldosterone system (RAAS) by causing vasodilation, natriuresis, and diuresis. In addition to suppression of

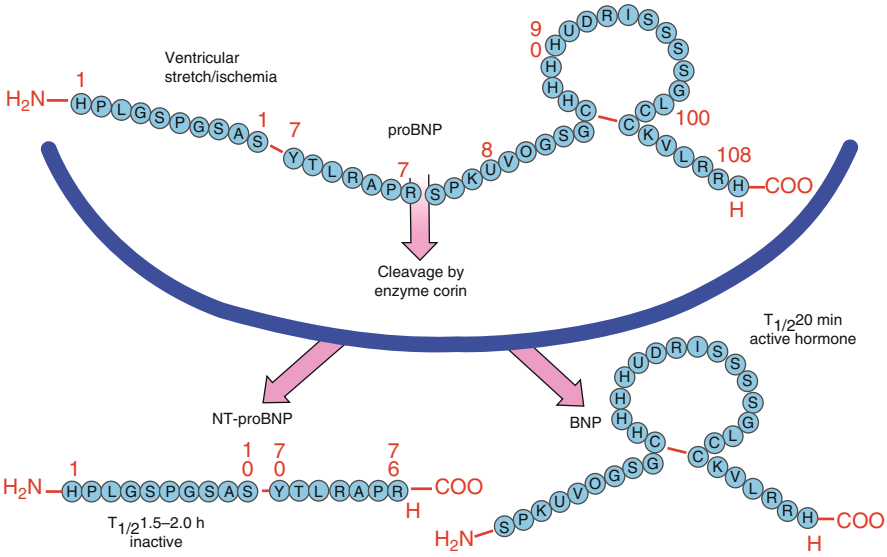


Fig. 12.1 Proteolytic processing of B-type natriuretic peptides (Reproduced from Motiwala and Januzzi [82], with permission from the Nature Publishing Group)

RAAS, ANP and BNP contribute to the inhibition of sympathetic overactivation [5]. Thus, natriuretic peptides have an important protective role in heart failure through their complex interactions with neurohormonal pathophysiology and the nervous, renal, cardiac, and vascular organ systems (Chap. 3).

12.3 Diagnosis of Heart Failure

Heart failure is a complex clinical syndrome that is the common end result of many different disease processes. Disorders of the myocardium, pericardium, valves, electrical rhythm, or great vessels can result in structural or functional impairments to the ventricle's ability to adequately fill with, or eject, blood. As the heart fails, regardless of etiology, decreased cardiac output results in neurohormonal changes that temporarily increase stroke volume. However, over time these neurohormonal changes can lead to volume overload and cardiac remodeling that ultimately results in disease progression. Decreased perfusion from low cardiac output and volume overload from elevated left ventricular pressures lead to the cardinal symptoms of heart failure: dyspnea, fatigue, and fluid retention.

Heart failure is considered a clinical diagnosis, and therefore careful physical exam and history are paramount to making an accurate diagnosis. Additional testing modalities such as chest radiography can also be used to augment a history and physical exam. However, the diagnosis of heart failure can be difficult for several

reasons including complex patient population, as well as nonspecific symptomology and exam findings. Careful clinical exam and history can often be complicated in older patients with multiple comorbid conditions. Dyspnea, lower extremity edema, and fatigue can be signs and symptoms of heart failure but are also common in patients with renal disease, chronic lung disease, or obesity. In addition, physical exam findings of increased jugular venous distention or a third heart sound are specific but not sensitive, i.e., the absence does not rule out heart failure. Similarly, chest radiography lacks sensitivity for heart failure, and the specificity of pulmonary edema is limited in the setting of other respiratory illnesses. It is not surprising that diagnostic uncertainty can reach 50 % in patients presenting to the ED with dyspnea [6]. For this reason, there is an important role for biomarkers such as natriuretic peptides to provide adjunctive data to aid in the diagnosis of heart failure (Chap. 1).

12.4 Role of Natriuretic Peptides in the Diagnosis of Heart Failure

Heart failure causes pathologic ventricular wall stretch and results in synthesis and eventual release of the biologically active BNP and inert NT-proBNP [4]. Because the conditions for synthesis and release of NPs are common in heart failure but not in other etiologies of dyspnea, fatigue, or volume overload, the diagnostic value of BNP and NT-proBNP was quickly realized after their discovery. The use of NPs has rapidly been incorporated into clinical practice. The testing of NPs is quick and easily accessible in most emergency, inpatient, and outpatient settings. A potential downside to easy accessibility is that they are often ordered outside of their intended use. A careful understanding of the caveats of NP testing and how to interrupt NPs within the composite of clinical judgment is paramount to maximizing their utility in the diagnosis of heart failure.

The assay for BNP became available prior to NT-proBNP and quickly proved to be useful in establishing and excluding the diagnosis of heart failure. In 2002, the multicenter, multinational Breathing Not Properly trial included 1,586 patients who presented to the ED with dyspnea [7]. BNP values were measured in every patient and blinded to treating physicians. Independent cardiologists, who were also blinded to the BNP results, established the "gold standard" diagnosis. A BNP cutoff of 100 pg/mL was 76 % specific and 90 % sensitive for the diagnosis of heart failure. Compared to components of the history, physical exam, and chest radiography, BNP was the strongest independent predictor of heart failure. In addition, the value of BNP correlated with the severity of heart failure as defined by the New York Heart Association (NYHA) class.

BNP is a quantitative marker of heart failure and is best interpreted along a continuum. When the BNP is low (<100 pg/mL), the clinical presentation is unlikely to be due to heart failure. Using a cutoff BNP value of 50 pg/mL, the negative predictive value of BNP is 96 %. Thus, a low BNP value is useful to exclude the

diagnosis of heart failure in the evaluation of dyspnea. In addition to being useful to "rule out" heart failure from the differential diagnosis, BNP is useful in establishing the diagnosis of heart failure. NP values are significantly higher in patients that present with symptoms due to heart failure as compared to other noncardiac etiologies (Fig. 12.2) [8].

The higher the value of BNP, the more likely the diagnosis is heart failure. Using a BNP value of >100 pg/mL, the specificity is 76 %. The ability to "rule in" heart failure increases with the value of BNP. A BNP value >400 pg/mL suggests that the patient's symptoms are due to heart failure with a specificity that exceeds 90 %. Using a two-cutoff approach (BNP < 100 pg/mL to exclude heart failure and BNP > 400 pg/mL to establish the diagnosis of heart failure), BNP is an accurate biomarker for heart failure. However, as previously noted, this should not be used in isolation. A two-cutoff approach establishes a "gray zone" (BNP values between 100 pg/mL and 400 pg/mL) where further testing and consideration of NP caveats are especially important. Overall, diagnostic accuracy for heart failure is improved when BNP measurement is used in combination with the composite of clinical judgment [9, 10].

Like BNP, NT-proBNP is a quantitative marker and is elevated in heart failure. BNP and NT-proBNP values correlate with each other but are not interchangeable. NT-proBNP values are much higher than BNP, mostly due to a longer half-life. In the ProBNP Investigation of Dyspnea in the ED (PRIDE) study, NT-proBNP was measured in 600 patients with dyspnea. NT-proBNP was highly sensitive and specific for the diagnosis of heart failure. A low NT-proBNP value (<300 pg/mL) can be used to exclude the diagnosis of heart failure, whereas an age-dependent

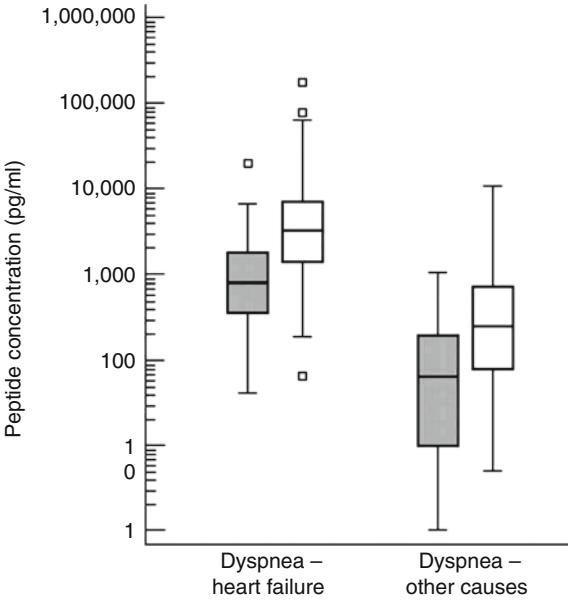
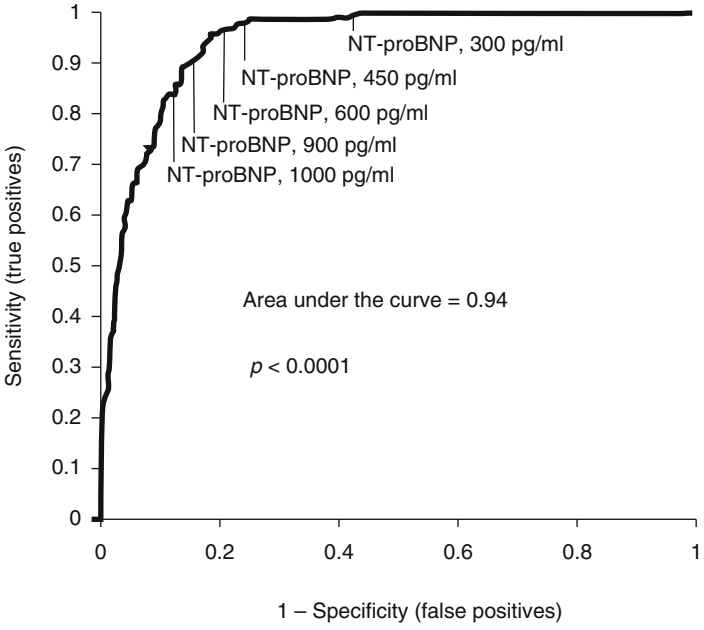


Fig. 12.2 Box and whisker plots of BNP (*gray*) and NT-proBNP (*white*) in patients with dyspnea attributable to heart failure as compared to dyspnea attributable to noncardiac etiologies. The central box spans from the lower to the upper quartile, the middle line is the median, and the whiskers extend from the minimum to the maximum concentrates (Reproduced and adapted from reference [8] with permission from the British Cardiovascular Society and BMJ)

cutoff was used to establish the diagnosis of heart failure. High NT-proBNP, >450, >900, and >1,800 pg/mL in patients aged <50, 50–75, and >75 years old, is highly specific for a diagnosis of heart failure (Fig. 12.3) [11, 12].

Both BNP and NT-proBNP are highly sensitive and specific for heart failure but are best utilized in conjunction with interpretation of all available clinical data including comprehensive history, physical exam, and other adjunctive testing. This is especially true when interpreting NP values in the "gray zone" or within the context of comorbid conditions that can affect the value of NPs. When used within the composite of clinical judgment, BNP and NT-proBNP improve diagnostic accuracy, decrease length of stay, and reduce total cost of treatment [10, 13].



Cut point	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
300 pg/ml	99 %	68 %	62 %	99 %	79 %
450 pg/ml	98 %	76 %	68 %	99 %	83 %
600 pg/ml	96 %	81 %	73 %	97 %	86 %
900 pg/ml	90 %	85 %	76 %	94 %	87 %
1,000 pg/ml	87 %	86 %	78 %	91 %	87 %

Fig. 12.3 Receiver operating characteristic (*ROC*) curve for NT-proBNP in evaluation of patients with dyspnea in the ED. Additional statistical information for various cutoffs are presented below the ROC curve (Reproduced from reference [11] with permission from Elsevier)

12.5 Role of Natriuretic Peptides in Prognosis and Treatment

Heart failure is difficult to diagnose clinically due to nonspecific symptoms and physical exam findings. Similarly, establishing the prognosis and the severity of heart failure at the time of presentation is also difficult using clinical parameters alone. Inpatient heart failure treatment is frequently necessary, and high readmission rates contribute significant cost to the health care system. In addition to being powerful tools in the diagnosis of heart failure, NPs have a role in establishing prognosis and monitoring response to heart failure treatment.

12.5.1 Prognosis

In the REDHOT trial, BNP was predictive of future outcomes in patients who were evaluated for dyspnea and discharged from the ED. Those with a BNP value >400 pg/mL had increased mortality at 90 days compared to patients with BNP < 400 pg/mL [14]. In patients admitted to the hospital, the absolute value of BNP and NT-proBNP and whether these values increased or decreased from the time of admission were predictive of future readmission and mortality [15, 16]. In addition, NPs have prognostic utility in chronic heart failure. In an evaluation of Valsartan Heart Failure Trial (Val-HeFT) comprising 4,300 outpatients with chronic HF, patients with the greatest increase in BNP despite therapy had the highest morbidity and mortality [17]. Used as prognostic markers, NPs may aid in the triage of patients with heart failure and in determining which patients may benefit from closer monitoring or more aggressive therapy.

12.5.2 Treatment

In acute heart failure, NP levels can decline quickly in response to treatment with diuretics and optimization of volume status. In addition, more gradual reductions occur with neurohormonal blockade. Long-term treatment with beta-blockers, aldosterone receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) lowers NP levels in chronic heart failure. Several studies have evaluated the utility of NPs for medication titration and monitoring response to treatment in the outpatient setting.

In the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial, 220 outpatients with chronic heart failure were randomized to medical care by current guidelines or a treatment goal of decreasing BNP < 100 pg/mL. Patients in the BNP-guided treatment group had less CHF-related mortality and hospitalizations, mainly due to an increase in ACE inhibitor and beta-blocker dosages [18]. Improved mortality at 1 year was also seen in the NT-proBNP-Assisted

Treatment To Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) trial. This trial included HF patients with persevered EF and HF patients with reduced EF. Mortality benefit was seen in patients <75 years who had treatment guided by NT-proBNP levels compared to those treated following prescribed clinical guidelines or with usual care [19]. This benefit with biomarker-guided care was not seen in HF patients over age 75 years. Similarly, a lack of mortality benefit with NP-guided therapy in patients >75 years of age was seen in the TIME-CHF study [20].

In the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study, 151 patients with heart failure with reduced ejection fraction were randomized to standard of care or treatment guided by NT-proBNP with goal NT-proBNP ≤ 1,000 pg/mL. Both patients <75 and ≥75 years of age had decreased cardiovascular events at 1-year post-randomization [21]. This result was driven by decreased hospitalization, where there was >50 % reduction in hospitalizations for acutely decompensated heart failure. There was no statistically significant effect on cardiovascular mortality. In addition to decreasing hospitalizations, the PROTECT study showed significant improvement in quality of life measured by the Minnesota Living with HF Questionnaires and greater improvements in echocardiographic parameters of cardiac structure and function in patients' treatment with NT-proBNP-guided therapy compared to standard of care [22, 23].

12.6 Caveats to the Use of Natriuretic Peptides

NPs are effective biomarkers in both establishing and excluding the diagnosis of heart failure. However, they are not perfect diagnostic tools and must be used within the context of clinical judgment. An understanding of the caveats of NPs and how to interpret their values within the context of comorbid medical conditions is paramount to the clinical utility of BNP and NT-proBNP. This is especially true when evaluating patients that have NP values that fall into the "gray zone" (BNP values between 100 and 400 pg/mL or NT-proBNP values between 300 and 450–1,800 pg/mL for ages <50, 50–75, >75 years old).

12.6.1 Heart Failure with Preserved Ejection Fraction

Heart failure with preserved ejection fraction (HFpEF), also called diastolic heart failure, is the clinical diagnosis of heart failure in the presence of a normal ejection fraction (EF>50 %). Patients with HFpEF make up approximately 50 % of all patients with heart failure, and this percentage may be increasing due to change in relative prevalence of various risk factors for heart failure such as obesity [24, 25]. The diagnosis is made clinically through interpretation of signs and symptoms and aided by diagnostic studies, such as an echocardiogram showing the presence of diastolic dysfunction.

BNP and NT-proBNP are sensitive and specific markers for heart failure in patients with preserved ejection fraction. Further analysis from the Breathing Not Properly study showed that BNP was markedly elevated in patients that presented to the ED with dyspnea due to HFpEF as compared to noncardiac etiologies [26]. In addition, the degree of elevation in the value of NPs correlates to the severity of heart failure symptoms by NYHA class and to the severity of objective markers of diastolic dysfunction on echocardiogram [26–28].

Though NP measurement is useful in the diagnosis of HFpEF, NPs are elevated to a lesser extent compared to patients with systolic dysfunction. In the Breathing Not Properly study, mean BNP was 413 and 821 pg/mL in HFpEF and heart failure with reduced EF, respectively [26]. Interpretation of NPs in patients with known preserved systolic function must take into account that NP levels are only moderately elevated in HFpEF compared to higher NP values seen in patients with heart failure with reduced EF. For establishing the diagnosis of HFpEF in the outpatient setting, lower cutoff values for BNP (>200 pg/mL) and NT-proBNP (>300 pg/mL) are suggested. For excluding the diagnosis of heart failure, cutoff values of BNP (<100 pg/mL) and NT-proBNP (<120 pg/mL) are used.

12.6.2 Obesity

Obesity is a known risk factor for cardiovascular events including heart failure [29]. The diagnosis of heart failure in obese patients can be particularly challenging as the interpretation of chest radiography and echocardiography and examination of jugular venous distention can be limited in obese patients. For this reason, the use of NPs for the diagnosis of heart failure in obese patients is appealing. However, an understanding of the relationship between obesity and NPs is essential as there is an inverse association between body mass index (BMI) and NPs in patients with heart failure.

Both BNP and NT-proBNP are lower in obese subjects (BMI >30) as compared to overweight (BMI 25–29.9) and lean (BMI < 25) subjects with heart failure [30–32]. The reason behind the decreased levels is not entirely understood as NPs have a complex relationship with adiposity and lipolysis. Although NP clearance and receptor expression are altered in obesity, NPs are most likely lower in obese patients due to suppression of synthesis and release of NPs from cardiac myocytes [33, 34]. Due to lower BNP levels in obese patients, cutoffs of 170 pg/mL for lean subjects, 110 pg/mL for overweight/obese subjects, and 54 pg/mL in severely/morbidity obese patients are used to maintain a sensitivity of 90 % [35]. Despite lower concentrations of NT-proBNP in overweight and obese patients, NT-proBNP retains it diagnostic capacity across all BMI categories [36]. No adjustment to the previously mentioned NT-proBNP cutoff thresholds is recommended [34]. Overall, due to the inverse relationship between BMI and NPs, it is important to consider obesity when interpreting NP values in the diagnosis of heart failure, especially when these values are in the “gray zone.”

12.6.3 Renal Dysfunction

Heart failure and chronic kidney disease (CKD) commonly coexist. CKD, cardiovascular disease, and heart failure share many of the same risk factors. Approximately 40 % of patients with heart failure have CKD as defined by serum creatinine ≥1.5 mg/dL or estimated glomerular filtration rate (GFR) <60 mL/min/1.7 m^2 [37]. Uncontrolled heart failure can cause progression of renal failure through a variety of mechanisms, and, conversely, renal failure can lead to the progression or development of heart failure [38]. In addition, use of efficacious therapies for heart failure, such as ACE inhibitors or aldosterone receptor antagonists (Chaps. 36 and 38), can be restricted by the presence of renal dysfunction [39]. The physiologic and pathologic interactions between the cardiac and renal systems are intricate, and, likewise, the relationship between NPs and renal dysfunction is complex.

BNP and NT-proBNP concentrations are increased in the setting of renal dysfunction. Patients with CKD tend to have increased intravascular volume, elevated pressures, and increased ventricular mass, which can all lead to physiologic elevations in NPs. In addition, decreased renal clearance of NPR-C and NEP may contribute to elevated levels. Because the majority of BNP is not renally cleared, the mechanism of elevated BNP in renal dysfunction is likely multifactorial and not simply decreased passive renal clearance [40]. The Breathing Not Properly study found a correlation between GFR and BNP and suggested a higher cutoff was reasonable for patients with GFR < 60 mL/min/1.7 m^2 [41]. Renal dysfunction can possibly explain why some patients have mildly elevated BNP values in the "gray zone" in the absence of heart failure. This further highlights the importance of using BNP within the composite of clinical judgment and not in isolation.

NT-proBNP, though not cleared by NPR-C and NEP, may or may not be more influenced by renal dysfunction than BNP [42]. Due to the association between NT-proBNP and renal dysfunction, the analysis from the PRIDE study suggested a higher cutoff of 1,200 pg/mL. This adjusted cutoff was sensitive and specific for the diagnosis of heart failure in patients with GFR < 60 mL/min/1.7 m^2 [43]. Still, NT-proBNP is a strong predictor of 60-day mortality regardless of renal dysfunction [43, 44].

12.6.4 Age and Gender

BNP and NT-proBNP increase with age [11, 45]. This may be due to decreased renal function, but like other endogenous hormones, age may alter production, secretion, or metabolism of NPs [46]. For reference, most young and healthy asymptomatic patients have a very low BNP value, usually less than 20–25 pg/mL [45]. Whereas age stratification is used in establishing the diagnosis of heart failure with NT-proBNP, the same is not suggested for BNP [47].

Healthy females on average have higher NPs than males at all ages [46, 47]. This may be due to increased estrogen or decreased testosterone. However, women with heart failure are more likely to have preserved ejection fraction, which is associated

with lower NP values, compared to men with heart failure. Therefore, women with heart failure may have lower NP values than men with heart failure, although this difference has been found to be small [47, 48]. Overall, NT-proBNP and BNP are accurate biomarkers for the diagnosis of heart failure regardless of gender.

12.6.5 Previous Diagnosis of Heart Failure

NPs are elevated in patients with chronic heart failure. In the Breathing Not Properly study, patients with a history of heart failure that presented with dyspnea caused by a noncardiac etiology had an intermediate BNP, compared to those without heart failure and patients with acute exacerbation of heart failure [7]. Patients with chronic heart failure can have an increased BNP during acute exacerbations. In addition, treatment with diuretics, beta-blockers, and ACE inhibitors can decrease BNP over time, however, not always back to a "normal" level. It may be useful to interpret BNP and NT-proBNP in comparison to a "dry" level in patients with chronic heart failure. A "dry" NP, measured when a patient is euvolemic and asymptomatic, can be used as an individualized baseline to judge whether symptoms of dyspnea or fatigue are due to an acute exacerbation of chronic heart failure or due to other, noncardiac, etiologies (Fig. 12.4)

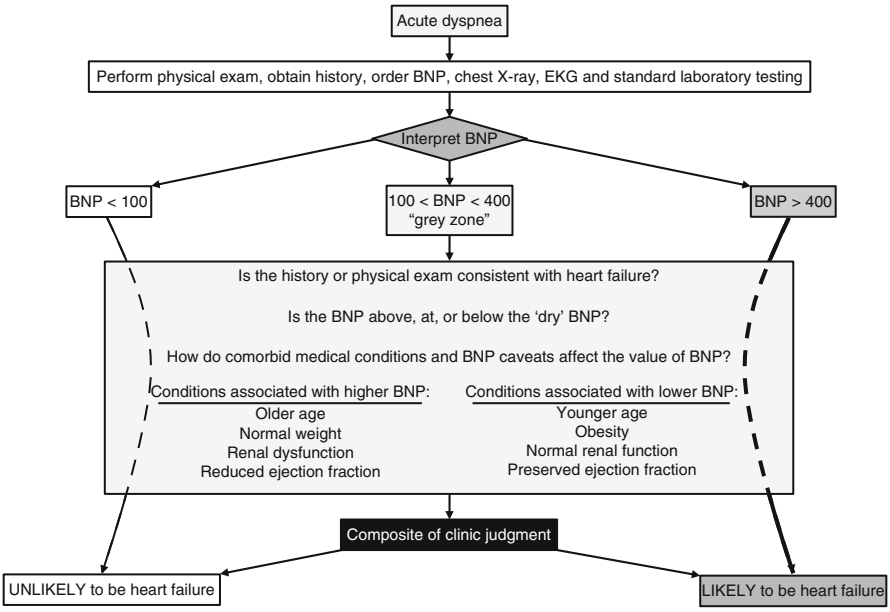


Fig. 12.4 Algorithm for the evaluation of acute dyspnea using BNP. BNP cannot be used in isolation to make the diagnosis of heart failure. Interpreting BNP in the context of comorbid medical conditions and knowledge of the caveats of BNP measurement is paramount to the accurate diagnosis of heart failure. BNP values are in pg/mL

12.7 Emerging Biomarkers in Heart Failure

In recent years, several new biomarkers have been studied as diagnostic and prognostic markers for heart failure. In the future, these additional biomarkers may be useful in the diagnosis of heart failure when used with BNP or NT-proBNP, particularly in patients that fall within the "gray zone." In addition, biomarkers to help establish prognosis could be used for the triage of patients in the ED or in monitoring response to therapy.

12.7.1 Troponin

Troponin is well established as a marker of myocardial injury in acute myocardial infarction. Troponin T or troponin I is frequently ordered in patients admitted with acute heart failure. In a study of 84,872 patients admitted with decompensated heart failure from the ADHERE, a positive troponin was associated with lower systolic blood pressure, lower ejection fraction, and higher in-hospital mortality [49]. Although troponin is not useful in the diagnosis of heart failure, it has independent prognostic value in predicting in-hospital mortality in heart failure (Chaps. 10 and 11).

12.7.2 Copeptin

Natriuretic peptides are one of several neurohormonal systems activated by heart failure. Arginine vasopressin (AVP), also termed antidiuretic hormone, is released by the hypothalamus, promotes renal water conservation, and has vasoactive properties. AVP is difficult to measure in serum because it is unstable and rapidly cleared. Copeptin is the C-terminal portion of provasopressin. It is more stable and easier to measure in serum than AVP while still secreted in equal amounts to AVP [50].

Copeptin is elevated in multiple conditions, including sepsis and hemorrhagic shock [51]. Used with NT-proBNP, copeptin is a good predictor of adverse events after acute myocardial infarction [52]. Although copeptin has limited diagnostic utility, it may be useful in the future as a prognostic marker for heart failure. Additionally, copeptin increases with severity of heart failure symptoms by NYHA class and may be better than BNP and NT-proBNP in heart failure when used as a prognostic marker for adverse events including mortality [53, 54].

12.7.3 MR-proANP

Mid-region pro-atrial natriuretic peptide (MR-proANP) is a stable fragment of the ANP propeptide and mirrors the release of the biologically active unstable ANP. MR-proANP is released in response to similar conditions as BNP and

NT-proBNP. In the Biomarkers in Acute Heart Failure (BACH) trial, MR-proANP was highly sensitive and specific for the diagnosis of heart failure and performed similar to both BNP and NT-proBNP [55]. In addition to diagnostic utility, MR-proANP may have prognostic value as the change in MR-proANP over time was shown to be a predictor of mortality [56]. In the future, MR-proANP may be used as an adjunctive diagnostic study for subgroups where diagnosis is difficult, such as patients with obesity, with renal failure, or with "gray zone" levels of BNP.

12.7.4 MR-proADM

Adrenomedullin (ADM) is a peptide hormone expressed by many tissues and organ systems. It has natriuretic, vasodilatory, and potent hypotensive effects. ADM is elevated in patients with chronic heart failure and increases with disease severity [57, 58]. However, its clinical utility has been limited due to biologic instability. Recently, immunoassays to detect the stable prohormone fragments of ADM have been developed. Mid-region pro-adrenomedullin (MR-proADM) demonstrated prognostic potential in the BACH trial. In 568 patients with acute heart failure, MR-proADM was superior to both BNP and NT-proBNP at predicting mortality within 14 days. In addition, when used with BNP and NT-proBNP, MR-proADM had additive incremental predictive value for 90-day mortality [56]. Although more research must be done, MR-proADM could be a useful alternative to NPs for prognosis and risk stratification.

12.7.5 ST2

The ST2 gene, a member of the interleukin-1 receptor family, is markedly upregulated in cardiac myocytes and fibroblasts subjected to mechanical strain [59]. The functional ligand of ST2 is interleukin-33 (IL-33), and together they play a role in the fibrotic response to myocardial injury [60]. The ST2 gene is also upregulated in an experimental model of heart failure, and the soluble form of ST2 is increased in the serum of patients after myocardial infarction [59]. Results from the PRIDE study demonstrated that ST2 is elevated in patients with heart failure, but it was not as useful as NT-proBNP in the diagnosis of heart failure [61]. The likely true role for ST2 is to guide therapy of cardiac medications in chronic heart failure. More recent studies have demonstrated that ST2 decreases in response to treating heart failure, particularly with beta-blockers, and in the future, ST2 may be used to predict which patients would have greater benefit from high-dose beta-blocker therapy [62, 63]. It appears that the future of ST2 is bright for this indication, especially when used in conjunction with NPs.

12.7.6 Galectin-3

Cardiac fibrosis is involved in cardiac remodeling and is an important contributor to the pathophysiology of both left ventricular systolic and diastolic dysfunction. Galectin-3 (Gal-3) is a beta-galactoside-binding lectin that appears to be a mediator of cardiac fibrosis [64]. Higher concentrations of Gal-3 are seen in heart failure, and Gal-3 may be a useful prognostic marker, particularly in HFpEF [65, 66]. In addition, higher concentrations of Gal-3 are associated with increased risk of developing new-onset heart failure and may be useful in the future in identifying early cardiac fibrosis in asymptomatic patients [67].

12.7.7 GDF-15

Growth differentiation factor 15 (GDF-15) is a cytokine and a member of the growth factor family. It is secreted from activated macrophages by stimulation from smooth muscle cells, cytokines, and adipocytes [68–72]. Expression from myocytes specifically is enhanced in the setting of ischemia and mechanical stress. Increased serum levels of this biomarker are associated with developing HF in healthy elderly individuals [73]. Additionally, in patients with chronic HF with reduced EF, GDF-15 corresponds to disease severity by NYHA class and was associated with overall prognosis [74]. This relationship has proven stronger in those with HFpEF over HF with reduced EF, further underlying the potential to be a marker of myocardial remodeling, stiffness, and potentially diastolic dysfunction [75]. GDF-15 may serve as a complementary fibrosis marker for HF given these clinical relationships.

12.7.8 Procalcitonin

Procalcitonin (PCT) is a precursor to the hormone calcitonin. Circulating amounts of PCT are elevated in severe bacterial infections but remain fairly low in viral infections and nonspecific inflammatory conditions [76]. While PCT is not organ specific, it has been used successfully to diagnose and guide antibiotic treatment of lower respiratory tract infections, including pneumonia [77, 78]. Differentiating pneumonia and heart failure can be challenging in a patient that presents with dyspnea. In addition, a superimposed pneumonia may be difficult to detect in the setting of heart failure due to the presence of cardiogenic pulmonary edema. PCT is an accurate diagnostic marker for pneumonia even in the setting of heart failure and may aid in the decision to administer antibiotic therapy [79]. In the future, PCT may be used in the evaluation of patients with suspected pneumonia in the setting where heart failure is also a possibility.

12.7.9 Remodeling Biomarkers

Serum proteins involved in cardiac remodeling after ischemic events and long-standing heart failure are another evolving area in the realm of heart failure. Extracellular matrix (ECM) markers, including collagen and matrix metalloproteinases (MMPs), are involved in cardiac turnover. MMPs are endopeptidases that cleave proteins and modulate the outcome of various pathological processes including MI, atherosclerosis, and congestive heart failure. The effect of upregulation of MMPs includes worsening mechanical stiffness, disorganized contraction, and tissue hypoxia. This biomarker has been shown in clinical trials to correlate with acute-phase reactants and greater dysfunction following myocardial infarction [80, 81]. Thus, analysis of MMPs may provide further insight into diastolic heart failure as well as establish which patients have increased collagen turnover and are more likely to have future progression of their HF.

12.8 Concluding Remarks

Heart failure can be a difficult diagnosis to make clinically. NPs are powerful tools for establishing and excluding the diagnosis of heart failure, determining prognosis, and monitoring response to heart failure therapy. Biomarkers should not be used in isolation to establish the diagnosis of HF, and knowledge of the caveats to BNP and NT-proBNP interpretation is important to maximize their clinical utility. Several new biomarkers have become available, and, soon, a more sophisticated and comprehensive multi-biomarker strategy will aid in the diagnosis, prognosis, and therapy titration in HF. In the future, standard of care will likely include measuring BNP or NT-proBNP on admission, serially during hospitalization, and on discharge to establish response to therapy, prognosis, and a "dry" BNP level to help guide outpatient management. Biomarkers such as MR-proANP may aid in the diagnosis of HF in subgroups where the diagnosis is difficult. Markers of cardiac fibrosis and cardiac remodeling, such as ST2, Gal-3, GDF-15, and MMPs, may establish the presences of early cardiac fibrosis prior to the clinical diagnosis of HF and predict which patients would have greater benefit from earlier or more aggressive medical management. A patient in the future will likely also have troponin, copeptin, or MR-proADM drawn to provide additional prognostic information to aid in triage and risk stratification. Altogether, the future is bright for biomarkers in heart failure.

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Chapter 13
MicroRNAs in Cardiovascular Disease: From Pathogenesis to Treatment

Ioana Barb, Britta Vogel, Hugo A. Katus, and Benjamin Meder

Abstract Cardiovascular diseases are among the major causes of morbidity and mortality worldwide. Currently, considerable effort is made to intensify preventive measures, refine diagnostic testing, and advance therapeutic strategies. In this context, miRNAs have emerged as a new class of key regulators involved in the pathogenesis of many cardiovascular disorders, entailing a deep scientific interest in assessing their biomedical potential. Numerous studies identified miRNA signatures that correlate with specific cardiovascular conditions, hereby emphasizing their potential as molecular biomarkers. In the therapeutic setting, modulations of miRNA expression and function in experimental models of cardiac hypertrophy and heart failure are promising approaches. The encouraging results of these proof-of-concept studies and first successful clinical trials in humans point to a bright future for miRNAs in cardiovascular medicine.

Keywords MicroRNA (MiRNA) • Biomarker • Therapeutics • Cardiac hypertrophy • Heart failure • Gene expression

13.1 Introduction

miRNAs act as posttranslational regulators of gene expression by interacting with their mRNA targets, either leading to subsequent inhibition of protein translation or mRNA degradation [1]. Interestingly, a single miRNA may affect multiple mRNAs, while one given mRNA may carry binding sites for numerous miRNAs. Furthermore,

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sets of related miRNAs can interfere at different levels of the same signaling pathway. Recent findings suggest that miRNAs can also interact with other noncoding RNA species, e.g., long noncoding RNAs (lncRNAs). LncRNAs may functionally regulate miRNAs by competing for the same mRNA binding site, thus increasing stability of that particular mRNA, or by acting as a decoy that binds and sequesters miRNAs, hence reducing the amount of available miRNAs [2, 3]. Such multidimensional interactions, which can be fine-tuned in response to a broad range of stimuli, create a complex regulatory network for a variety of cellular processes. Although the release mechanisms of miRNAs are only partly understood, it is known that they can transit between different cells and tissues and might therefore play a crucial role in cell-to-cell communication [4]. Consequently, endogenous miRNAs can be found in different blood components, for instance, in circulating cells, as well as in plasma and serum, where they are usually bound to proteins or lipoprotein complexes or packed in microvesicles, exosomes, and apoptotic bodies [5].

An increasing body of evidence supports the idea of miRNAs serving as a therapeutical target (Chap. 14). A broad range of cardiovascular diseases originates from the common feature of cellular response to pathological stimuli. These cellular responses often include unusual cellular growth and consecutive hypertrophy or cardiomyocyte loss with compensatory repair mechanisms such as fibrotic remodeling. A large variety of studies indicate that such repair mechanisms evoke specific miRNA dysregulations, resulting in alteration of gene expression and hence driving cardiac pathology. The possibility of targeting these nodal points in vivo, in the case of miRNAs offered by antisense technologies, has driven the aspirations for miRNAs to become a new therapeutical option in the near future. Since miRNAs target multiple mRNA molecules at the same time, thereby influencing the expression of numerous genes involved in the same biological pathway, they are assumed to have a profound influence on endpoint cellular effects. The main focus of the first proof-of-principle studies was to manipulate a certain disease-associated miRNA and, thus, change the underlying pathological miRNA profile back to a nearly normal, physiological state. In different subsets of animal models, in vivo delivery of chemically altered miRNA modifiers was successfully used to assess therapeutic effects in a preclinical setting [6].

Even more refined than therapeutic approaches are diagnostic biomarkers based on miRNAs. Over the past few years, the human miRNome has been shown to (falsely) respond to a variety of stimuli, hereby promoting disease onset and progression. Given the fact that these changes in miRNA expression profiles are specific to certain disease entities and molecular disruptions generally precede structural and functional changes, miRNA signatures emerged as promising candidates for the diagnostic workup of cardiovascular disorders. Since miRNAs are easily accessible in various body fluids (e.g., whole blood, serum, plasma, or saliva) and are extraordinary stable analytes on long-term storage and several freeze-thaw cycles, they meet important pre-analytical criteria of noninvasive biomarkers [5]. For a broad range of cardiovascular diseases, such as myocardial infarction [7], heart failure [8–10], coronary artery disease [11–16], and essential hypertension [17], miRNA patterns with high diagnostic value have been identified.

MiRNAs regulate gene expression by pairing to target mRNAs, thus inducing translational repression. Novel findings indicate an orchestrated coregulation with long noncoding RNAs. Since its discovery, this small RNA species has opened new frontiers in cardiovascular medicine.

13.2 Technologies for miRNA Profiling and Manipulation

The small size, the low abundance, and the sequence conservation between miRNAs have made miRNA profiling in biosamples technically challenging. Several technologies were developed and successfully implemented to measure their expression levels for diagnostic purposes. The microarray technology has been proven a valuable tool for high-throughput analysis since it allows assessment of expression profiles of numerous miRNAs within one single experiment [18]. The quantitative reverse transcription polymerase chain reaction (qRT-PCR), on the other hand, facilitates the detection of even extremely low amounts of total RNA [19]. Recently, next-generation sequencing (NGS) has profoundly changed the field of biomarker development. NGS has been successfully used for miRNA profiling in various tissues as well as different biofluids, such as whole blood, serum, urine, or cerebrospinal fluid [20–22]. The miRNA data generated by NGS is highly reproducible when compared with gold standard quantitative real-time PCR [23]. But apart from all this, NGS also offers the possibility to discover new miRNAs or other small RNA species associated with the disease investigated.

The therapeutic application of miRNAs is done by using either miRNA mimicry or antisense technologies, which rely on two main principles: overexpression and inhibition of specific miRNAs. Chemically altered oligonucleotides have been successfully used in gain-/loss-of-function studies to prove the functions of miRNAs in different animal models of cardiovascular disease. Generally, miRNA mimics aim to raise the expression level of pathologically downregulated miRNAs, whereas miRNA inhibitors reduce the activity of upregulated, disease-driving miRNAs. Due to considerable design and delivery challenges, miRNA overexpression is still more challenging compared to antisense technology. At present, adenoviral vectors are used for the delivery of miRNA mimics to ensure continuous expression of the miRNA construct. The availability of numerous different viral serotypes and their preferential tropism towards certain tissues in combination with distinct gene promoters may facilitate tissue-specific delivery [24]. Antisense sequences require various chemical modifications in order to enhance cellular uptake, to increase their resistance towards nucleases, and to improve their binding affinity [25]. Inhibitors of miRNA, known as antagomirs, are small, synthetic RNAs that complementarily bind to the miRNA of interest with the aim of silencing their target in vivo. Antagomirs are linked to cholesterol entities via a

2′-O-methyl (2′-OMe) group and several phosphorothioate moieties to confer better cellular uptake, higher stability, and improved protein-binding properties. Other chemistries make use of several unconjugated phosphorothioate antisense molecules with different 2′-sugar modifications (e.g., 2′-OMe, 2′-MOE, 2′-F, LNA) [25, 26]. Furthermore, locked nucleic acids (LNA) are oligonucleotides (15–16 nucleotide in length) designed to target the 5′ region of a specific miRNA in a highly affine interaction resulting in a thermodynamically strong duplex configuration [27]. Some LNA-modified inhibitors, also known as tiny 8-mer oligonucleotides, have been developed to target the seed region of a specific miRNA only [28]. Since different miRNA family members of the same miRNA family generally contain the same seed region but differing 3′ regions, they can all be targeted by one single 8-mer tiny LNA. Furthermore, concepts using decoy or "sponge" methods described by Ebert and colleagues [29] offer the advantage of a continuous inhibition of miRNA function in cell lines and transgenic model organisms. The mRNA sponge sequesters complementary miRNAs, thus rescuing endogenous targets from suppression or degradation.

Regardless of the underlying chemistry, all therapeutic agents must fulfill certain safety criteria ensuring that they do not harm the treated individual. One main problem associated with miRNA-based therapies are off-target effects that arise especially after systemic delivery. But also with site-specific miRNA delivery (i.e., cardiac or intracoronary injection), unwanted effects might occur, e.g., because the miRNA analog unintentionally targets additional genes, thus initiating unexpected changes in gene expression. As an example, Grueter et al. [30] found that their therapeutic agent, aimed at inhibiting the cardiac-specific miR-208a, also inadvertently prevented the development of metabolic syndrome in mice that received a high-fat diet, by regulating a set of transcription factors involved in metabolic control. A representative of the new miRNA-based class of drugs, Miravirsen, is currently undergoing clinical trial testing in patients with hepatitis C [31]. Miravirsen, an antisense inhibitor of miR-122, reduces the stability and propagation of the hepatitis C virus by suppressing the interaction between the viral genome and miR-122, a liver-specific miRNA. As a side effect, Miravirsen also reduces cholesterol metabolism considerably. In addition to such side effects, the chemical modification of such agents may constitute a relevant source of toxicity. Their phosphorothioate entity, for example, may play a role in the activation of the complement cascade, hereby initiating an innate immune response, whereas subjects treated with LNA-modified antisense oligonucleotides may suffer from hepatotoxicity [25].

The ever-expanding field of small RNA research technologies enables reliable detection, profiling, and manipulation of miRNAs. The most common approach employed in the development of novel miRNA-targeting therapies relies on chemically modified, antisense oligonucleotides.

13.3 The Role of miRNAs in Cardiovascular Pathology

13.3.1 Cardiac Hypertrophy

Nonphysiological cardiac hypertrophy is the result of maladaptive mechanisms in response to myocardial injury, high blood pressure, volume overload, or mutations in genes encoding structural or functional proteins. Regardless of the underlying etiology, cardiac hypertrophy is generally associated with an increased risk of developing heart failure and malignant arrhythmias (Chap. 16).

Novel therapies targeting miRNAs aim at hindering unfavorable remodeling processes (e.g., fibrosis, hypertrophy, apoptosis) induced by cardiac stressors, thereby moderating the progression of cardiovascular disease.

Van Rooij et al. were among the first to hypothesize that miRNAs play an important role in cardiac hypertrophy in response to stress stimuli. In order to identify altered miRNA profiles, microarray analyses were performed in two distinct animal models: thoracic aortic-banded and calcineurin-overexpressing mice. Several miRNAs were found to be dysregulated in the retrieved cardiac tissue samples. Most of these miRNAs were analogously dysregulated in human failing hearts as shown by northern blotting. Furthermore, single miRNAs were capable of inducing hypertrophy in cultured cardiomyocytes [32]. Interestingly, these changes in miRNA profiles were similar to those observed in fetal cardiac tissue, as shown by Thum et al. Therefore, the reactivation of a fetal miRNA program probably contributes to altered gene expression associated with human heart failure [33]. Aside from emphasizing the pivotal role of miRNAs in the development of cardiac hypertrophy, such initial studies drew attention towards this new species of noncoding small RNAs and their contribution to cardiac pathology.

Care et al. conducted one of the first studies that manipulated specific miRNAs to influence the development of cardiac hypertrophy in vivo. First, the expression levels of miR-133 and miR-1 were assessed in three different murine models of cardiac hypertrophy: TAC-operated mice, cardiac Akt-kinase-overexpressing mice, and exercised rats. Northern blot analysis showed decreased expression levels of both miR-1 and miR-133 in these animals. Patients suffering from hypertrophic cardiomyopathy revealed similar downregulation patterns of these two miRNAs compared to controls. In order to further elucidate the role of miR-133 in cardiac hypertrophy in vivo, miR-133-specific antagomirs were administered by subcutaneously implanted, osmotic minipumps. Remarkably, these mice developed serious cardiac hypertrophy as indicated by echocardiographic parameters and histological data collected 1 month after treatment. On the other hand, when a miR-133 transgene expressing adenoviral vector was delivered transcoronarily into a mouse model

of cardiac hypertrophy, the gene transfer resulted in a significant reduction in cell size of left ventricle myocardium 14 days after treatment [34].

The myocardial hypertrophy is often accompanied by apoptosis and fibrotic repair. While most studies focused on the altered expression levels of miRNAs in cardiomyocytes, Thum et al. analyzed miRNA dysregulation patterns in other cardiac cell types. Interestingly, the level of miR-21 was significantly increased in cardiac fibroblasts of failing hearts, leading to an enhanced ERK-MAP kinase activity. This process controls fibroblast survival as well as growth factor release, thus regulating the degree of interstitial fibrosis in affected hearts. Remarkably, the systemic delivery of an antagomir targeting miR-21 reduced interstitial fibrosis and ameliorated cardiac dysfunction in mice with cardiac hypertrophy induced by pressure overload [35]. This effect seems to be dependent on the anti-miR chemistry, indicating the importance of the specific manipulation method [36].

Most miRNAs modulate cellular responses by interacting with key effectors of important cell signaling pathways. For instance, the miR-208 and miR-499 families drive hypertrophic growth by regulating the expression of myosin heavy chain [37–39], whereas the overexpression of miR-98 suppresses angiotensin II-induced hypertrophy by targeting cyclin D2 [40]. In addition, downregulation of miR-26b leads to upregulation of the GATA4 transcription factor, which also plays an essential role in the development of cardiac hypertrophy by orchestrating the expression of several fetal genes [41]. Another important prohypertrophic signaling pathway is based on the calcium-dependent calcineurin/NFAT interaction [42]. Various miRNAs act as modulators of this particular pathway. For instance, miR-9 can attenuate cardiac hypertrophy by suppressing myocardin expression, a downstream target of NFATc3, the level of which is increased upon hypertrophic stimulation with isoproterenol and aldosterone [43]. miR-23a and miR-199b, both upregulated in cardiac hypertrophy, also mediate their effects via the calcineurin-NFATc3 pathway. However, their effects depend on the suppression of different negative regulators of NFAT (e.g., muscle ring finger-1 or Dyrk1a) [44, 45]. A normalization of Dyrk1a expression by in vivo inhibition of miR-199b suppresses NFAT activity, hence reversing both cardiac hypertrophy and fibrosis in heart failure mice [45].

Ucar et al. reported that hypertrophic stimuli led to a significant upregulation of the cardiac miR-212/132 family (Fig. 13.1). miR-212/132 knockout mice were protected against pressure overload-induced hypertrophy and heart failure, whereas the overexpression of miR-212/132 led to cardiac hypertrophic growth, heart failure, and death. By negatively regulating the antihypertrophic transcription factor FoxO3, these miRNAs also activate the prohypertrophic calcineurin/NFAT signaling pathway. Remarkably, antagomir-132 injection prevented the development of cardiac hypertrophy in mice subjected to pressure overload, hinting at a possible therapeutic relevance of these findings [46].

Recently, Li et al. found that miR-328 induces cardiac hypertrophy by targeting SERCA2a. The overexpression of miR-328 led to severe hypertrophy accompanied by reduced SERCA2a level in both transgenic mice and in cultured neonatal rat cardiomyocytes. The subsequent normalization of miR-328 levels through the use of anti-miR-328 led to a reversal of both the structural and molecular changes [47].

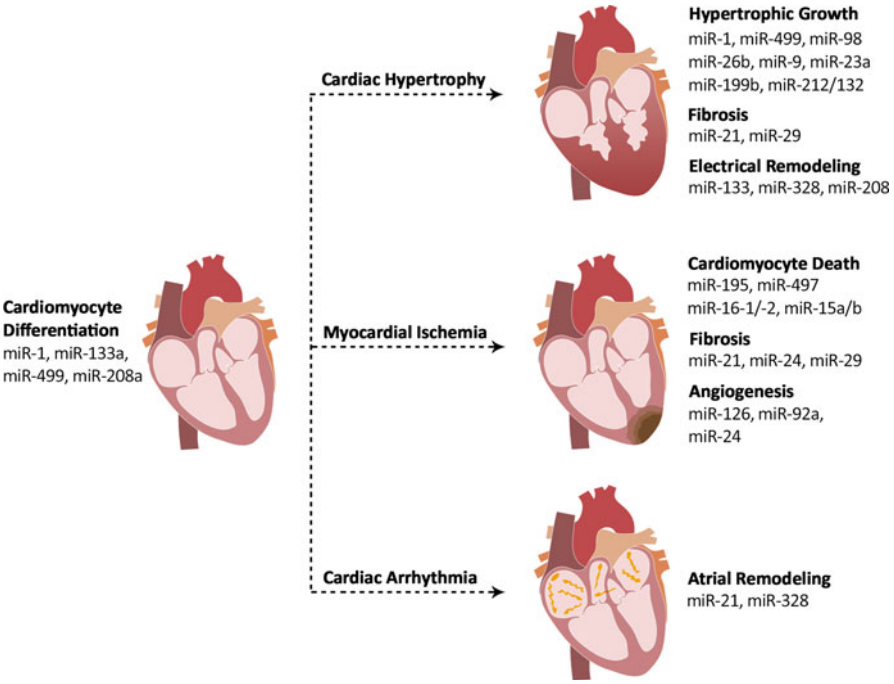

Fig. 13.1 MicroRNAs involved in the pathogenesis of cardiovascular disease. The figure illustrates the contribution of selected miRNAs to remodeling of the heart. Manipulation of these miRNAs may hinder the progression of cardiovascular pathology, with promising therapeutic prospects

The aforementioned studies suggest that miRNAs can function either as agonists, driving and enhancing the cardiac hypertrophic response (e.g., miR-208, miR-23a, miR-199b, miR-499, miR-21, miR-328, miR-212/132), or as antagonists, suppressing or attenuating cardiac hypertrophy (e.g., miR-1, miR-133, miR-26b, miR-29, miR-9, miR-98), by interfering with specific signaling cascades (Fig. 13.1). They exemplify how understanding the molecular mechanisms underlying certain pathologies can lead to innovative therapeutic approaches.

13.3.2 Heart Failure (HF)

As delineated above, a multitude of cardiovascular diseases (e.g., cardiomyopathies, coronary artery disease, cardiotoxic injury, valvular heart disease, cardiac hypertrophy, myocarditis) can result in cardiac hypertrophy and failure. Heart failure is defined as severe impairment in cardiac structure or function in a way that the heart may no longer maintain sufficient blood circulation to peripheral organs. Patients typically present with dyspnea, ankle swelling, fatigue,

pulmonary crackles, or increased filling of the jugular veins. However, symptoms might not be typical in all cases, and especially patients in early disease stages are often asymptomatic. Clinical management of HF patients is thus challenging and would greatly benefit from novel molecular biomarkers that could not only aid in diagnosis but also facilitate individual risk assessment and allow estimation of prognosis.

Tijsen et al. investigated the potential of circulating plasma miRNAs as biomarkers in heart failure patients. In an initial screening phase, microarray analysis was performed on plasma samples collected from 12 healthy and 12 HF patients. The 16 candidate miRNAs were subsequently assessed by real-time PCR in an independent patient cohort, consisting of 50 dyspnea cases – 30 HF and 20 non-HF patients – and 39 healthy controls. Six miRNAs were significantly upregulated in HF patients compared to other dyspnea subjects and healthy controls. Moreover, the collected data indicated miR-423-5p as a good diagnostic predictor of HF with an area under the curve (AUC) of 0.91. Remarkably, the expression level of miR-423-5p correlated with disease severity (i.e., with NT-proBNP levels and left ventricular ejection fraction), as well as clinical symptoms (i.e., NYHA classification) [8]. The miRNA profiles in plasma and serum differ from those found in whole blood samples, because the latter contain miRNAs from all circulating cells. In a recent study conducted by Vogel et al., a set of dysregulated miRNAs were found in patients suffering from nonischemic systolic HF [9]. While selected miRNAs have already good diagnostic value as single markers (e.g., miR-558, miR-122*, miR-520d-5p), combining several miRNAs to a multivariate signature consistently improves the diagnostic power, yielding an AUC value of 0.81, being superior to natriuretic peptides in this cohort. Remarkably, the expression level of miR-519e* also correlated with cardiac events (i.e., rehospitalization due to HF, heart transplantation, myocardial infarction, cerebral ischemia, and cardiovascular death) and hence prognosis (Table 13.1).

13.3.3 Coronary Artery Disease (CAD) and Myocardial Infarction (MI)

Coronary artery disease refers to the manifestation of atherosclerosis in coronary vessels. The progression of atherosclerotic plaques narrows the lumen of coronary arteries, leading to an insufficient blood supply of the downstream myocardium (Chaps. 19 and 25). Independently, the rupture of any unstable plaque and the subsequent thrombus formation leads to complete or partial vessel occlusion, followed by ischemia and necrosis. Unfortunately, endogenous repair mechanisms are often insufficient for an effective regeneration of the entire ischemic myocardium at risk, resulting in loss of vital cardiac tissue and detrimental remodeling processes. This can result in cardiac fibrosis and impaired cardiac contractility, some of the key factors in the development of heart failure (Chap. 3).

Table 13.1 MiRNAs as biomarkers for cardiovascular disease

Cardiovascular disease	MiRNA biomarkers	Biosample	Reference
Heart failure	miR-423-5p	Plasma	[8]
	miR-519e*, miR-558, miR-122*, miR-520d-5p, miR-200b*, miR-622, miR-1231, miR-1228*	Whole blood	[9]
Coronary artery disease	miR-140-3p, miR-182, miR-92a, miR-92b	Whole blood	[11]
	miR-19a, miR-484, miR-155, miR-222, miR-145, miR-29a, miR-378, miR-342, miR-181d, miR-150, miR-30e-5p	Whole blood	[12]
	miR-126, miR-17, miR-92a, miR-145, miR-155, miR-133, miR-208a	Plasma	[13]
	miR-340*, miR-624*, miR-451, miR-454, miR545, miR615-5p, miR-1280	Platelets	[14]
	miR-134, miR-370, miR-198, miR-135, miR-147	PBMCs	[15]
	miR-146a, miR-146b	PBMCs	[16]
Acute myocardial infarction	miR-1, miR-133a, miR-133b, miR-499-5p, miR-122, miR-375	Plasma	[48]
	miR-1, miR-133a	Serum	[49]
	miR-208a, miR-1, miR-133a, miR-499	Plasma	[50]
	miR-208b, miR-1, miR-133a, miR-499-5p	Plasma	[51]
	miR-208b, miR-499	Plasma	[52]
	miR-1, miR-133a, miR-208a	Serum	[53]
	miR-1291, miR-663b, miR-145, miR-30c	Whole blood	[7]
	miR-636, miR-7-1*, miR-380*, miR-1254, miR-455-3p, miR-566, miR-1291	Whole blood	[54]
Essential arterial hypertension	miR-let7e, miR-296-5p, hcmv-miR-UL112	Plasma	[17]

The table gives an overview of selected diagnostic studies mentioned in this chapter

The miRNAs identified in plasma/whole blood samples of patients with coronary artery disease originate from various cell types involved in the underlying pathogenesis. A miRNA-based biomarker that could differentiate unstable from stable atherosclerotic lesions may play a crucial role in detecting patients at risk for an acute myocardial infarction.

Contribution of various cell types (e.g., endothelial, immune, platelets, smooth muscle cells) is observed during the formation of atherosclerotic plaques. The activation of these cells might lead to the release of cell-specific miRNAs, which are then assessable in serum or plasma samples of CAD patients. Fichtlscherer and colleagues found a specific pattern of endothelial-originated (e.g., miR-17,

miR-126, miR-92a), inflammatory (e.g., miR-155), and smooth muscle-derived (e.g., miR-145) miRNAs in the plasma of patients with stable CAD (Table 13.1). Counterintuitively, these miRNAs were downregulated in affected patients, although the activation of vascular and inflammatory cells during atherosclerotic changes is a well-known process. Speculations regarding this miRNA downregulation include the idea that circulating miRNAs derived from activated cells might be taken up into atherosclerotic lesions. Furthermore, cardiac miRNAs (e.g., miR-133, miR-208a) showed increased plasma levels, which might hint towards recurrent subclinical ischemia with cardiomyocyte death and subsequent miRNA release into the blood stream. Another cell type that is deeply involved in atherosclerotic plaque formation, as well as thrombus formation during AMI, are platelets. At least two miRNAs derived from platelets (miR-340*, miR-624*) were shown to be upregulated in CAD patients when compared to controls [14]. Furthermore, several studies revealed different miRNAs to be dysregulated in whole blood samples of CAD patients [11, 12]. However, these studies were conducted in relatively small patient cohorts and results therefore need to be interpreted with care.

In patients with prevalent CAD, unstable atherosclerotic plaques hold the risk of plaque rupture and subsequent acute myocardial infarction (Chaps. 19 and 25). Therefore, the identification of patients with such high-risk lesions may help prevent serious cardiovascular events. Specific miRNAs derived from peripheral blood mononuclear cells (PBMC) (e.g., miR-134, miR-370, miR-198) were found to be significantly increased in patients with unstable angina pectoris compared to those experiencing stable angina [15]. Moreover, the PBMC-derived miR-146a was shown to be an independent indicator for cardiac events [16].

Undoubtedly, a major interest of cardiovascular research lies in the discovery of novel biomarkers for MI. Cardiac troponins are today's gold standard biomarkers for the detection of acute myocardial infarction. They can be measured in patients' blood samples after being released from dying cardiomyocytes using antibody-dependent assays [55]. The development of high-sensitivity cardiac troponin T assays (hs-cTnT) allowed the detection of even very low amounts of cTnT, resulting in higher diagnostic sensitivity and improved risk prediction, but at the cost of reduced specificity [56, 57]. This is due to the fact that troponin levels may also be elevated in response to many other cardiovascular diseases, such as pulmonary thromboembolism, myocarditis, acute tachycardia, or heart failure, and hence, novel biomarkers could help increase specificity and add precision to the diagnosis of MI (Chaps. 10 and 11).

A set of studies suggest that circulating cardiac-specific and muscle-enriched miRNAs are dysregulated due to cardiac necrosis in the course of MI. The most frequently found candidates in plasma and/or serum are miR-1, miR-133a, miR-499, and miR-208b [48–52]. Meder and colleagues found 121 non-cardiac-specific miRNAs significantly dysregulated in peripheral blood samples of MI patients, with miR-663b and miR-1291 showing best statistical power. Remarkably, combining 20 different miRNAs into a multivariate signature could improve diagnostic power (AUC = 0.99) when compared to single markers. In addition, the levels of miR-145 and miR-30c highly correlated with TnT values and disease severity [7]. Differences between studies are due to the analytes used, the methods for miRNA detection, and

most likely also due to the release kinetics during MI, since sample collection occurred at different time points after the initial cardiac event. In a kinetic study conducted on patients with hypertrophic obstructive cardiomyopathy undergoing transcoronary ablation of septal hypertrophy (TASH), Liebetrau et al. showed that the release pattern of different cardiac miRNAs was time dependent. miR-1 and miR-133a were already significantly increased 15 min after the procedure and showed peaks at 75 min and 75–480 min, respectively, whereas miR-208a showed a significant elevation 105 min post TASH with no further increase thereafter [53]. The authors hence concluded that miRNA expression patterns are altered already at a very early stage of MI, with different miRNAs showing different release kinetics. On a genome-wide level, our group identified several miRNAs that are early dysregulated during ST elevation MI. We relied on whole blood samples to also capture active mechanisms of cells involved in the pathogenesis of MI, such as vascular injury, inflammation, or plaque rupture. A subset of seven miRNAs (miR-636, miR-1291, miR-1254, miR-566, miR-455-3p, miR-380*, miR-7-1*) could reliably distinguish affected individuals from controls already very early during MI, even before observable changes in cTnT levels were noted.

The remodeling process following myocardial ischemia and necrosis is based on the formation of fibrotic scar tissue, which relies on the deposition of collagen components in response to the stimulation of extracellular matrix (ECM) genes. In this context, downregulation of the miR-29 family members is associated with cardiac fibrosis [58]. These specific miRNAs are able to simultaneously target multiple genes involved in fibrotic repair mechanism (i.e., elastin, fibrillins, collagens). Therefore, miR-29 mimics might be able to suppress the expression of ECM genes, hence inhibiting the development of excessive fibrosis that might result in dilatation of the ventricle. Furthermore, miR-24, also closely related to ECM remodeling, is able to improve heart function by reducing fibrosis in infarct border zones of murine hearts. The effects, which were evident 2 weeks after myocardial infarction in mice that underwent intramyocardial injection of lentivirus miR-24, presumably rely on the ability of miR-24 to target the furin-TGF-β signaling pathway [59].

The cardioprotective effect of miRNAs relies on their ability to influence angiogenesis, prevent calcium overload, and modulate apoptosis. Novel therapies may therefore lead to an increased reperfusion, a reduced infarct size, and an improved contractile function in post-myocardial infarction patients.

The expression of the miR-15 family, a group of six related miRNAs (miR-15a, miR-15b, miR-16-1, miR-16-2, miR-195, miR-497) with similar seed regions but different 3′-sequences, is known to be enhanced after myocardial infarction in both porcine and murine models [60]. Remarkably, silencing of the miR-15 family members through systemic delivery of small LNA-modified inhibitors (8 or 16 nucleotides in length) designed to target the shared seed region of the related miRNAs reduced infarct size and improved cardiac function. This illustrates how miRNA modulators can be used to target multiple, closely related miRNAs and hence might

evoke a strong effect. Interestingly, the comparison of intravenous, subcutaneous, intraperitoneal, and gavage administration of the therapeutic agents within this study suggested a similar inhibition through all administration routes, except the oral delivery which was slightly less efficient than the others.

Rapid reperfusion of the ischemic myocardium is considered to be the most effective approach in limiting myocardial infarct size and improving patient's clinical outcome. However, restoring the blood flow may paradoxically also lead to cardiomyocyte death and significant expansion of the infarct zone, a phenomenon known as myocardial reperfusion injury. Several miRNAs show dysregulated patterns in the advent of ischemia-reperfusion (I/R) injury, suggesting that a possible cardioprotective approach could derive from their manipulation. By generating a mouse model with cardiac overexpression of miR-494 and subjecting it to I/R injury, Wang and colleagues showed that transgenic hearts displayed an improved recovery of their contractile properties during reperfusion and a significantly reduced apoptosis level compared to wild-type hearts. Remarkably, myocardial infarction size was significantly smaller in miR-494-overexpressing hearts. The cardioprotective effects described here presumably rely on the activation of the Akt-mitochondrial signaling pathway as an endpoint of a very complex regulatory process involving both pro- and antiapoptotic targets of miR-494 [61]. Furthermore, heat shock proteins, which play an important role in the physiological recovery of the myocardium especially in uncomplicated cases of acute myocardial infarction, are also targeted by miRNAs. Ren et al. showed that the role of miR-320 as a cellular regulator during I/R injury is based on its ability to target heat shock protein 20. Knockdown of miR-320 using a cholesterol-linked antagomir significantly reduced cardiac infarct size in mice [62].

An important process during myocardial reperfusion is the rapid increase of the intracellular Ca^{2+} concentration after blood flow restoration. The cardioprotective role of miR-214 during I/R injury seems to rely on the translational repression of the sodium/calcium exchanger 1 (Ncx1), an important regulator of calcium influx and various other downstream factors involved in the calcium signaling pathway. Accordingly, miR-214 knockout mice experienced higher mortality rates and increased injury after MI [63]. Thus, the manipulation of miR-214 might inhibit calcium overload in reperfused cardiomyocytes, thereby preventing myocardial damage.

Angiogenesis is an important factor that triggers cell survival and myocardial regeneration after an acute myocardial infarction. Several miRNAs (e.g., miR-126, miR-92a, miR-24, miR-21, miR-503) regulate angiogenesis, and their manipulation might therefore offer the possibility to increase long-term cardiac perfusion, which in turn can lead to a functional recovery of the myocardium especially in the infarct border zone. For instance, miR-92a controls the growth of new blood vessels by targeting different proangiogenic proteins (e.g., the integrin subunit α5). Overexpression of miR-92a in endothelial cells suppressed angiogenesis in vivo, whereas a chemically modified inhibitor of miR-92a led to an increased growth of blood vessels upon systemic delivery in mice with limb ischemia and myocardial infarction [64]. Moreover, a recent study reported a similar beneficial effect of miR-92a antagonism in a porcine animal model of I/R injury. Besides systemic delivery, a site-specific application could also reduce infarct size and the loss of contractile

function post ischemia [65]. Fiedler et al. assessed the role of miR-24 in endothelial cells and found a significantly increased level of this particular miRNA following cardiac ischemia. Remarkably, the inhibition of miR-24, which targets several transcription factors (GATA2, PAK4), stimulated angiogenesis and reduced infarct size in mice notably. Interestingly, low-dose treatment (5 mg/kg) with a specific antagomir resulted in a selective cellular uptake by endothelial cells, whereas high doses (80 mg/kg) led to a nonspecific enrichment of the antagomir in all cardiac cell types [66]. This example conveys an important message regarding the connection between cell-type selectivity of miRNA analogs and applied dosage.

Despite all the advanced treatment options, MI might still cause irreversible cardiac damage. Excessive scar formation leads to severe contractile dysfunction of the myocardium, which can result in heart failure. Advances in the field of regenerative medicine are thus of great interest, exploiting miRNAs as possible candidates to enhance myocardial regeneration. A broad range of studies conducted for this purpose focused on two main mechanisms: the reactivation of cardiomyocyte proliferation and the stimulation and differentiation of cardiac progenitor cells.

The manipulation of different miRNAs (e.g., miR-15 family, miR-195, miR-133, miR-17-92, miR-590, miR-199a), which are known to impact on the cell cycle, was shown to promote cardiomyocyte proliferation in various animal models [67]. The upregulation of the miR-15 family members, for instance, is associated with a definite withdrawal of cardiomyocytes from the cell cycle during neonatal development. Therefore, a postnatal knockdown of these miRNAs through anti-miRs administered in vivo increased the number of mitotic cardiomyocytes with promising regenerative potential [68]. However, excessive cell cycle progression may also result in cellular hypertrophy or apoptosis. Therefore, promitotic mechanisms must be assessed carefully, especially before they are considered for clinical applications.

Cardiac cells with stem cell properties can proliferate and differentiate into different cell types such as cardiomyocytes and endothelial or vascular smooth muscle cells. However, their regenerative potential is rather limited, especially after extensive cell loss like the one occurring post myocardial infarction. Since miRNAs act as regulators of both proliferation and differentiation, their manipulation might result in a regenerative potential of such cardiac progenitor cells [69]. Inline Jayawardena et al. could show that lentiviral-mediated delivery of several miRNAs (e.g., miR-1, miR-133, miR-208, miR-499) into infarct border zones of murine hearts induced the conversion of fibroblasts to cardiomyocytes in situ [70]. Using alternative strategies, a subset of miRNAs was shown to enhance viability of injected stem cells in infarcted hearts [71] or influence intercellular communication for the purpose of local and maybe even distant reprogramming of stem cells [72].

13.3.4 The Vascular System

Vascular injury and remodeling contribute to numerous vascular pathologies, including atherosclerosis, essential arterial hypertension, pulmonary arterial hypertension, aneurysm formation, and restenosis after angioplasty. miRNAs play an

important role in the pathogenesis of several vascular-related diseases by orchestrating the molecular mechanisms underlying vascular remodeling and dysfunction.

Important contributors to vascular remodeling processes are vascular smooth muscle cells (VSMCs). Unlike most differentiated cells, VSMCs undergo phenotype switching, thus alternating between a differentiated and a dedifferentiated state in response to various extracellular stimuli [73]. This phenotypic modulation capacity is essential for vascular repair, since dedifferentiated VSMCs show increased proliferation rates, an enhanced production of extracellular matrix components, and the ability to migrate. Once the vascular damage is repaired, healthy VSMCs return to a differentiated, contractile phenotype [74]. While under physiological conditions the phenotypic plasticity of VSMCs contributes to normal homeostasis, its dysregulation may rapidly promote the development and progression of vascular pathology (e.g., atherosclerosis, pulmonary hypertension, restenosis after angioplasty). The VSMC-enriched miR-143/145 are important regulators of VSMC differentiation. Several animal models of vascular disease, including carotid artery-ligated mice, carotid balloon injury rats, or ApoE knockout mice, show significantly decreased expression profiles of miR-143/145 [75–77]. The functional modulation of these particular miRNAs in vivo prevented neointimal formation by reducing VSMC proliferation in animal models of vascular injury [78, 79]. Furthermore, Lovren et al. used a lentivirus-mediated overexpression of miR-145 in ApoE-deficient mice to limit atherosclerotic plaque development and to prevent plaque rupture with promising therapeutic prospects [80]. Moreover, low levels of miR-145 can be detected in the serum of patients suffering from coronary artery disease, suggesting the potential of miR-145 as a biomarker that may predict the severity or size of atherosclerotic lesions [13], while on the other hand, increased levels of miR-145 can be detected during AMI [7]. Other miRNAs involved in the phenotype switch of VSMCs include miR-1, miR-133, miR-21, miR-221, miR-146a, miR-24, and miR-26a [74, 81].

Angiogenesis is a finely tuned process that relies on the activation, proliferation, and migration of endothelial cells. Therefore, miRNAs that influence endothelial cell function (e.g., miR-126, miR-92a, miR-23/27/24, miR-503, miR-21) are of major interest in vascular pathologies. While it is widely recognized that diabetes mellitus interferes with endothelial cell function and with postischemic, compensatory angiogenesis, the exact molecular mechanisms are not fully understood. In a study conducted by Caporali and colleagues, miR-503 showed an increased expression level in endothelial cells of ischemic limb muscles of diabetic mice. Remarkably, the adenoviral delivery of an miR-503-targeting decoy ameliorated impaired angiogenesis in diabetic animals and restored blood flow in the ischemic limbs [82]. However, angiogenesis is not always helpful; under certain circumstances, it may have devastating effects. The hallmark of age-related macular degeneration (AMD), a major cause of blindness in elderly patients, is the ischemia-triggered choroidal neovascularization, a process that relies on angiogenesis. Zhou et al. showed that in vivo inhibition of two specific miRNAs (miR-23, miR-27) reduced choroidal neovascularization in mice with laser-induced choroidal injury, thus preventing the occurrence of neovascular macular degeneration in this animal model [83].

Essential arterial hypertension is a major risk factor for myocardial infarction, congestive heart failure, chronic renal failure, and stroke (Chaps. 30 and 31). Vascular remodeling is a major factor which contributes to an increased total peripheral resistance, which not only facilitates the progression of arterial hypertension but also leads to serious complications that may compromise the function of multiple organs. Although the mechanism underlying vascular remodeling is usually associated with cellular growth, other processes such as apoptosis, low-grade inflammation, and fibrosis also contribute to this pathology [84]. Furthermore, an abnormal activation of the renin-angiotensin-aldosterone system (RAAS) may also play an important role in the pathogenesis of essential arterial hypertension. In this context, Nossent et al. showed that SNPs located in miRNA binding sites of genes related to RAAS can influence not only blood pressure but also the risk of myocardial infarction [85]. In a recent study, Leung et al. evaluated transcriptomic responses to angiotensin II (Ang II) in VSMCs in an attempt to elucidate the gene regulatory networks targeted by Ang II, since these may contribute to the pathogenesis of arterial hypertension. A group of novel lncRNAs were discovered in the Ang II-induced rat VSMCs. One of these lncRNAs was lnc-Ang362, the host transcript of two miRNAs involved in VSMC proliferation (miR-221, miR-222). Remarkably, knockdown of this particular lncRNA by small interfering RNAs significantly reduced VCMC proliferation [86]. Although little is known about the effects of lncRNAs in vascular pathology, these newly identified noncoding transcripts may also be exploited as therapeutic targets in the future [87–89].

As far as biomarkers related to essential arterial hypertension are concerned, Li and colleagues identified a specific miRNA signature in the plasma of hypertensive patients by performing microarray-based miRNA expression profiling (miR-296-5p, let-7e, hcmv-miR-UL112) [17]. Interestingly, one of the miRNAs found to be significantly elevated in plasma samples of hypertensive patients was human cytomegalovirus (CMV) encoded (hcmv-miRUL112). Since the CMV titers were also significantly elevated in hypertensive patients compared to controls, the authors speculated a possible link between essential hypertension and CMV infection, with possible diagnostic and therapeutic consequences (Table 13.1).

13.3.5 Atrial Fibrillation (AF)

Atrial fibrillation is one of the most frequent cardiac arrhythmias encountered in daily practice. It can cause serious complications, including the exacerbation of a preexisting congestive heart failure or thromboembolic events. Recurrent or persistent AF is generally associated with both structural (e.g., fibrosis) and electrical remodeling processes in the atria that synergistically lead to an enhanced cardiac vulnerability (Chap. 50).

The increased rate of impulses during fibrillation causes a high influx of calcium ions, which threatens the integrity of cardiomyocytes. Therefore, an adaptive mechanism involving the decrease of the L-type Ca^{2+} channel density and the duration of

the atrial action potential aims to prevent calcium overload. However, this electrical remodeling process facilitates AF recurrence and maintenance. In this context, Lu et al. [90] hypothesized that miRNAs might regulate calcium channel-encoding genes involved in the process of electric remodeling. Microarray screening and RT-PCR validation experiments showed a significant upregulation of miR-328 in a canine model with tachypacing-induced atrial fibrillation. Moreover, augmented expression of this specific miRNA by both viral delivery and genetic overexpression of precursor miR-328 induced atrial electric remodeling in different animal models. In contrast, loss of function of miR-328 reduced vulnerability for atrial fibrillation and suppressed detrimental remodeling processes. This presumably relies on the ability of miR-328 to target two important genes involved in calcium homeostasis (CACNA1C and CACNB1).

Fibrosis of atrial tissue is a hallmark of atrial fibrillation. miR-21 plays an important role in ventricular fibrotic remodeling by targeting Sprouty-1, a negative regulator of MAP kinase, thus stimulating fibroblast survival [35]. Therefore, miR-21 has been regarded as a possible candidate regulator of atrial fibrosis as well. In atrial tissue samples of myocardial infarction rats, increased levels of miR-21 were associated with a dysregulation of its cognate genes (e.g., Sprouty-1, collagen-1, collagen-3). Anti-miR-21 treatment not only reduced atrial miR-21 expression levels in vivo but also remarkably decreased the duration of atrial fibrillation as well as the amount of fibrotic tissue in the atria [91]. These results suggest that the manipulation of miR-21 expression levels may be beneficial in patients suffering from atrial fibrillation.

13.4 Concluding Remarks

At present, the development of diagnostic and therapeutic options constitutes a promising avenue of miRNA research in cardiovascular medicine. Over the last few years, genetic and pharmacological approaches relying on different chemistries have been developed, in order to enable miRNA manipulation in several small and large animal models that closely simulate human cardiovascular disease. The experience gathered from extensive work carried out on these animal models suggests that miRNA-targeting therapies may prove extremely useful especially with regard to remodeling processes, such as fibrosis, angiogenesis, apoptosis, hypertrophy, and atherogenesis, all initiated by distinct cardiovascular stressors. Such stressors include ischemia and I/R injury, pressure or volume overload, inflammation, and an abnormal electrical activity. The ability to positively influence detrimental remodeling processes may hinder the progression of cardiovascular disease (e.g., reduce scar size or stimulate angiogenesis in border zones in the case of myocardial infarction), thus preventing the occurrence of heart failure. Obviously, the clinical efficacy, long-term treatment effects, and safety of miRNA-based therapies need to be carefully assessed in the forthcoming years, to exclude toxic and other adverse effects. On the other hand, miRNAs hold great promise for the field of

cardiovascular biomarker development as demonstrated by a wide range of studies on coronary artery disease, myocardial infarction, and heart failure. Multivariate miRNA signatures may surpass current gold standards or add to their diagnostic power. Moreover, clinical correlations between miRNA profiles and patients' outcome and prognosis tend to be in the focus of recent studies. Although much remains to be learned about this class of regulatory RNAs, the considerable progress made in understanding miRNA biology over the past 10 years allows for quite some optimism.

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Chapter 14
MicroRNA Therapeutics in Cardiovascular Disease

Antoine Bril

Abstract MicroRNAs are endogenous single-stranded RNAs of approximately 22 nucleotides in length which decrease the level of expression of specific proteins. miRNAs are involved in many pathologic conditions such as cancers and neuropsychiatric and metabolic diseases. In cardiovascular diseases, miRNAs have been shown to be involved in the proliferation of cardiomyocytes and non-myocyte cardiac cells, in cardiac hypertrophy and apoptosis, in the occurrence of atrial and ventricular arrhythmias, in vascular angiogenesis and smooth muscle cell pathologies, and in atherosclerosis. In heart failure, miRNAs have been shown to promote or inhibit hypertrophy and remodeling as well as to modulate cardiac pump function. By considering a few specific examples illustrating the value and complexity of targeting miRNAs, this chapter will describe the key data demonstrating the potential of miRNAs either to prevent cardiac hypertrophy (miR-208) or to improve cardiac function (miR-25) in heart failure. In the biogenesis of miRNAs, a passenger strand miRNA, called miRNA*, is usually degraded. The effects of miR-21* illustrate a situation where miRNA* exhibits a biological activity. Finally, miRNA-based therapeutics is nearly reaching human trials in the cardiovascular disease area. However, several questions remain to be fully investigated to progress such therapeutic approaches successfully. These include strategies to improve druggability parameters and delivery characteristics of selected candidates as well as approaches required to demonstrate clearly the efficacy/safety ratio of such novel therapies.

Keywords miRNA • Heart failure • Cardiovascular disease • Therapy • Oligonucleotide • Drug discovery

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14.1 Introduction

Since their initial discovery in *C. elegans*, microRNAs (miRNAs) have been extensively studied, and their biology has been widely investigated. Many studies performed in plants, viruses, bacteria, and mammals including humans have described their genesis, degradation, and regulation.

MicroRNAs are endogenous single-stranded RNAs of approximately 22 nucleotides in length. They decrease the level of expression of specific proteins by annealing to specific sequences located in the 3′ untranslated regions of target messenger RNAs (mRNAs). Many review articles have summarized the biology of the formation and action of miRNAs [1–3]. Briefly, miRNA genes are transcribed in the nucleus by RNA polymerase II into a hairpin structure called primary microRNAs (pri-miRNAs) and then processed by the RNase III Drosha in a complex with the RNA-binding protein DiGeorge syndrome critical region 8 (DGCR8). The resulting pri-miRNA is a double-stranded 70-nucleotide-long structure exported to the cytoplasm by exportin-5. In the cytoplasm, the pre-miRNA forms a complex with the endonuclease DICER, the transactivation responsive RNA-binding protein (TRBP), and the adenosine deaminase action on RNA-1 (ADAR1) and is cleaved in a resulting miRNA-miRNA* duplex. The passenger strand, i.e., miRNA* or miRNA star, is then degraded, and the mature miRNA could associate with Argonaute to bind its mRNA target and degrade it.

In the cytoplasm, the association of miRNAs with their mRNA targets is within a multiprotein complex called the RNA-induced silencing complex (RISC). It is now well established that a given miRNA targets several mRNAs and that individual mRNAs are often simultaneously targeted by many miRNAs. Therefore, the regulatory signaling network resulting from miRNA biology is very complex and requires well-defined strategies for developing therapeutic interventions. Today, more than 2,000 miRNA sequences identified within the human genome are reported in specialized databases (www.mirbase.org), and almost all cellular processes are regulated by miRNAs. miRNAs have been involved in most pathologies such as cancers and neuropsychiatric and metabolic diseases [4–7]. Many review articles have described the many miRNAs that have been shown to play a role in various cardiovascular diseases [8–13]. This review will summarize the efficacy of miRNAs as potential therapeutic targets for heart failure by considering specific examples illustrating the importance and complexity of targeting miRNAs from a drug discovery perspective. In a second part, some of the questions that remain to be fully investigated to enable the delivery of novel therapeutic strategies will be described.

14.2 miRNAs as Molecular Therapeutic Targets for Heart Failure

The importance of miRNAs as therapeutic targets for cardiovascular diseases has been deciphered mainly by investigating the expression pattern of various miRNAs in pathologic situations and measuring the consequences of genetically altering the

level of expression of selected miRNAs. The first major study illustrating a role for miRNAs in cardiac biology was the demonstration of the role of miR-1 on cardiomyocyte differentiation [14] and the investigation of miRNAs in cardiac hypertrophy and failure [15]. Van Rooij et al. [15] described the expression pattern of a number of miRNAs both in experimental hypertrophy and in samples from idiopathic end-stage failing human hearts. Since then, many studies have established the relationship between miRNAs and cardiovascular diseases.

In the study by van Rooij et al. [15], later confirmed using a larger set of miRNAs [16], an overlap is observed between the pattern of expression in the human failing hearts and the hypertrophic mouse heart suggesting a common molecular signature for cardiac remodeling. When overexpressing specific miRNAs in transgenic mice under the myosin heavy chain promoter, different phenotypes have been observed. Whereas miR-24 induced embryonic lethality, other miRNAs such as miR-124 did not induce any detectable phenotypic effect. The overexpression of miR-195 was able to recapitulate the hypertrophic phenotype observed in experimentally induced cardiac overload. Findings from this early study suggest that a specific miRNA could be responsible for the molecular genesis of diseases such as heart failure and that selecting the right miRNA could lead to promising insights into heart diseases and cardiovascular therapies. Since then, all the pathophysiologic processes involved in cardiovascular diseases including cell hypertrophy and proliferation, cell death and apoptosis, arrhythmias, and fibrosis have been shown to involve miRNAs, and computational tools have been developed to identify miRNA-target interactions and to facilitate biological discoveries [17] (also see Chap. 13).

In investigating further the role of cardiac-expressed miRNA, Olson's laboratory created the first ever miRNA knockout (KO) mice dedicated to cardiovascular research and discovered that miRNA-208, which is expressed from intron 27 of α-myosin heavy chain gene, is required for stress-induced cardiac hypertrophy. In these experiments, miR-208 KO mice exhibit blunted cardiac hypertrophy in response to pressure overload [18]. Interestingly, it was shown by Callis et al. [19] that transgenic overexpression of miR-208a is by itself sufficient to induce cardiac hypertrophy in mice. Actually, the biology related to miR-208 appears more complex than what was thought initially. While the overexpression of miR-208 is related with the occurrence of cardiac arrhythmias in mice, its genetic deletion resulted in aberrant cardiac conduction [19]. Taken together, these data demonstrate that the expression level of a single miRNA in the heart could be critical for both hypertrophic growth and the cardiac conduction system. In fact when investigating the role of systemic delivery of miR-208a inhibitors, Montgomery et al. [20] reported that systemic delivery of miR-208a inhibitors prevented the pathological myosin switch, a well-established marker of cardiac hypertrophy [21], and reduced cardiac remodeling while improving cardiac function and survival.

Interestingly, miR-208a has also been shown to regulate systemic energy homeostasis via a negative regulation of the mediator complex 13 protein expression [22]. The pharmacological inhibition of miR-208a or cardiac-specific overexpression of mediator complex 13 in mice induces resistance to high-fat diet-induced obesity and improves systemic insulin sensitivity and glucose tolerance [22]. These findings have two main consequences when considering a particular miRNA as a possible

therapeutic target for cardiovascular diseases. First, they reinforce earlier findings demonstrating the role of the heart in controlling systemic metabolism and therefore add evidence that for miRNA therapeutics for cardiovascular diseases the benefit-risk ratio for targeting a given miRNA requires preclinical and clinical investigations broader than focusing attention to cardiovascular function as it is done for each and every drug treatment. Second, these results clearly suggest that the patient population for which a miRNA therapeutic could be developed may need to be defined according to a revised more molecularly defined taxonomy. The findings also suggest that a single miRNA therapeutic may not be beneficial for all the pathogenic phenotypes identified in a particular disease such as heart failure.

Recently, the potential of miRNAs as targets to improve cardiac function in cardiovascular diseases and particularly in heart failure has been investigated using a high-throughput physiological screening approach. High-throughput physiologic screenings are methods in which a system-based, hypothesis-free approach without a predetermined molecular target is used to identify novel drug candidate that may be effective on a given phenotype [23, 24]. Among various hallmarks characterizing heart failure, a decline in cardiac function represents a well-established phenotype. Improving cardiac contractility by modulating the activity of intracellular calcium-handling proteins is currently being tested clinically using gene therapy to introduce the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a), the primary protein responsible for calcium uptake by the sarcoplasmic reticulum during the excitation-contraction coupling in cardiomyocytes [25, 26] (Chap. 4).

Wahlquist et al. [27] used human embryonic kidney 293 cells co-transfected with a green fluorescent protein reporter fused to the 3′ untranslated region of SERCA2a gene to screen a whole genome collection of miRNAs and identified 144 miRNAs that are able to downregulate the calcium ATPase. Among the 82 miRNAs confirmed by testing a dose range, 15 were both evolutionarily conserved and upregulated in human heart failure. Finally, the most potent miRNA on a physiological measure of the calcium flux in cardiomyocytes was miR-25, and its effect was similar to that of short interfering RNA (siRNA) directed against SERCA2a. While the overexpression of miR-25 in the heart both decreased expression of SERCA2a and induced contractile dysfunction in mice, the administration of an antisense oligonucleotide against miR-25 reversed heart failure established in mice by chronic aortic constriction and improved survival rate in these mice [27]. This study, which reinforces the value of physiological screening strategies to identify novel therapeutic approaches [28, 29], suggests that targeting miR-25 may represent an alternative possibility to bypass the potential risks of gene therapy aimed at restoring SERCA2a expression level [30, 31]. These data show miR-25 to be part of a dynamic regulation of cardiac function by fine-tuning the complex intracellular calcium cycling mechanism. However, it requires further validation as a previous study has shown opposite results in which in vivo inhibition of miR-25 generates spontaneous contractile dysfunction in mice and sensitizes the murine myocardium to heart failure [32]. The efficacy of interacting with miR-25, whose expression is altered in various cancers, remains to be confirmed in different models and pathologic conditions to confirm or not its value as a therapeutic target for heart failure. Finally, although it is recently being

suggested that the most abundant miRNA in a cell may be the one having a prominent physiological role [33], the other miRNAs identified in the physiological screening used by Wahlquist et al. [27] might also play a role in heart failure (Chap. 13).

Alternative to mature miRNAs, passenger strands (miRNA* or miRNA star) usually released and degraded during the formation process of miRNAs could also represent valuable molecular targets for heart failure. Such a hypothesis has recently been described by Bang et al. [34] who showed that the passenger strand microRNA miR-21* behaves as a novel paracrine factor released from fibroblasts and inducing cardiac myocyte hypertrophy. In the progression from hypertrophy to failure, fibroblasts not only proliferate and favor fibrosis but also secrete extracellular matrix proteins and proinflammatory cytokines aggravating cardiac remodeling. Experimentally, cardiomyocytes cocultured with fibroblasts or in the presence of conditioned fibroblast media developed hypertrophy. Because miRNAs have been shown to be actively transported in microvesicles/exosomes in circulating fluids as well as between endothelial and cardiovascular cells [35, 36], Bang et al. [34, 37] tested the hypothesis that miRNAs could represent a paracrine cross talk between cardiac fibroblasts and cardiomyocytes. While miR-21 has been shown as a fibroblast mediator for generating hypertrophy and failure [38] and to be involved in metabolic diseases [39], the present study interestingly shows that the corresponding miR-21* is specifically packaged into and transported by exosomes from cardiac fibroblasts to cardiomyocytes and promotes cellular hypertrophy. In vivo studies demonstrated that miR-21* was detected in the pericardial fluids of mice submitted to aortic constriction-induced hypertrophy and that a systemic administration of an anti-miR-21* prevented angiotensin-induced hypertrophy [34]. Although many questions remain to be answered before considering miRNA-containing vesicles as therapeutic opportunities for cardiovascular diseases, this study clearly shows that mature miRNAs as well as miRNA* could play a significant role in the intercellular cross talks involved in pathogenesis of chronic diseases such as heart failure.

14.3 miRNA Therapeutics for the Treatment of Heart Failure

On the basis of the progress made in the antisense technologies, several options are currently being investigated for miRNAs as novel drug treatments. Today, the most advanced miRNA therapies are anti-miR-122 compounds for the treatment of hepatitis C virus infection with a miRNA inhibitor in phase 2 clinical trials [40]. In the cardiovascular disease area, no miRNA-based therapeutics have yet reached human trials, and many questions remain to be fully investigated to progress such strategies successfully.

Drug Strategies Used to Modulate miRNA Function In diseases where miRNAs could be considered as playing a beneficial rather than a pathogenic role, mimicking

the activity of endogenous miRNA appears the most rational therapeutic strategy. Double-stranded chemically modified miRNAs have therefore been developed as miRNA mimics, and miRNA mimic-related agents such as MRX34, a lipid-formulated miR-34 mimic for the treatment of cancers, are reaching the clinical stage [4, 41]. As far as inhibiting miRNA activity is concerned, several strategies have been studied including vector-based approaches or miRNA sponges, small molecules, and antisense oligonucleotides.

Several reviews have recently summarized extensively the advances made in the development of miRNA inhibitors [4, 40, 42]. miRNA sponges that are large vectors require tissue-specific expression to be active and have been used mainly for in vitro experiments and for investigating small animal models. Small molecules targeting miRNAs or SMIRs that have been identified by screening compound libraries on reporter-based assays necessitating a micromolar concentration to be active are not suitable yet for drug discovery and development. Therefore, both miRNA sponges and SMIRs have limited therapeutic potential. As a consequence, most therapeutic approaches currently used to inhibit miRNA activity are based on antisense oligonucleotide technologies. To achieve efficient in vivo inhibition of the target miRNA and allow improved affinity, stability, and pharmacokinetic properties, oligonucleotides are chemically modified. Briefly, the modifications performed mainly affect the 2′ position of the sugar ring and are 2′-fluoro, 2′-O-methyl, or 2′-O-methoxyethyl modifications and locked nucleic acid (LNA) which is the creation of a bicyclic nucleic acid by connecting the 2′ oxygen to the 4′ carbon via a methylene bridge. All these modifications greatly enhance binding affinity. Another modification is the substitution of the phosphodiester bonds with phosphorothioate bonds to increase nuclease resistance. Combinations of several of these chemical modifications lead to the most efficacious results in terms of binding affinity, nuclease resistance, and miRNA-inhibitory activity. Today, strategies that combine LNA technology with other chemical modifications, and among them fully LNA-modified 8-mer phosphorothioate oligonucleotides called tiny LNAs, are the most promising approaches.

Delivery of miRNA-Based Therapeutics Besides the use of liposome formulation, cholesterol conjugation and phosphorothioate linkage have been shown to improve the pharmacokinetic properties of antisense oligonucleotides. However, delivering miRNA inhibitors for cardiovascular diseases remains a challenge, and the development of novel formulation and delivery strategies is required to overcome this challenge, as this has been the case for biopharmaceuticals products [43]. Today, the most advanced therapeutic approaches involving miRNAs as molecular targets are directed toward severe hepatic diseases such as HCV infection or liver cancers. As an example, patients receiving subcutaneous administration of miravirsen (currently in phase II clinical trial for the treatment of hepatitis C), a LNA-modified DNA phosphorothioate antisense oligonucleotide that sequesters mature miR-122, showed dose-dependent reduction of HCV RNA levels [44], suggesting that the systemic delivery of miRNA inhibitors represents a possible therapeutic strategy. However, because systemically administered miRNA inhibitors, both antagomirs

and anti-miRs, predominantly accumulate in the liver and the kidney, this first proof-of-concept study may not be completely relevant for cardiovascular diseases for which high doses may be required to reach targets.

Because miRNAs physiologically act on a number of mRNA targets possibly with opposing effects depending on the tissue, the high doses required for demonstrating efficacy in the cardiovascular system may be deleterious for other organs. While further developments are necessary to improve the cardiovascular targeting of miRNA inhibitors, alternative delivery strategies could also be evaluated. Recently, Hinkel et al. [45] investigated the effect of a regional administration of a LNA anti-miR-92a in a model of ischemia-reperfusion-induced injury in pigs. In this study, the authors compared the efficacy of LNA-92a administered either systemically by intravenous infusion or locally by catheter-based delivery into the left anterior descending coronary artery or the anterior interventricular vein. When the treatment activity was measured by the expression level of the targeted miRNA, systemic and regional administrations of LNA-92a exhibited a similar activity. However, only regional administration of LNA-92a reduced infarct size and improved the postischemic myocardial function [45]. Although the level of efficacy obtained in this study appears limited compared to classically adopted interventions such as ischemic preconditioning or clinically established therapies [46, 47], these results clearly demonstrate the potential of a local delivery of miRNA inhibitors for cardiac indications such as myocardial ischemia or heart failure. This study highlights the fact that defining the correct efficacy endpoint remains to be further investigated and suggests that the expression level of the targeted miRNA may not always represent a valuable surrogate for pharmacokinetics/pharmacodynamics relationships.

Characterization of the Efficacy of miRNA Therapeutics Along with absorption, distribution, metabolism, and elimination (ADME) parameters that are investigated in every drug discovery program, several issues that may be prominent with miRNA therapeutics require special consideration. The results of the study by Hinkel et al. [45] illustrate the need for better understanding of the relationship between target engagement and miRNA therapeutics in measuring efficacy in animal models and eventually in patients. While the miRNA inhibitor represses the expression of its target mRNA, the function measured on the physiological endpoint depends on the route of administration. Because a given miRNA can modulate the expression of many target mRNAs and therefore regulate the expression level of many proteins, it is usually difficult to correlate target engagement with therapeutic efficacy. Alternative strategies, compared to those classically used in drug discovery, are therefore required. Investigating the summation of relatively small effects and comparing the resulting physiology in a tissue and in another requires novel systems-based approaches. If these methodologies using computational analysis of a large amount of data are emerging, they need to be created and developed not to oversimplify the downstream effect of miRNA functions.

The second key question to be investigated refers to both the onset and the duration of action of miRNA therapeutics. In contrast to most classic pharmacological interventions targeting a membrane receptor, an intracellular enzyme or a

protein-protein interaction, the action of miRNA inhibitors appears delayed, while, on the other hand, their effect on mRNA targets is fairly immediate [20, 48]. There is no definitive explanation for such a delay in biological action and the time required for regulating the protein expression level.

Evaluation of the Safety Profile of miRNA Therapeutics As for any novel therapeutic intervention, investigating the adverse effects and the off-target effects of long-term miRNA modulation is of prime importance.

miRNA therapeutics that are designed to be perfectly complementary to their mature miRNA targets could represent very safe therapeutic opportunities. Since miRNAs can target many mRNAs, a miRNA modulator that is specific for only one seed region could affect several pathways. Therefore, unwanted systemic effects should be monitored.

Besides nonspecific hybridization-dependent effects, any chemical modification done to improve the stability, affinity, and pharmacokinetic properties of miRNA therapeutics could cause additional adverse effects such as an activation of the immune system or a liver toxicity. A similar point of vigilance has been described with most antisense oligonucleotide strategies, and chemical modification of anti-miRNA as well as shortening the sequence that targets miRNA could reduce this risk.

Liver toxicity is another risk observed with chemically modified anti-miRNAs, and this effect appears to be induced in a sequence-independent manner. Swayze et al. [49] showed that LNA-modified oligonucleotides induced hepatotoxicity as indicated by increased transaminase activity and increased organ to body weight ratio in preclinical toxicology studies. The potential hepatotoxic effect of miRNA, a risk described for many new molecular entities and a topic of many investigations [50], requires careful examination in a case-by-case basis depending on the targeted disease, the demonstrated efficacy, and the alternative treatment opportunities available.

14.4 Concluding Remarks

In cardiovascular physiology and pathology, miRNAs represent an emerging field from which several therapeutic opportunities could be derived. Genetic and pharmacologic studies of various miRNAs have shown them to be involved in the genesis and progression of many diseases such as those associated with aging [51], and the studies summarized in this chapter using heart failure as an example provide an illustration of their potential to deliver novel therapeutic modalities. Many unknowns that remain to be investigated to move miRNA biology to therapeutic reality especially when considering cardiovascular diseases represent opportunities for the development of novel technologies, methodologies, and treatments that eventually will benefit patients. Among them are the development of integrative system biology approaches to understand fully the miRNA effects at cellular, organ, and

organism levels; the identification of delivery systems to ensure that the right dose is reaching the right molecular target, in the right tissue at the right time in a disease; and a careful understanding of potential adverse effects when administered either alone or in combination with conventional therapies. In addition to small noncoding RNAs (miRNAs), studies using high-throughput sequencing screens have described many long noncoding transcripts (long noncoding RNAs), of more than 200 nucleotides long. Together, small and long noncoding RNAs are increasingly demonstrated as key players in gene regulatory networks involved in cardiovascular biology and pathophysiology [52–55]. Both small and long noncoding RNAs are therefore opening new avenues to improve the understanding and the treatment of cardiovascular diseases like heart failure.

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Chapter 15
Gene Therapy in Cardiovascular Disease

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Veritas filia temporis – Aulus Gellius

Abstract Cardiovascular gene therapy applications began about 25 years ago. Since then, an in-depth understanding has accumulated on the underlying mechanisms of molecular structure as well as the development and function of the cardiovascular system in normal and disease states. In accordance with this, gene-based approaches have undergone substantial changes. Cardiovascular gene therapy should ideally deliver the genetic material to a specific target and reach a level of expression sufficient for therapeutic action. To achieve this, one needs to select a strategy with gene overexpression or gene silencing, suitable vectors and promoters, specific molecular targets known to be involved in a certain cardiovascular disease, and organ-targeted delivery techniques. Pharmacologic intervention has substantially increased survival and decreased morbidity in acquired and congenital cardiovascular diseases but still has multiple limitations including the targeting of symptoms rather than the pathological mechanism, difficulty in achieving efficacy, large variation between dose and concentration-dependent pharmacokinetics, and side effects. The progress in molecular biology and pharmacogenomics technology could allow for the development of gene containing drugs, which have the potential in the near future to momentously improve the management of a variety of clinical cardiovascular problems.

Keywords Gene delivery vectors • Gene transfer techniques • Cardiovascular molecular targets • Cardiovascular gene therapy • Coronary heart disease • Heart failure

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15.1 Introduction

Currently, gene-based therapy is recognized as a potentially powerful new therapeutic weapon for treating recurrent and/or refractory cardiovascular disease. Genetic manipulation may supplement or be applied without standard pharmacotherapy. Advantages of gene therapy approaches over traditional treatment include the ability to change the structure and function of the cell at the molecular level and to directly target intracellular signaling pathways. These effects can lead to cellular reprogramming with tissue regeneration that cannot be accomplished with existing drugs. Moreover, gene therapy provides the possibility to maintain a constant high concentration of transgene in desired tissues or organs over time, with a potential for more favorable cost because it does not require daily use for chronic disease. Currently, it is unclear if and how transgene expression could be terminated after exerting its therapeutic effect.

During the last decade, the concept and purposes of gene therapy have changed considerably. Today, it includes not only replacement of a defective gene with a functional copy but also use of nucleic acid transfer to treat or prevent complex multigenic diseases. Moreover, the earlier objectives were only to cure diseases not amenable to regular pharmacotherapy; gene therapy now includes viral and nonviral transfer of different genes to treat the majority of cardiovascular disease, genetic modification of stem cells for transplantation, delivery of antisense technology or ribozyme RNA to inactivate a specific gene at the mRNA level, vaccination with transgene inducing expression of antigens for immunization, sequence-specific gene silencing with short hairpin RNA, etc.

At the beginning of the era of gene transfer, researchers perceived it only as a tool to explore new genes and their functions, to study signal transduction and regulation, and to develop transgenic animal models. Creation of vectors for the insertion of genes into mammalian cells and the decoding of the human genome opened the door for the clinical use of gene-based treatment. As expected, the development of such a treatment has encountered many challenges and uncovered previously unknown insights into gene interactions and regulation.

The first cardiovascular gene transfer was demonstrated in 1989 with the transfection of porcine endothelial cells ex vivo with retrovirus carrying a marker gene [1]. The first clinical trial was performed later using direct introduction of a VEGF gene construct as naked DNA to treat hind limb ischemia [2]. Recently, the first gene therapy drug (Glybera) was approved by the European Medicines Agency for the treatment of lipoprotein lipase deficiency [3]. Despite this progress, we must note with regret that the number of cardiovascular clinical trials as of 2014 is 162 compared to 1,331 for cancer, placing fourth among gene therapy clinical trial targets in spite of the fact that cardiovascular disease is still the leading cause of death in the world [4] (Fig. 15.1a).

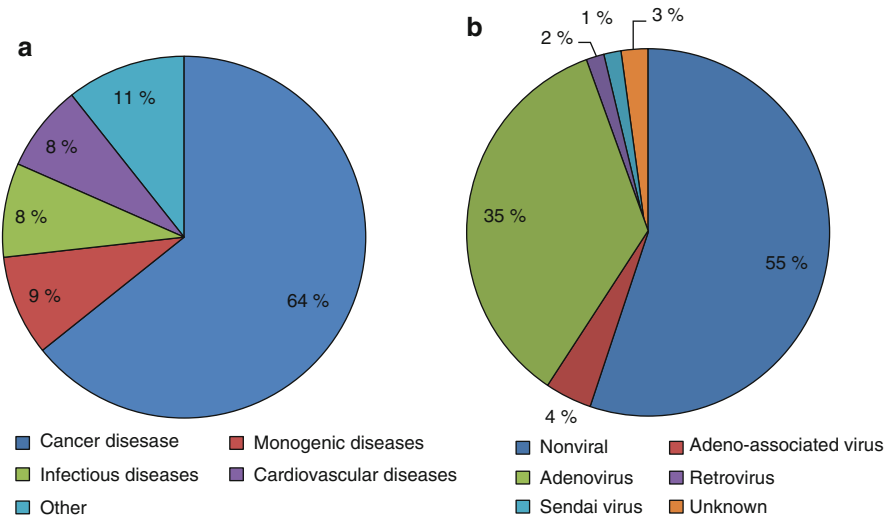

Fig. 15.1 Gene therapy clinical trial data. (**a**) Relative distribution of clinical trials by disease. (**b**) Relative distribution of cardiovascular gene therapy clinical trials by vector used

15.2 Gene Therapy Strategy

Two basic types of gene therapy strategies are currently employed in cardiovascular disease.

The *first strategy* is the exogenous overexpression of a target gene, aiming to increase the activity of a gene whose endogenous function may be impaired or downregulated as a result of mutation or a pathological process. In this case, cDNA encoding the deficient gene is delivered to the nuclei and the replaced gene product is expressed and interacts with a defined cell mechanism. The goal is to restore normal function or reverse disease progression.

The *second strategy* is the inactivation or silencing of target genes exhibiting maladaptive activity. Potential approaches in this strategy include (i) expression of a peptide or protein inhibitor, (ii) the use of truncated proteins to express only the part of the protein aimed at direct inhibition of enzyme function or disruption of protein-protein interactions, and (iii) the use of RNA interference technology [5]. This strategy can be performed at the transcriptional level (antisense oligonucleotides) or at the posttranscriptional level (ribozymes and small interfering RNA).

- Double-stranded oligonucleotides (decoy) have been used to inhibit transcription factors involved in the activation of pathogenic genes [6].
- Short single-stranded deoxyoligonucleotides (antisense oligonucleotides) bind to the target gene mRNA and prevent it from being translated.

- Small interfering RNAs (siRNAs) are short RNAs that knock down the endogenous activity of a pathogenic gene by induction of sequence-specific gene modification.
- Proof of principle of efficient RNA interference using adenovirus-based vector was demonstrated in the phenotyping of cardiac myocytes [7].
- Ribozymes are used to degrade target mRNA transcripts copied from the gene. Selective blockade with ribozyme oligonucleotides in a rat model resulted in inhibition of neointimal formation after vascular injury [8].

15.2.1 Ex Vivo and In Vivo Gene Therapy

Ex vivo gene therapy involves the harvest of cells from a patient followed by therapeutic gene replacement or addition into the target cell genome via vector. After this transduction, the cells are returned to the patient to exert their therapeutic effect. As an example, a study on VEGF was performed in a murine model. After 7 days in culture (ex vivo), endothelial progenitor cells (EPCs) were transduced with an adenovirus encoding the VEGF 164 gene. This manipulation augmented EPC proliferative activity and enhanced adhesion and incorporation of EPCs into quiescent and activated endothelial cells. After that, gene-modified EPCs were administered to mice with hind limb ischemia. Neovascularization and blood flow recovery were both improved, and limb necrosis was reduced by 63.7 % compared to control animals [9]. This ex vivo technique can allow for increased transgene expression, but can only be applied to certain cell types. Conversely, in vivo gene therapy involves the introduction of a virus carrying the genetic material directly into body tissue.

15.3 Main Prerequisites for Successful Cardiovascular Gene Therapy

Achieving specificity and efficiency of cardiovascular gene therapy requires the application and interaction of several essential factors:

(i) Selection of appropriate transfer vector and promoter
(ii) Development of targeted route and technique of gene delivery
(iii) Validation of the correct transgene molecular targets

Genetic material must be transferred into cells and expressed either at a constant level with insertion of the DNA into the cell genome or on a temporary basis with preservation of the DNA in an episomal state. Only use of special vehicles called vectors results in sufficient transport of genetic information into a cell. Vectors can be divided into viral and nonviral delivery systems. The optimal vector should be safe, have the ability to be transduced in vivo or ex vivo with reinfusion to the

patient, restrict expression to the desired tissue, provide the desired longevity of expression, have sufficient capacity for the genetic material to be transferred, and minimize the risk of an immune response.

15.3.1 Nonviral Vectors

Nonviral gene therapy targeting the cardiovascular system began to develop before viral vectors and is still the most prevalent approach in clinical trials (Fig. 15.1b). The basic advantages of nonviral vectors include a relative lack of inflammatory and immune responses (allowing gene reintroduction) as well as low toxicity and the absence of a potential for mutagenesis, removing the safety concerns characteristic of viruses. Moreover, there is no limiting size for transgene and both ease of production and stability over time [10]. The materials used in nonviral cardiovascular applications include plasmid DNA (pDNA) and small nucleic acids (antisense oligonucleotides or small interfering RNAs). pDNA is a double-stranded DNA encoding the gene of interest. The most significant limitation of nonviral vectors is a low transfer efficiency resulting in poor transgene expression. To improve this, many investigators have begun using chemical-based vectors such as cationic lipids and cationic polymers which promote cell uptake and trafficking and protect DNA from intracellular degradation. Left ventricular injection of pDNA in vivo was first performed about 25 years ago. Marker gene expression was observed in myocytes 3–4 weeks after delivery [11]. By 1998, a phase I clinical trial demonstrated the safety and efficiency of gene transfer of pDNA encoding vascular endothelial growth factor (VEGF) in patients with thromboangiitis obliterans (Buerger's disease) [12]. The same year, naked pDNA encoding VEGF was used as a sole therapy for patients with symptomatic ischemic heart disease (IHD). All patients had reduction in angina and improvement of myocardial perfusion on coronary angiography [13]. In another clinical trial, 28 patients with coronary heart disease (angina class II–III) received catheter-based intracoronary delivery of VEGF-plasmid liposome. This study demonstrated the safety and feasibility of liposome-mediated gene transfer [14].

15.3.2 Viral Vectors

Genetic engineering of vector from virus requires that coding genes and *cis*-acting sequences be separated into distinct nucleic acid molecules to prevent their reconstitution by recombination into productive viral particles. Linking of the viral *cis-acting* sequences (noncoding DNA regulating gene transcription) to the therapeutic gene produces replication-deficient particles able to transfer new genetic information [15]. The majority of viral vectors used for cardiovascular applications were derived from human pathogens from which essential genes have been deleted.

Table 15.1 Available vector systems for cardiovascular gene therapy

I. Nonviral	
Advantages	*Limitations*
(*a*) *Naked pDNA*	
Simple methodology	Low transduction efficiency
No limit to transgene size	Transient gene expression
Little immunogenicity and oncogenicity	
(*b*) *Antisense oligonucleotides*	
Easy to produce	Limited efficiency
No immune response	Degradation by nucleases
No integration in host cell genome	Transient effect
II. Viral	
Advantages	*Limitations*
(*a*) *Adenovirus*	
High transgene capacity	Immune-inflammatory response
High transduction efficiency	Short-term expression
Transfer to cardiac and vascular cells	
(*b*) *Adeno-associated virus*	
Long-term gene expression	Limited transgene capacity
Low immunogenicity	Difficult to produce in large quantities
High tropism to cardiac and vascular cells	
(*c*) *Lentivirus*	
Long-term expression	Integration into the host cell genome
Low immune response	Limited cardiovascular tropism
	Risk of oncogenicity

Several viral vectors have been explored successfully for cardiovascular gene transfer because of their various advantages (Table 15.1).

15.3.2.1 Lentiviral Vectors

These vectors are derived from primate and nonprimate immunodeficiency viruses. Expression and therapy are sustained and induce nonsignificant immune response. Maintenance of uncompromised cellular function and gene transfer to nondividing cells make these vectors attractive for a wide range of disease targets including cardiovascular diseases. It was shown that lentivirus-based vectors can effectively transduce well-differentiated cardiac myocytes and fibroblasts [16]. Third-generation lentiviruses with a majority of their native genome deleted can transduce human saphenous vein endothelial cells and smooth muscle cells (SMC) better than adeno-associated virus (AAV) serotypes [17]. The major limitation of lentiviral vectors is the risk of mutagenesis and oncogenesis.

15.3.3 Adenoviral Vectors

Adenoviruses contain a double-stranded DNA genome which remains episomal after introduction. Although this type of vector has historically been the most commonly used for preclinical and clinical studies in cardiovascular gene therapy, the pendulum is swinging toward the use of adeno-associated virus for many of these applications. The prevalent use of this vector is due to high expression kinetics, large cloning capacity, broad target cell tropism, efficient levels of transgene expression, and ease of high-titer manufacturing. Porcine hearts infected with an adenovirus vector containing the β-galactosidase (β-gal) gene showed significantly increased β-gal enzymatic activity compared to hearts injected with β-gal plasmid, with the efficiency of adenovirus-mediated gene transfer 140,000 times superior to plasmid DNA injection [18]. Clinical trials using recombinant adenoviral vectors to deliver angiogenic growth factors demonstrated therapeutic benefit [19]. However, adenoviral vector disadvantages such as innate and adaptive immune responses, transient gene expression, and a propensity to trigger inflammatory and toxic reactions in the host undoubtedly restrict its use.

15.3.3.1 Adeno-associated Viral Vectors

Lack of human pathology, low immunogenicity, strong tissue tropism for the heart and vessels, and efficient transduction of cardiomyocytes and SMC make this vector very attractive for cardiovascular applications. AAV can transfer a single-stranded DNA only about 20–25 nm (4.7 kb) in size. At least 11 AAV serotypes have already been described and a much larger number can be engineered through recombination of existing AAV viral capsid sequences [20]. The development of new AAV capsids significantly promoted AAV gene transfer technology in the last decade. Efficient transduction and persistent transgene expression in cardiac tissue were demonstrated in different animal models [21]. The ability of various AAV serotypes to transduce vascular cells in vitro and in vivo has also been proven [22]. Major concerns about AAV vector are its small packaging capacity, difficult production of high-titer vector stocks, and presence of preexistent neutralizing antibodies in at least 50 % of the human population.

15.4 Gene Delivery Techniques for Cardiovascular Applications

A great number of gene delivery techniques have been identified since the onset of cardiovascular gene therapy (Fig. 15.2). Two major conclusions should be drawn from the data: the route of gene delivery is no less important than the vector system, and gene delivery should be organ targeted with minimal or optimally zero collateral expression.

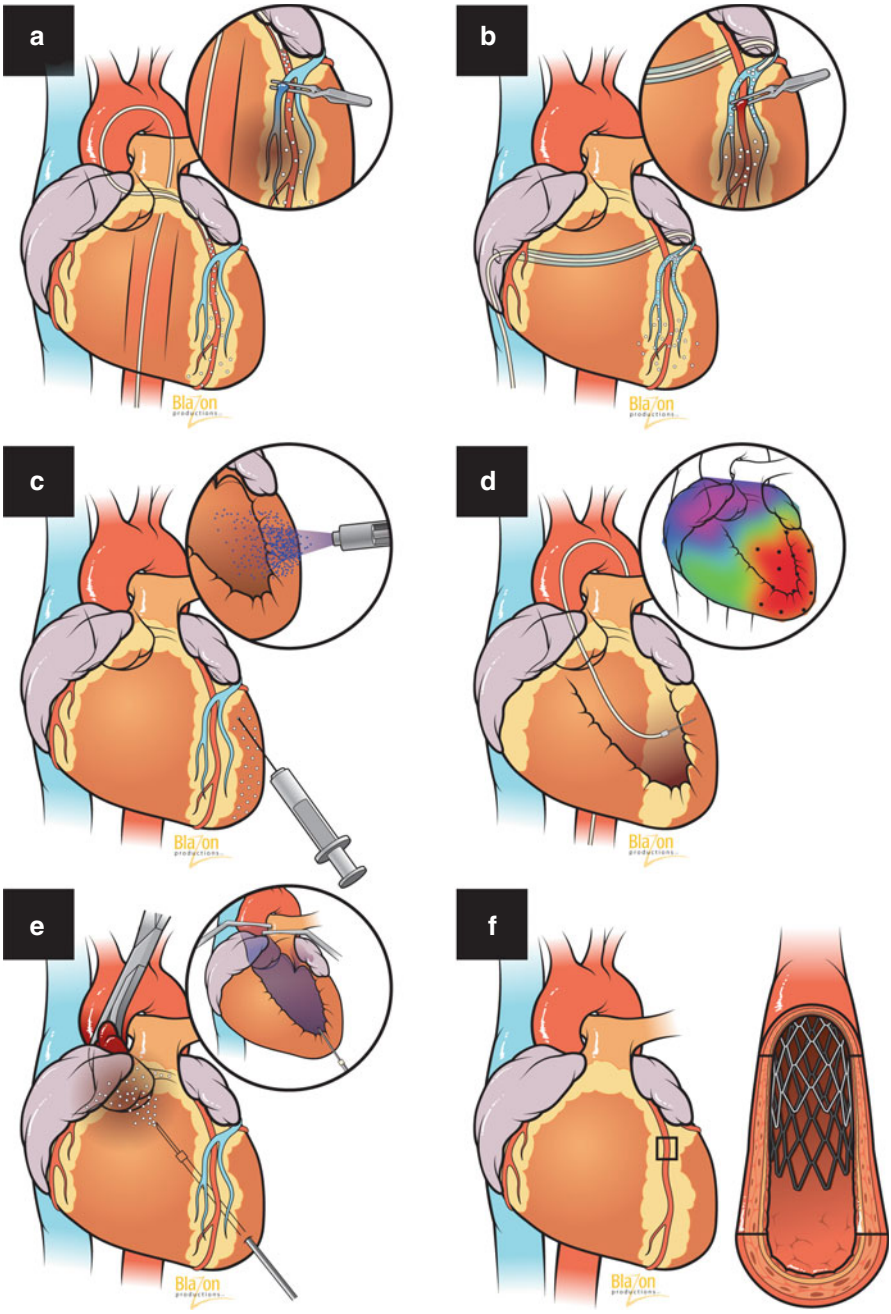

Fig. 15.2 Gene therapy delivery methods. (**a**) Antegrade intracoronary delivery (*inset*: with venous blockade). (**b**) Retrograde transcoronary sinus (*inset*: with arterial occlusion). (**c**) Intramyocardial injection, epicardial approach (*inset*: liquid jet injection). (**d**) Intramyocardial, endocardial approach (*inset*: image-guided delivery). (**e**) Intracavitary injection to left ventricle with aortic occlusion (*inset*: with aortic and pulmonary artery occlusion). (**f**) Transvascular intracoronary wall delivery via gene-eluting stent (*inset*: stent within artery)

15.4.1 Transvascular Route

Intravenous administration is the least invasive and simplest route for gene transfer. It finds its application in the treatment of diseases such as systemic hypertension and hyperlipidemia. However, in peripheral arterial disease as well as acquired and congenital cardiac disorders, this technique is ineffective due to first-pass pulmonary and hepatic uptake of vector and systemic dilution in blood circulation. Efficacy of antegrade intracoronary administration is much better, although it cannot escape systemic leakage. In an effort to achieve increased transduction, researchers began to use concomitant coronary venous blockade [23], transient coronary occlusion [24], and increased perfusion pressure [25]. Retrograde gene delivery through the coronary sinus enhanced expression due to a more than tenfold increase in coronary passage time [26] and an increase in venous capillary filtration rate [27]. Another significant advancement was the creation of a *closed-loop recirculatory system* which allowed separate heart and systemic circulation [28, 29]. Gene-eluting stents for *localized transvascular wall delivery* in cardiovascular pathology represent a new attractive alternative to standard angioplasty and vascular interventions. However, this method still needs additional research to assess its transduction efficiency.

15.4.2 Direct Intramyocardial Delivery Using Mechanical and Physical Approaches

Unlike the transvascular route, during direct gene delivery, transgene enters the extracellular matrix and somatic cells, bypassing the blood compartment which includes plasma proteins, blood cells, and neutralizing antibodies which substantially inactivate the vector. Moreover, this method allows for the application of high concentrations of transgene directly at the target site. This approach has been successfully applied in animal models of ischemia and cardiac arrhythmias as well as several clinical trials to induce angiogenesis [30]. Relatively low transduction efficiency led to use of image guidance devices such as the Noga system and a variety of physical and mechanical approaches enhancing cell membrane permeability for gene transfer. The most commonly used are *electroporation* which involves high-intensity electric pulses, *sonoporation* which involves attachment of genes to gas-filled microbubbles which are destroyed by ultrasound after injection, use of energy sources such as *laser* to induce tiny holes in cell membranes, and transfer of gene nanoparticles under the influence of a *magnetic field. Liquid jet injection*, *gene gun particle bombardment, and microinjection* are additional mechanical methods which have found application in direct gene delivery for cardiovascular disease.

15.5 Molecular Targets

Identification of potential targets in cardiovascular disease is a very complex and laborious process closely associated with the development of basic science in molecular biology and genetic engineering. For each new target, it is necessary to determine signaling pathways, cell membrane receptors, transcription factors, intracellular trafficking, and many other items that make it possible to influence them through gene therapy (Table 15.2).

15.5.1 Coronary Heart Disease (CHD)

CHD alone causes one of every six deaths in the United States. In 2014, an estimated 620,000 Americans will have a new coronary attack (defined as first hospitalized myocardial infarction or CHD death) and 295,000 will have a recurrent attack [31]. The failure rate of interventional coronary revascularization as a result of restenosis, multiple stenotic lesions, or suboptimal anatomy remains relatively high. Therefore, the possibility that a one-time delivery of transgene to myocardium may induce global therapeutic angiogenesis or improve contractile function appears very attractive. For CHD, the current genetic targets are varied (Fig. 15.3). It is quite likely that in the future, gene products must act on multiple molecular pathways or supplement existing pharmacotherapy of revascularization procedures.

A vast amount of preclinical and clinical research including phase I–II/III trials has been published regarding angiogenesis [32]. All studies demonstrated excellent safety and feasibility of using recombinant growth factors in CHD [33]. Preclinical gene therapy studies with vascular endothelial growth factor (VEGF) in various animal models of myocardial ischemia have demonstrated improvement in contractility and reduction of both infarct size and peri-infarct fibrosis [34, 35]. Although there was no clear demonstration of a clinical benefit in patients, important factors affecting efficient gene transfer in CHD were identified [36]. The exogenous administration of angiogenic factors including VEGF, hepatocyte growth factor, fibroblast growth factor (FGF), hypoxia-inducible factor-1α (HIF), angiopoietin-1, and insulin-like growth factor is a reasonable approach for therapeutic neovascularization. A phase II KAT trial provided evidence that VEGF-165 gene therapy during percutaneous coronary intervention increased myocardial perfusion [14]. The AGENT study with symptomatic CAD showed that after adenovirus-mediated FGF gene transfer, ischemic defect decreased in patients who were not candidates for revascularization [37]. In the REVASC clinical trial, adenovirus containing VEGF-121 was delivered by direct intramyocardial injection. Administration of VEGF121 resulted in objective improvement in exercise-induced myocardial ischemia [38]. A multicenter, randomized, double-blind, placebo-controlled clinical trial using HIF demonstrated improved perfusion by positron emission tomography analysis [39]. It is not surprising that animal experiments on healthy subjects without comorbidities using recombinant growth factors for angiogenesis were very promising yet the

Table 15.2 Gene therapy targets in cardiovascular disease

Cardiovascular diseases	Aims	Target genes
Hyperlipidemia	1. Reduction of LDL cholesterol	ApoB, apoE, apoA-1, eNOS, LDL receptor, NF-κB, VLDL receptors, decoy MSR, TNF-α, TIMPs
	2. Target atherosclerotic lesions	
	3. Modulation of MSR activity	
Systemic hypertension	1. Inhibition of genes involved in BP elevation	Kallikrein, adrenomedullin, eNOS atrial natriuretic peptide, angiotensinogen, β-adrenergic receptor, ACE, angiotensin receptor
	2. Inhibition of vasoconstriction-promoting genes	
Pulmonary hypertension	1. Suppression of pulmonary SMC proliferation and differentiation	BMPR2, eNOS, CGRP, prostacyclin synthase, adrenomedullin, VEGF, HGF
	2. Inhibition of pulmonary vascular remodeling	
Heart failure	1. Enhancing excitation-contraction coupling	SERCA2a, S100A1, phospholamban, PP-1, βARs, βARKct, adenylyl cyclase, Bcl-2, P13, Akt, HSP, TNF-α, HO-1, SDF, angiotensin II, endothelin 1, TIMP-1, parvalbumin, TGF-β system
	2. Reduction of adverse remodeling	
	3. Inhibition of apoptosis	
	4. Abrogation of fibrosis	
	5. Cytoprotection, stem cell repair	
Cardiac arrhythmias	1. Heart rate control	Gαi2, KCNE3, connexin-43, KiR(2.1b), TGF-β, βARs, HCN2, Kv1.5
	2. Biological pacemaker function	
	3. Repolarization and reduction of QT interval	
	4. Modulation of cardiac conduction	
Peripheral arterial disease	1. Therapeutic angiogenesis	VEGF, HGF, FGF, HIF-1α, Del-1, PDECGF, eNOS, TIMPs, HO-1, prostacyclin, SCDF-1α, sonic hedgehog, netrin, thrombopoietin, C-type natriuretic peptide, COX, Ras, Fas ligand, β-interferon, βAR kinase
	2. Stabilizing plaque and diminishing risk of rupture	
	3. Prevention of thrombosis	
	4. Limit restenosis after angioplasty	
	5. Hindering intimal hyperplasia in vein grafts	

apoB apolipoprotein B, *apoE* apolipoprotein E, *apoA-1* apolipoprotein A-1, *eNOS* endothelial nitric oxide synthase, *LDL* low-density lipoprotein, *NF-κB* nuclear factor kappa-light-chain enhancer of activated B cells, *VLDL* very low-density lipoprotein, *MSR* macrophage scavenger receptor, *TNF-α* tumor necrosis factor-α, *TIMP* tissue inhibitor of metalloproteinase, *ACE* angiotensin-converting enzyme, *BMPR2* bone morphogenetic protein receptor type II, *CGRP* calcitonin gene-related peptide, *VEGF* vascular endothelial growth factor, *HGF* hepatocyte growth factor, *SERCA2a* sarco(endo)plasmic reticulum Ca^{2+} ATPase isoform 2a, *S100A1* S100 calcium-binding protein A1, *PP*-1 protein phosphatase-1, *βARs* β-adrenoreceptors, *βARKct* β-adrenergic receptor kinase-1 (carboxy terminus), *Bcl*-2 B-cell lymphoma 2 gene, *P13* p13 tumor supressor gene, *Akt* protein kinase B, *HSP* heat shock protein, *HO*-1 heme oxygenase-1, *SDF* stromal cell-derived factor, *TGF*-β transforming growth factor β, *Gαi2* G-protein i subunit α type 2, *KCNE3* potassium voltage-gated channel Isk-related family member 3, *KiR(2.1b)* human cardiac inwardly-rectifying K+ channel 2.1b, *HCN2* potassium/sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 2, *Kv1.5* voltage dependent potassium channel Kv1.5, *FGF* fibroblast growth factor, *HIF-1α* hypoxia-inducible factor 1-α, *Del-1* developmental endothelial locus-1, *PDECGF* platelet-derived endothelial cell growth factor, *SCDF*-1α stromal cell derived factor-1α, *COX* cytochrome c oxidase, *Ras* rat sarcoma G-protein superfamily, *Fas* tumor necrosis factor receptor subfamily 6

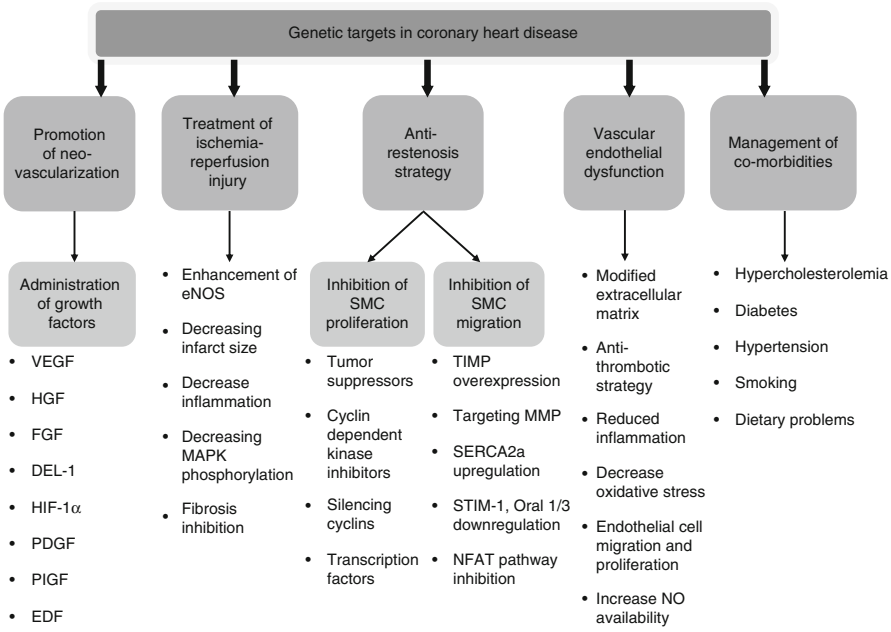

Fig. 15.3 Genetic targets in coronary heart disease. *VEGF* vascular endothelial growth factor, *HGF* hepatocyte growth factor, *FGF* fibroblast growth factor, *DEL-1* developmental endothelial locus-1, *HIF-1* hypoxia-inducible factor-1, *PDGF* platelet-derived growth factor, *PIGF* placental growth factor, *EDF* erythroid differentiation factor, *eNOS* endothelial nitric oxide synthase, *MAPK* mitogen-activated protein kinase, *SMCs* smooth muscle cells, *TIMPs* tissue inhibitor metalloproteinases, *MMPs* matrix metalloproteinases, *SERCA2a* sarcoendoplasmic reticulum calcium adenosine triphosphatase isoform 2a, *SIM-1* stromal interaction molecule-1, *Oral 1/3* ORAI calcium release-activated calcium modulator 1/3, *NFAT* nuclear factor of activated T cells, *NO* nitric oxide

clinical studies demonstrated limited benefits. Furthermore, most of the clinical trials in CHD involved the use of gene therapy for "no-option" patients (patients whose cardiovascular health is poor enough to preclude any other treatments). With these conditions limiting the effectiveness of gene therapy, a single delivery may not cause measurable improvement. Thus, it is very important to choose patients who may respond to gene therapy treatment and to standardize the stage of disease, pharmacological treatment, angiographic findings, and comorbidities.

15.5.2 Hyperlipidemia and Atherosclerosis

Many patients with dyslipidemia cannot achieve optimal cholesterol levels with existing pharmacological therapies [40] (Chap. 28). Therefore, hypercholesterolemia is a promising target for gene therapy. Familial hypercholesterolemia (FH) is an inherited monogenetic disorder caused by low-density lipoprotein (LDL) receptor deficiency. A considerable number of proof-of-principle research studies have been performed in animal models of homozygous FH [41]. The first pilot study of liver-directed gene

therapy in patients with FH demonstrated significant and prolonged reductions in LDL cholesterol [42]. In general, gene therapy approaches for atherosclerosis are progressing in two directions: to decrease cholesterol levels in the blood through liver-directed molecular therapy and to target atherosclerotic lesion directly or atherosclerosis-related vascular complications [43]. Apolipoprotein B100 (ApoB) is the main form of LDL and therefore a major target for gene therapy. Blockade of serum ApoB mediated by short interfering RNAs (siRNA) induced up to a 95 % reduction of liver ApoB mRNA and serum ApoB protein and a significant reduction of serum LDL in a mouse model with humanlike lipid profile [44]. Inhibition of ApoB synthesis with mipomersen (second-generation antisense oligonucleotide) decreased LDL cholesterol concentration by 25 % in 34 patients [45]. Another gene therapy product modulating cholesterol level is PCSK9, which binds to LDL receptors. A phase 1 trial demonstrated that inhibition of PCSK9 synthesis by RNA interference (RNAi) in 32 participants is a potentially effective mechanism to reduce LDL cholesterol [46]. Endothelial nitric oxide synthase (eNOS) gene transfer enhanced the antiatherogenic parameters of the atherosclerotic vessels and can reduce inflammatory cell infiltration and wall lipid deposition. Another way to decrease inflammation in atherogenic processes is targeting NF-kB which acts as a regulator of inflammatory events in endothelial cells [47].

15.5.3 Primary Systemic Hypertension

Hypertension has adverse effects on cardiovascular function and is a major risk factor for development of aortic dissection, intracerebral hemorrhage, ischemic heart disease, peripheral vascular disease, and renal insufficiency. The most effective antihypertensive drugs are short-term acting, must be taken everyday, and produce significant side effects. Finally, all of these medications decrease symptoms but do not cure the underlying causes; thus, their discontinuance results in the reappearance of high blood pressure (Chaps. 30 and 31). Genetic manipulation for hypertension in theory can induce a permanent effect with precise specificity based on molecular structure and, on a conceptual level, such an approach would be better than pharmacological therapy.

Potential gene strategies for control of hypertension are (i) use of antisense oligonucleotides to inhibit genes involved in elevated blood pressure pathways, like members of the renin-angiotensin system, angiotensin II, and beta-adrenergic receptors, and (ii) overexpression of genes encoding proteins that induce vasodilatation like kallikrein, atrial natriuretic peptide, or endothelial NOS.

15.5.3.1 Overexpression of Vasodilator Genes

DNA construct containing the human eNOS caused a significant reduction of systemic blood pressure for 6 weeks in hypertensive rats [48]. A single injection of the human adrenomedullin gene resulted in a prolonged reduction of blood pressure with a maximal reduction of 41 mmHg 9 days after gene delivery [49]. A maximal

blood pressure reduction of 50 mmHg was observed in rats receiving kallikrein gene delivery, as compared to rats receiving only marker gene [50]. These and other studies provide support for the use of vasodilator gene overexpression to control hypertension.

15.5.3.2 Antisense Knockdown Approach

Downregulation of angiotensinogen mediated by antisense oligonucleotides effectively reduced blood pressure in rats with cold-induced hypertension [51]. A prolonged antihypertensive effect of angiotensin type 1A receptor downregulation via antisense oligonucleotide was shown in a renovascular model of hypertension [52]. Antisense inhibition of β_1-adrenergic receptor mRNA has advantages over currently used β-blockers in providing a profound and prolonged reduction in blood pressure without affecting heart rate in spontaneously hypertensive rats [53].

Despite these and other positive results, several issues should be resolved before this strategy will be implemented in practice:

(i) Creation of experimental models with the possibility to reverse established hypertension
(ii) The development of a vector system that can regulate transgene expression
(iii) The discovery of an ideal gene target for hypertension
(iv) The assessment of safety controls for viral gene delivery systems [54]

15.5.4 Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a hemodynamic and pathophysiological condition involving abnormal proliferation of vascular endothelial cells with intimal thickening and muscularization of the distal pulmonary arteries, which leads to an increase in mean pulmonary arterial pressure of more than 25 mmHg at rest. Different congenital and acquired cardiovascular diseases are associated with PAH. Development of obstructive pulmonary vascular remodeling ultimately causes right-side heart failure with a 5-year mortality rate of 50 % [55] (Chap. 45 and 59).

During the past decade, patients with familial PAH were found to have germline heterozygous mutations in bone morphogenetic protein receptor II (BMPR2). Mutations in BMPR2, a member of the transforming growth factor-beta (TGF-beta) receptor superfamily, resulted in cell proliferation and differentiation in the pulmonary tree [56]. Activation of the BMPR2 axis led to the suppression of proliferation and the activation of apoptosis in human pulmonary artery smooth muscle cells [57]. BMPR2 replacement gene therapy appears attractive to correct heredity-caused PAH [58].

Nitric oxide (NO) synthesized by eNOS is a potent vasodilator and is considered to play an important role in the proliferation of pulmonary vascular smooth muscle cells. Overexpression of eNOS-derived NO significantly attenuated muscularization

of small arterioles and therefore inhibited remodeling of the pulmonary vasculature induced by hypoxic pulmonary vasoconstriction [59]. Smooth muscle cell proliferation and migration characterize the pathogenesis of pulmonary hypertension.

Calcitonin gene-related peptide (CGRP) has a high pulmonary vascular activity which is reduced in the case of pulmonary hypertension. Studies have shown CGRP can inhibit pulmonary smooth muscle cell proliferation by binding to CGRP receptors [60]. The lungs of rats transplanted with CGRP-expressing endothelial progenitor cells demonstrated a decrease in both mean pulmonary artery pressure and total pulmonary vascular resistance at 4 weeks. Morphologic examination of pulmonary vasculature also showed that pulmonary vascular remodeling was remarkably inhibited as the vascular medial wall thickness was reduced [61].

In certain etiologies of PAH, the gene therapy approach is required to use short-acting proteins such as prostacyclin synthase (PS) [62]. PS catalyzes the synthesis of prostacyclin and PS deficiency plays a part in the development of PAH. PS has a major role in modifying the pulmonary vascular response to chronic hypoxia and its overexpression protected lungs of transgenic mice from PAH [63].

Inhalation of the vasodilator peptide adrenomedullin can decrease pulmonary vascular resistance in patients with idiopathic PAH [64]. Other genes that have shown therapeutic effects in PAH include vascular endothelial and hepatocyte growth factors which possess angiogenic effects that cause lung regeneration and protect from endothelial injury.

15.5.5 Peripheral Arterial Disease

Peripheral arterial disease is a slowly progressing vascular circulatory disorder caused by the advance of atherosclerosis. Clinical manifestations accompanying poor prognoses include development of ischemic lesions, claudication, intractable rest pain, and critical leg ischemia.

Alternative applications of gene therapy include management of vascular stenosis, restenosis, and postoperative graft failure. Therapeutic angiogenesis improves tissue perfusion through the growth and proliferation of blood vessels after delivery of angiogenic growth factors. A high number of experimental and clinical trials were performed with vascular endothelial growth factors (VEGF), hepatocyte growth factor, fibroblast growth factor, and hypoxia-inducible factor-1α. Increased resting and maximum flow after intra-arterial administration of VEGF mediated by plasmid was first demonstrated in humans with critical leg ischemia 18 years ago [2]. There have since been about 20 clinical trials with proangiogenic cytokines. The main objectives pursued by therapeutic angiogenesis are:

(i) Proliferation and migration of endothelial cells followed by formation of new vessels
(ii) Remodeling of preexisting collaterals
(iii) Improvement of vessels' vasomotor function
(iv) Tissue regeneration [65].

The ability of gene-based therapy to alleviate the pathophysiological changes in PAD was demonstrated in diverse animal models and multiple clinical trials. However, for the achievement of positive long-term clinical results, several obstacles must be overcome: transient therapeutic gene expression, off-target effects, selection of patients suitable for clinical trials, and identification of the ideal vectors and delivery routes [36].

15.5.6 Heart Failure

Modern pharmacological therapy for heart failure (HF) requires the use of many drugs at the same time which can lead to complex drug interactions and side effects. Despite the fact that IHD is the most common cause of HF, gene therapy targets for the treatment of these two diseases differ [66].

Gene therapy to rescue the failing myocardium in HF has focused primarily on excitation-contraction coupling and reduction of adverse remodeling regardless of etiology [67]. The main molecular targets are calcium cycling proteins, the β-adrenergic system, homing of stem cells, and apoptosis [68]. Targeting Ca cycling proteins in turn involves *overexpression of SERCA2a* [69–71], *phospholamban inhibition* [72], and *S100A1 overexpression* [73]. β-adrenergic signaling targets include *overexpression of β-AR* [74], *inhibition of GRK2 with βARKct* [75, 76], and a*ctivation of adenylyl cyclase expression* [77]. The ability to promote the homing of stem cells in ischemic cardiomyopathy was demonstrated with the SDF1/CXCR4 complex [78].

15.5.6.1 SERCA2a

Dysregulation of intra- and extracellular calcium cycling transport which occurs via the sarcoplasmic reticulum (SR) calcium adenosine triphosphatase (Ca^{2+} pump (SERCA2a)) in both the systolic and diastolic phases is one of the major characteristics of HF. SERCA2a downregulation or inhibition causes a prolongation of Ca^{2+} transient and an increase in systolic and diastolic intracellular Ca^{2+} [68, 79]. Improvement of contractility has been demonstrated in a number of experimental and clinical studies. Cardiac overexpression of SERCA2a in HF significantly improved LV function, decreased markers of oxidative stress, decreased both myocyte apoptosis and hypertrophy, and arrested adverse remodeling in large animal ischemic cardiomyopathy [70, 71] (Chap. 4). The first SERCA2a clinical trial in patients with HF began in 2008 [80]. At 6 months follow-up, patients reported improvement and stabilization of clinical symptoms and functional tests [69].

15.5.6.2 AC6

Adenylyl cyclase (AC6) regulates the transition of adenosine triphosphate to cyclic adenosine monophosphate and initiates many cardiac intracellular and extracellular signaling pathways. Diminished AC6 activity is associated with downregulation and desensitization of β-adrenergic receptors in HF [77]. Intracoronary delivery of

adenovirus encoding AC6 halted LV remodeling in different HF models. A clinical trial of AC6 gene transfer for HF is in progress [81].

15.5.6.3 SDF-1/CXCR4

Stromal cell-derived factor-1 (SDF-1) and its receptor CXCR4 play an important role in the process of stem cell mobilization to the ischemic cardiac environment and are therefore crucial for myocardial repair. Endocardial delivery of DNA plasmid encoding SDF-1 in 17 patients with ischemic cardiomyopathy (NYHA class III) demonstrated with improvement in 6-min walk distance and quality of life [78].

15.5.6.4 βAR

β-Adrenergic receptor (βAR) signaling system plays a pivotal role in cardiac function and has emerged as an attractive therapeutic molecular target in HF [82]. The carboxyl terminus of the β-adrenergic receptor kinase (βARKct), a competitive inhibitor of G protein-coupled receptor kinases (GRKs), has the potential to resolve βAR signaling abnormalities related to HF (Chap. 5). βARKct delivery enhanced cardiac contractility and increased adrenergic reserve in a large animal model [76]. The same trend was observed in different HF models [83, 84]. With an increasing basic understanding of cardiac pathology, the establishment of more efficient techniques of gene transfer, and the discovery of new molecular pathways, gene delivery will undoubtedly become an essential complement to conventional therapy of heart failure.

15.5.7 Cardiac Arrhythmias

Many cardiovascular diseases are associated with impairments to the heart's electrophysiological function. The current available therapeutic options are far from perfect. Indeed, ventricular arrhythmias were detected in 43 % of human sudden death cases [31] and several clinical trials have associated antiarrhythmic pharmacotherapy with increased mortality [85] (Chap. 52). The development of new gene transfer methods with percutaneous cardiac catheterization procedures has placed arrhythmias within reach of gene therapy. This strategy targeting arrhythmias includes heart rate control and biological pacemaker function, repolarization and prolonged QT interval, and modulation of cardiac conduction [86, 87].

Atrial fibrillation (AF) is the most common chronic arrhythmia associated with an adverse prognosis. It is estimated that 2.2 million Americans have intermittent or sustained AF. AF typically appears secondary to other heart diseases such as hypertension, valvular disease, or ischemic heart disease (Chap. 50). Gene-mediated rate control was demonstrated in a physiologically relevant model of persistent AF. After 3 weeks of atrial fibrillation, swine received atrioventricular nodal gene transfer with adenovirus encoding the cGi gene. cGi caused a sustained 15–25 % decrease in heart rate and resulted in reversal of the clinical symptoms [88].

One of the main manifestations of failing myocytes is delayed terminal repolarization with QT interval prolongation. Adenoviral gene delivery of KCNE3, a regulatory component of the delayed rectifier potassium channel, accelerated cardiac repolarization and corrected the QT interval [89]. Targeted overexpression of connexin-43 in the healed infarct border zone improved conduction velocity and reduced ventricular tachycardia susceptibility [90]. In a postinfarcted large animal model with reproducibly inducible ventricular tachycardia, the effects of KCNH2-G628S gene transfer on the arrhythmia were evaluated. One week after gene delivery, all transgenic animals had complete elimination of ventricular arrhythmia [91]. Continuing research in this area may result in successful clinical application of gene therapy for the treatment or prevention of arrhythmias.

15.5.8 Gene Therapy Breakthrough and Challenging Opportunities

The concept of gene therapy was introduced in the 1970s after the development of recombinant DNA technology. Despite initial great expectations, the field was slowed down by the failure of initial clinical trials, reports of well-known complications, and both safety and ethical concerns. These early setbacks resulted in widespread skepticism, which to a certain degree persists to this day. However, recent successes of gene therapy undoubtedly inspire molecular biologists and geneticists, including treatment of Leber's congenital amaurosis after subretinal delivery of recombinant adeno-associated viral vector carrying RPE65 gene [92], progress in X-linked adrenoleukodystrophy patients treated with genetically corrected ex vivo CD34 cells [93], and achievement of remission in chemotherapy-refractory B-cell lymphoma after injection of genetically modified T cells [94]. Since 2008, several very promising clinical trials have begun in ischemic heart disease and heart failure including targeting calcium cycling proteins (sarcoplasmic reticulum calcium adenosine triphosphatase overexpression, phase I and phase II/III), effector molecules for β-adrenoreceptors (adenylyl cyclase overexpression, phase I), and endocardial delivery of DNA plasmid encoding stromal cell-derived factor (phase I). These clinical trials based on molecular biology demonstrate a new direction for cardiovascular gene therapy which, unlike surgical approaches, can improve heart and blood vessel function by correcting the pathophysiological disease mechanism on the cellular level. And unlike pharmacological approaches, gene therapy can achieve long-term benefit in chronic cardiovascular diseases from as few as a single treatment.

15.6 Concluding Remarks

Gene therapy is a very promising and rapidly growing part of contemporary medicine, and it is very important to correctly implement it in the treatment of cardiovascular disease. Much effort has been devoted to overcoming safety and ethical

concerns. Nevertheless, questions still remain about the potential for mutagenesis and malignant transformation when certain viral vectors integrate into the host genome, vector toxicity, and the potential for an immune response. Other issues currently being investigated include restriction of collateral organ biodistribution, targeting of specific cells, and relatively low transduction efficiency. Clinically reliable delivery techniques also require improvement to create a minimally invasive closed recirculatory system. Optimization of these issues would allow for gene therapy to become an accepted treatment for cardiovascular disease.

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Part II
Cardiac Hypertrophy and Cardiomyopathy

Chapter 16
Cardiac Hypertrophy and Hypertrophic Cardiomyopathy: Introduction and Management

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Abstract The magnitude of hypertrophic response of the left ventricle to pressure overload is variable and likely is mediated by genetic factors as well as other identified mechanisms. Myocardial hypertrophy is a common phenotype of multiple cardiac disease entities. Left ventricular hypertrophy (LVH) causes significant morbidity and mortality in adults. Increased pressure overload is a key stimulus for the development of LVH in hypertensive patients as well as in those with aortic valve stenosis through several molecular mechanisms. Hypertrophic cardiomyopathy (HCM) is present in 1 in 500 people in the general population and is the most common genetically transmitted cardiomyopathy. HCM can be caused by more than 1,400 different mutations and is transmitted in an autosomal dominant pattern. Many individuals affected by HCM are undiagnosed, and most do not experience lethal events or symptoms. However, those who develop symptoms such as dyspnea, angina, and lightheadedness can experience functional disability secondary to heart failure and stroke as well as to sudden cardiac death (SCD). The majority of HCM patients are treated medically with the initial aim of reduction of symptoms along with reducing the risk for SCD. Therapy of patients with HCM can be classified into medical, interventional/device, and surgical treatments.

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16.1 Part I: Introduction to Cardiac Hypertrophy and Hypertrophic Cardiomyopathy

Patients develop left ventricular hypertrophy (LVH) secondary to left ventricular (LV) pressure overload. However, the magnitude of hypertrophic response of the LV to pressure overload is variable and likely is mediated by genetic factors as well as other pathophysiological mechanisms. One in three Americans suffers from systemic hypertension. Of these, about 40 % have secondary LVH. Causes of LV pressure overload include, in addition to systemic hypertension, aortic stenosis, discrete subvalvular aortic stenosis (DSAS), supravalvular aortic stenosis, aortic coarctation, HCM, and hypertensive HCM. Cardiac hypertrophy may lead to LV diastolic dysfunction, which is a major cause of congestive heart failure (CHF). In addition, an increase in LV mass due to LVH is associated with an increased risk of sudden death [1, 2].

16.1.1 Pathophysiologic Mechanisms of Myocardial Hypertrophy

Myocardial hypertrophy is a common phenotype of multiple cardiac disease entities. Although, right ventricular hypertrophy is a relatively common finding in LVH [3, 4], it is the latter that causes the vast majority of hypertrophy-associated morbidity and mortality in adults. Adaptive (and sometimes maladaptive) responses to hemodynamic load (i.e., athlete's heart, hypertensive heart disease, valvular disease) have a different underlying pathophysiology, when compared with infiltrative cardiomyopathies (i.e., amyloidosis, Fabry disease, mucopolysaccharidosis), mitochondrial disorders, and familial hypertrophic cardiomyopathies. What these disease entities do have in common is that our understanding of their putative mechanisms is far from complete. More recently some overlap of genetic and molecular mechanisms of different types of cardiomyopathies have been identified [5]. Table 16.1 summarizes causes and clinical findings of myocardial hypertrophy. In this chapter, we present the pathophysiology of the two most common pathological forms of myocardial hypertrophy in more detail: (1) hypertensive heart disease and (2) familial hypertrophic cardiomyopathies (HCM), the latter of which is the primary focus of this chapter.

Macroscopically, LVH is an increase of myocardial muscle mass. On a cellular level, there is considerable evidence that hypertrophy is caused by re-expression of many fetal genes and downregulation of adult genes. Re-expression of β-myosin heavy chain—most commonly found in areas of fibrosis and perivascular myocardial regions— and atrial natriuretic factor and α-skeletal actin is thought of as

Table 16.1 Overview and characteristics of diseases associated with left ventricular hypertrophy

	Athlete's heart	**Hypertensive heart disease**	**Hypertrophic cardiomyopathy**	**Cardiac amyloidosis**	**Mitochondrial myopathy**	**Mucopolysaccharidosis**	**Anderson-Fabry disease**
Onset age	Adolescence/ adulthood	Adulthood	Adolescence/ adulthood	Adulthood	Early childhood/ adolescence	Early childhood/ adolescence	Adulthood
Clinical presentation	No typical symptoms	Heart failure symptoms; typical angina; palpitations	No typical symptoms; dyspnea/angina at exercise in case of LVOT; syncope	Mostly symptoms of heart failure (despite normal LV function)	Systemic disease (no typical cardiac symptoms)	Systemic disease (no typical cardiac symptoms)	No typical symptoms
ECG	Possible high voltage QRS; resting bradycardia; ST segment abnormalities	Possible high voltage QRS; ST segment abnormalities	High voltage QRS; ST segment abnormalities	Absence of high ECG voltages despite LVH; conduction abnormalities	Dependent on subtype: conduction abnormalities; AV block	Conduction abnormalities; AV block	Conduction abnormalities; AV block
Echocardiography	Concentric LVH	Concentric LVH	Concentric assymmetric LVH	Concentric LVH; "sparkly" pattern; restrictive LV filling pattern; atrial enlargement; thickened cardiac valves and papillary muscles	Dependent on subtype: hypertrophic, dilative, restrictive pattern	Concentric LVH; valvular thickening with dysfunction (mostly aortic and mitral valve)	Concentric LVH; focal hypokinesia and wall thinning basal inferolateral; thickened aortic and mitral leaflets

(continued)

Table 16.1 (continued)

	Athlete's heart	**Hypertensive heart disease**	**Hypertrophic cardiomyopathy**	**Cardiac amyloidosis**	**Mitochondrial myopathy**	**Mucopolysaccharidosis**	**Anderson-Fabry disease**
CMR	Ischemic as well as nonischemic patterns of LGE	No specific LGE pattern; rather patchy pattern	Patchy or confluent LGE at the insertion points of the right ventricle into the LV and in the septum	LGE in the entire subendocardial circumference	Intramural LGE basal inferolateral in CPEO/KSS; unique HCM-like LGE in MELAS	No data	Subepicardial LGE basal inferolateral
EMB	Myocyte hypertrophy; expansion of interstitial and perivascular fibrosis by progressive collagen accumulation	Myocyte hypertrophy; expansion of interstitial and perivascular fibrosis by progressive collagen accumulation	Myocyte hypertrophy with nuclear enlargement; myofiber disarray and interstitial/ replacement fibrosis; reduced arteriolar density	Green-appearing fibrils during Congo red staining under polarized microscopy; rodlike bundles in EM	Myocyte hypertrophy with vacuolated cardiomyocytes; proliferation of abnormal mitochondria; mosaic appearance of COX deficiency	Vacuolated myocytes with enlarged cytoplasm in LM; GAG laden cells (called "clear" cells)	Intramyocyte accumulation of glycosphingolipids; empty myocytes in LM; lamellar, dense bodies in EM
Extracardiac manifestations	None	Possible vascular complications	None	Nephrotic syndrome and renal insufficiency; cholestatic liver failure; malabsorption and gastrointestinal bleeding; peripheral or autonomic neuropathy; macroglossia or periorbital purpura	Dependent on subtype: ptosis, proximal myopathy, fatigue, exercise intolerance, encephalopathy, and ataxia	Growth retardation; skeletal deformities; CNS involvement; ocular and hearing impairment; respiratory difficulties; gastrointestinal disorders	Renal failure; corneal deposits; nervous, gastrointestinal, and cutaneous manifestations

Inheritance	–	–	Mostly autosomal dominant; rarely autosomal recessive, X linked or maternal	ATTR: autosomal recessive	Mostly maternal inheritance	Mostly autosomal recessive; only MPS II X linked	X linked: males diseased; females carriers
Specific treatment	–	Antihypertensive treatment strategies	–	Chemotherapy in AL	–	Stem cell transplantation; enzyme replacement therapy	Enzyme replacement therapy

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AL acquired monoclonal immunoglobulin light chain amyloidosis, *ATTR* hereditary transthyretin-related form of amyloidosis, *AV* atrioventricular, *CMR* cardiac magnetic resonance, *CNS* central nervous system, *COX* cyclooxygenase, *CPEO* chronic progressive external ophthalmoplegia, *EM* electron microscopy, *EMB* endomyocardial biopsy, *GAG* glycosaminoglycans, *HCM* hypertrophic cardiomyopathy, *KSS* Kearns-Sayre syndrome, *LGE* late gadolinium enhancement, *LM* light microscopy, *LV* left ventricular, *LVH* left ventricular hypertrophy, *LVOT* left ventricular outflow tract, *MELAS* mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, *MPS* mucopolysaccharidosis

causally involved in the development of LVH. However, β-myosin heavy chain may simply be marker of LVH rather than a causative signal, because it was found in similar quantities both in hypertrophied and non-hypertrophied myocytes of hypertrophied rodent hearts [6]. Cellular myocyte hypertrophy involves both recruitment of contractile elements and myocyte proteins, but increases in myocardial mass also stem from an increase in cells that make up the connective tissue: fibroblasts, vascular smooth muscle cells, and endothelial cells. These changes of the extracellular matrix are key in the development of cardiac dysfunction and the clinical phenotype of the cardiomyopathy. There is a complex interplay between mechanical (hemodynamic) and neurohumoral stress inducing hypertrophic gene expression in hypertensive heart disease [7]. Abnormalities of the myocardial microvasculature cause an imbalance between oxygen delivery and the increased metabolic demands of the hypertrophied myocardium—functional ischemia causing anginal symptoms and perpetuation of cell death and myocardial fibrosis. In hypertensive heart disease, several molecular mechanisms and a few genetic determinants of a hypertrophic response have been identified [8]. In contrast, in familial HCM, several (but not all) genetic causes have been identified, and our understanding of the molecular mechanisms remains incomplete [9–11].

16.1.1.1 LVH in Hypertensive Heart Disease

Increased hemodynamic burden is a key stimulant for the development of LVH in hypertensive (and valvular) heart disease. LVH is an initially effective compensatory mechanism to overcome increased afterload to maintain constant wall stress [12]. While pressure overload invariably leads to concentric LVH, volume overload leads to eccentric hypertrophy with increases of left ventricular internal dimensions, which can also be seen in end-stage cardiomyopathy due to pressure overload [2, 13].

The anatomical classification proposed by Ganau et al. [14] is based on echocardiographic measurements of left ventricular geometry and left ventricular muscle mass. Left ventricular geometry is determined by *relative wall thickness* (*RWT*) calculated as doubling the width of the left ventricular inferolateral wall and divided by the left ventricular end-diastolic internal diameter in end diastole. A RWT $\geq$0.44 is diagnostic for concentric LVH, while a RWT <0.44 with increased left ventricular mass is indicative of eccentric remodeling. This category can be further distinguished from physiologic hypertrophy, which is characterized by mild increases of left ventricular mass and a RWT between 0.32 and 0.44 [12]. For the determination of left ventricular mass in this classification, the following formula is most commonly used:

$$\text{Left ventricular mass} = 0.8 \times \left(1.04 \times \left[\left(\text{LVIDd} + \text{PWTd} + \text{SWTd}\right)^3 - \left(\text{LVIDd}\right)^3\right]\right) + 0.6 \text{ g}$$

Left ventricular mass is usually indexed to body surface area (Du Bois or Mosteller method) [15, 16]. LVIDd indicates left ventricular internal diameter in diastole,

PWTd posterior wall thickness in diastole, and SWTd septal wall thickness in diastole.

In clinical practice, echocardiography is widely available, has a reasonable cost, and is accurate in the clinical setting for the determination of left ventricular mass. While magnetic resonance imaging has greater precision than echocardiography, it has a higher cost, more limited availability, and limited tolerability [17, 18]. Thus, echocardiography is still the primary method to assess the presence, magnitude, and hemodynamic complications associated with LVH.

The correlation between blood pressure measured in the physician's office and left ventricular mass is not linear [19]. There are at least four explanations for this finding: (1) office blood pressure is not a reliable surrogate for overall hemodynamic burden, while 24-h ambulatory blood pressure is a much better surrogate and indeed correlates much closer with left ventricular mass [20]. (2) Both office and 24-h ambulatory blood pressure monitoring provide estimates of hemodynamic stress at one point in time, while the amount of lifetime hemodynamic stress clearly will determine the development of LVH to a much greater degree. Hypertensive heart disease is a chronic condition that develops over many years. (3) Neurohumoral stimulation linked to the development of LVH may differ between individuals with hypertension. (4) A genetic propensity for the development of LVH may exist both in hypertension and valvular disease. Racial/ethnic differences in the probability of developing LVH strongly suggest a genetic component [21–23].

16.1.1.2 Molecular Mechanisms of Hypertensive Heart Disease

(a) *Renin-angiotensin-aldosterone system* (*RAAS*): Angiotensin II released by the myocardium activates G proteins and Rho proteins, which in turn increase protein synthesis in myocardial cells and collagen synthesis in fibroblasts [24–27]. These effects have been found to be independent of afterload in a mouse model suggesting a direct involvement of angiotensin II in LVH [28]. In addition, angiotensin II stimulates fibrosis via endothelin release [29]. Angiotensin II AT_1 receptor blockers and angiotensin-converting enzyme (ACE) inhibitors effectively reduce LVH in hypertensive individuals corroborating the importance of the RAAS in the development of LVH [30] (Chap. 36). Aldosterone also seems to be involved in the development of hypertrophy. Mineralocorticoid receptors are abundantly expressed in cardiomyocytes [31], and aldosterone itself induces vascular [32] and myocardial inflammation [33], myocardial fibrosis [34], and LVH [35]. In a hypertensive model of endothelial dysfunction, eplerenone prevented cardiac inflammation and fibrosis [36]. The nonselective aldosterone antagonist spironolactone and the selective aldosterone receptor antagonist, eplerenone, provided clear clinical benefit in patients with systolic heart failure [37, 38], but the benefit is less clear in patients with diastolic heart failure, in whom LVH oftentimes was the common denominator [39, 40] (Chap. 38). Studies to better assess the clinical effectiveness of aldosterone blockers for the treatment of LVH are in process.

(b) *Endothelin-1*: Endothelin-1, one of three human isoforms of endothelin, is a potent vasoconstrictor produced by endothelial cell. Endothelin has been shown to induce hypertrophy in animal models, and this phenotype can be suppressed by a pharmacologic endothelin-1 receptor blocker, such as bosentan [29, 41, 42]. Direct evidence of endothelin-1 as a mechanism for LVH in humans, however, is lacking (Chap. 45).

(c) *Heat shock proteins are* intracellular proteins, which increase numerically in cells that are exposed to thermal or other forms of stress, and regulate nuclear transcription factors. These factors have been suppressed with gene therapy and antioxidant therapy producing an anti-hypertrophic effect even in the presence of pressure overload [43]. A proteasome inhibitor (PS-519) known to suppress heat shock proteins also prevented isoproterenol-induced LVH in animals with or without preexisting LVH [44].

(d) *G proteins*: Many substances involved in the hypertrophic response to pressure and stress, including phenylephrine, angiotensin II, and endothelin-1, bind to myocyte membrane receptors that activate G proteins and small G proteins (i.e., Rho proteins). These proteins regulate transcription and have been shown to be involved in phenylephrine-induced LVH [45].

(e) *Calcineurin* : *It* is a calcium-/calmodulin-dependent serine-threonine phosphatase that induces myocardial growth in response to different pathological stimulus. It dephosphorylates cytosolic factors (e.g., nuclear factor of activated T cell (NFAT)), enabling them to translocate to the nucleus to activate transcription. Transgenic mice that overexpress calcineurin or its transcription factor targets develop cardiac hypertrophy [46] (Chaps. 4 and 18).

16.1.2 Genetic Factors of Hypertensive Heart Disease

Heritability of left ventricular mass has been reported to be low in first-degree family members with the estimated heritability of adjusted left ventricular mass having values between 0.24 and 0.32 [47]. A markedly higher heritability of left ventricular mass of 0.59 was demonstrated in twins [22]. There can be a large variability of left ventricular mass in patients with similar office blood pressure. The high rates of LVH in certain race/ethnic populations [21] support a genetic predisposition for the development of LVH in response to pressure overload. There are now some genes that have been identified to correlate with LVH in hypertensive patients.

(a) *Corin*, a membrane-bound serine protease expressed in cardiomyocytes, converts atrial and brain natriuretic peptide (ANP, BNP) to their active form. Corin knockout mice develop hypertension and cardiac hypertrophy [47]. Mutations of the corin I555 (P568) gene were exclusive to African-Americans in multiethnic samples with an allelic prevalence of 6–12 % and a clear association with both hypertension and LVH. Thus, corin mutations may explain in part the high prevalence of HTN and LVH in African-Americans [48].

(b) ACE gene polymorphism is also associated with both greater tissue and plasma ACE levels, as well as greater probability for LVH [49, 50] (Chap. 36).
(c) *Protein C* overexpression causes progressive LVH and diastolic dysfunction in animals.
(d) Bradykinin 2 receptor gene polymorphism, specifically the 9 bp receptor gene deletion is associated with greater left ventricular mass in subjects undergoing physical training [51]. Unlike LVH associated with pressure overload, the pathogenesis of LVH in HCM is clearly genetically mediated. However, genetic determinants of LVH in hypertensive hypertrophic cardiomyopathy may be important. As HCM can be associated with elevated LV systolic pressures due to left ventricular outflow tract (LVOT) obstruction, hemodynamics may also be a cause for exaggerated hypertrophy, and thus, there may be overlap between those two disease entities.

16.1.2.1 LVH in Hypertrophic Cardiomyopathy

Originally described in 1869 based on pathologic examination [52], HCM is present in 1 in 500 of the general population and the most common genetically transmitted cardiomyopathy. HCM can be caused by more than 1,400 different mutations [53] and is usually transmitted in an autosomal dominant pattern. Familial HCM describe a phenotype of thickened myocardium (≥15 mm) in the absence of increased afterload (such as hypertension or aortic stenosis) or other explanations for the thickened myocardium (see Table 16.1). A genetic abnormality in gene loci encoding sarcomere proteins is often present (Table 16.2), and over 1,400 gene variations have been linked to HCM. However, in more than 50 % of probands tested, a causative gene cannot be identified [54], underscoring the complexity and variability of the genetics in HCM. Figure 16.1 illustrates the structure of proteins involved in HCM-causing mutations. Mutations in two genes—*MYH7* and *MYBPC3*—account for as many as 75 % of HCM gene-positive individuals [11]. A small subgroup of gene-positive HCM patients has two or more sarcomere protein gene mutations, which may be associated with an earlier onset and/or more rapid disease progression [55, 56]. The utilization of genetic testing is increasing. We believe the most useful applications of genetic testing are twofold: (1) in patients with a clinical suspicion of HCM, the disease can be confirmed, and (2) in family members of an affected gene-positive HCM patient, the presence of the gene defect can be confirmed or excluded. The latter situation provides assurance to gene-negative family members preventing unnecessary serial testing of these individuals, reducing stress, anxiety, and health-care costs [54]. In contrast, patients who are diagnosed with HCM in childhood or adolescence will need to be followed closely for the development of LVH. Whatever the genetic constellation, the clinical phenotype is highly variable, even within families of the same gene mutation, ranging from an asymptomatic course without macroscopic evidence for disease to an individual who has severe and rapid progressive LVH and cardiomyopathy and possibly early sudden cardiac

Table 16.2 HCM-associated genes

HCM gene	Protein defect	Estimated prevalence in HCM probands (%)	Strength of evidence for causality	Location
No gene identified	NA	50	NA	NA
MYBPC3	Cardiac myosin-binding protein C	15–25	++	Intermediate filament
MYH7	β-Myosin heavy chain	15–25	++	Thick filament
TNNT2	Cardiac troponin T	7	++	Thin filament
TNNI3	Cardiac troponin I	<5	++	Thin filament
TPM1	α-Tropomyosin	<5	++	Thin filament
MYL3	Myosin light chain 3	<1	++	Thick filament
MYL2	Cardiac regulatory myosin light chain	<2	++	Thick filament
MYH6	α-Myosin heavy chain	<1	+	Thick filament
TNNC1	Cardiac troponin C	<1	++	Thin filament
ACTC	a-Actin	<1	++	Thin filament
MYOZ2	Myozenin-2	<1	+	Z-disc
ACTN2	Alpha-actinin-2	<1	+	Z-disc
CSRP3	Cysteine and glycine-rich protein 3	<1	+	Z-disc
TCAP	Telethonin	<1	+	Z-disc
CASQ2	Calsequestrin	<1	+	Ca^{++} handling
JPH2	Junctophilin 2	<1	+	Ca^{++} handling

death [54]. Figure 16.2 shows necropsy specimens from the hearts of two patients with HCM: one who had asymmetric septal hypertrophy and one who had concentric LVH. Some studies have identified high-risk [57, 58] and low-risk [59] mutations; however, conflicting reports exist [60] regarding the prognostic capability for predicting SCD. At present there is a lack of consensus about the role of genetic testing in predicting the magnitude or progression of LVH or the development of LVOT gradients, mitral regurgitation, or the clinical course and status as well as the need for strategies to prevent sudden death such as an implantable cardiac defibrillator (ICDs) [54, 61]. The relatively high cost of genetic testing, the inability to detect a disease-causing mutation in phenotypically affected patients (up to 50 %), and genetic variations of uncertain significance remain a challenge when using genetic testing in clinical practice [54].

As seen in Fig. 16.3, HCM is associated with cardiomyocyte hypertrophy, myofiber and myofibrillar disarray with more or less pronounced interstitial fibrosis, and an abnormal microvasculature with intimal hyperplasia and medial thickening are characteristic of HCM. The magnitude of myofiber disarray in HCM is quantitatively increased in comparison with other conditions with LVH [62]. Animal models including the use of transgenic mice [63, 64], transgenic rabbit [65], Maine coon

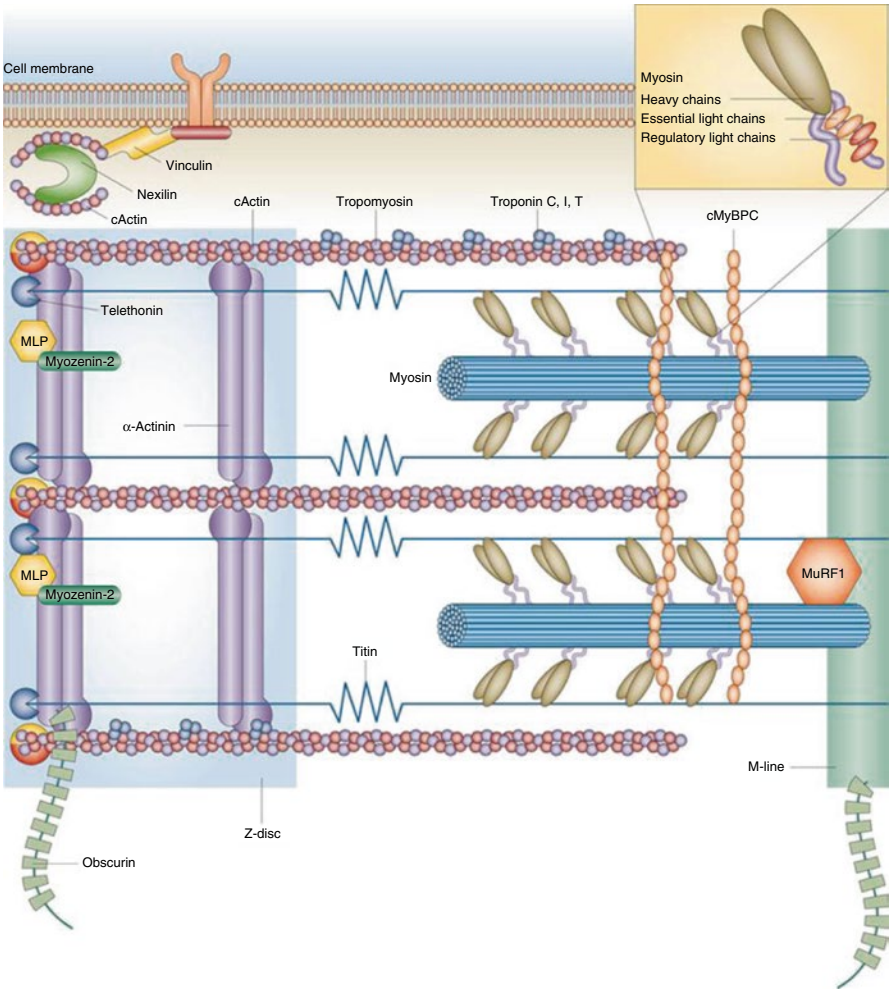

Fig. 16.1 Structure of proteins involved in HCM-causing mutations. *cActin* α-cardiac muscle actin 1, *cMyBPC* cardiac myosin-binding protein C, *MLP* cysteine and glycine-rich protein 3 (muscle LIM protein), *MuRF1* E3 ubiquitin-protein ligase TRIM63 (muscle-specific RING finger protein 1) (Adapted with permission from Frey et al. [11])

cats [66], and zebrafish [67] are being used to study the molecular mechanisms that translate a genetic defect into the hypertrophic phenotype. Several of these mechanisms have been proposed as being responsible for the clinical phenotype of HCM patients, and it is thought to be likely that HCM is a multifactorial disease:

(a) *Depressed contractile function*: One mechanistic hypothesis attributes myocardial contractile dysfunction from myocyte disarray and changes of the connective tissue (i.e., fibrosis) as the cause for progressive hypertrophy in the form of a compensatory mechanism [68–72]. There are several factors that cannot be

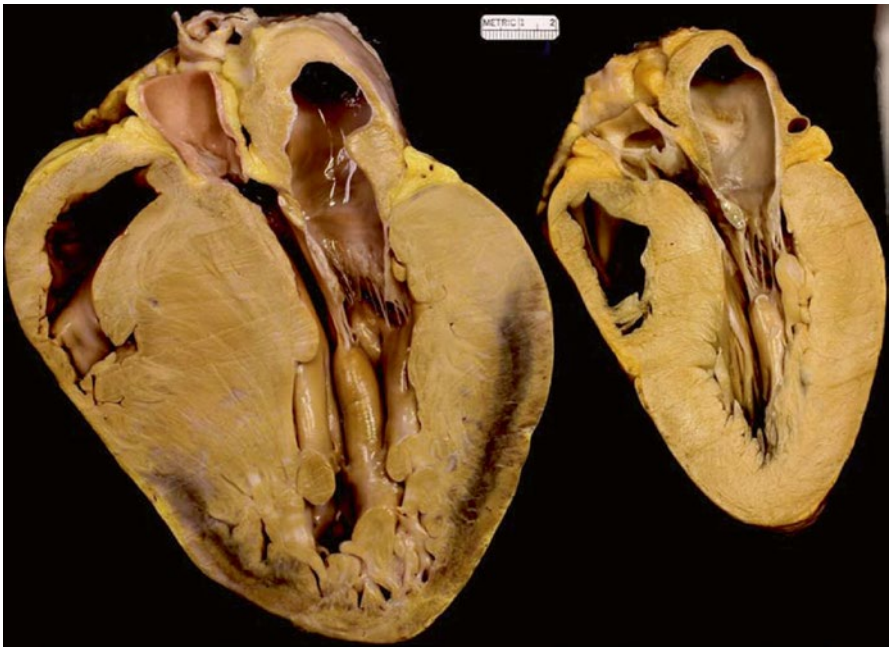

Fig. 16.2 Two heart necropsy specimens from teenagers with hypertrophic cardiomyopathy who had sudden death. Both specimens demonstrate left ventricular hypertrophy; *left*, asymmetric septal hypertrophy in the specimen; *right*, concentric hypertrophy in the specimen (Adapted with permission from Roberts [154])

explained by this compensatory hypothesis: (1) Hypertrophy often develops or progresses during the physiologic growth phase with and after puberty with no or slow progression thereafter even if diastolic and sometimes systolic function worsens. The protein defect on the other hand is present since heart development; thus, a purely compensatory mechanism seems unlikely. (2) Hypertrophy usually is asymmetric (but not always), while compensatory LVH is generally concentric (but not always). (3) A gain in function of the affected myocardium has been observed more recently with an increased energetic cost of cardiac contraction rather than left ventricular dysfunction as discussed next [73].

(b) *Abnormal calcium handling*: Several animal studies suggested that hypertrophic myocytes exhibit an increased sensitivity and affinity to Ca^{2+} of the mutated proteins causing increased cross-bridge turnover and actin-activated ATPase activity [73–75]. This gain of function creates a greater energetic cost of each contraction, and energy depletion subsequently leads to cell death [73]. The enhanced calcium sensitivity has also been shown to increase susceptibility to ventricular arrhythmia by shortening the effective refractory period, increasing the heterogeneities in ventricular conduction and delayed after depolarization [74, 76] (Chap. 4).

(c) *Myocardial fibrosis*: Myocardial fibrosis appears to be the result of premature cell death and expansion of interstitial cells and proteins. Premature myocyte

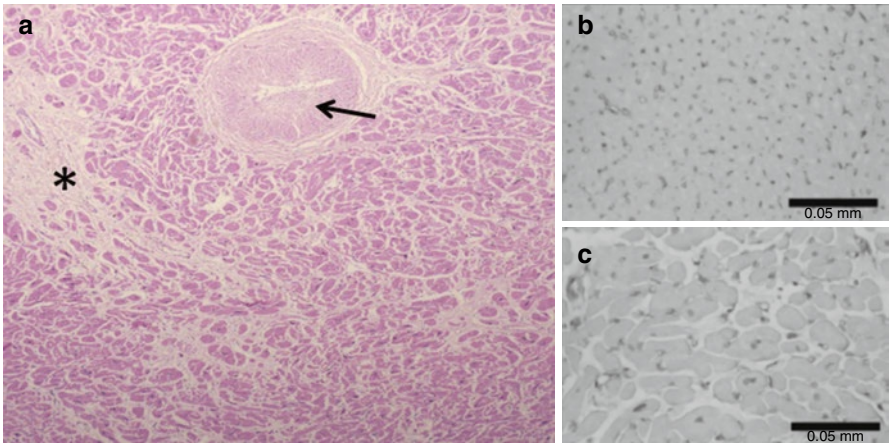

Fig. 16.3 Myocyte disarray, interstitial fibrosis (*), and vascular remodeling with intimal hyperplasia and medial thickening are typical for HCM but also other forms of LVH (panel **a**). Myocardial capillary density (panel **c**) is markedly decreased in HCM compared to a normal heart (panel **b**) (Sources: Panel **a**: Robert J Siegel, MD. Panels **b** and **c**: Adapted with permission from Kofflard et al. [155])

demise is thought to be related to changes in the microvascular architecture in conjunction with the aforementioned abnormal energy homeostasis. One key signal for fibroblast stimulation is the transforming growth factor-β (TGF-β). Indeed suppression of TGF-β [64] with the angiotensin II AT_1 receptor antagonist losartan [77] decreased fibrosis in animal models. The Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM [VANISH] trial [78] is testing whether angiotensin II AT_1 receptor blockers can reduce myocardial fibrosis in HCM patients. Late gadolinium enhancement on cardiac magnetic resonance imaging (MRI) identifies the extent of myocardial fibrosis and scarring and is associated with an increased risk of sudden death [54, 79]. Serum by-products of fibroblast-secreted collagen are elevated in HCM patients with hypertrophy, in gene-positive probands without hypertrophy and in HCM patients without MRI evidence of scarring. These findings suggest that myocardial fibrosis could be an early causative pathophysiologic mechanism in the development of hypertrophy, rather than a result of hypertrophy [80].

(d) *Abnormal biomechanical sensing*: Some of the HCM mutations involve proteins linked to the Z-disc and the M-band as shown in Table 16.2. These regions have been described to exert hypertrophic signaling from stretch-sensitive transcriptional modifiers in response to biomechanical stress [81]. Alterations in these regions may be involved in stimulating local hypertrophy. This hypothesis, however, is largely speculative at this time [11].

(e) *Abnormal energy production*: Several observations suggest an abnormal supply and demand of cardiac sarcomere adenosine triphosphate [ATP] which is central to contraction and relaxation (myosin ATP) and calcium homeostasis (sarcoplasmic reticulum). ^{31}Phosphorus-NMR demonstrates abnormal cardiac

energetics in both HCM patients and gene-positive probands when compared to healthy controls; this finding suggests that altered ATP production and use could be a causative factor in the development of the HCM phenotype [75]. Furthermore, mitochondrial abnormalities can be observed in gene-positive individuals without a hypertrophic phenotype, which suggests that these altered energetics in HCM and are a cause, but not the result, of hypertrophy [82]. As discussed in Table 16.1, the same mechanism is found to cause myocardial hypertrophy in genetic diseases, which also causes mitochondrial dysfunction. Abnormal cardiac energetics cause diastolic dysfunction from deficient calcium reuptake in the sarcoplasmic reticulum and a state of calcium overload in systolic and diastolic heart failure [83]. These findings are consistent with the clinical presentation of many HCM patients [73].

(f) *Abnormal microvasculature*: Scar burden (by cardiac MRI) and microvascular dysfunction appear to be closely related in HCM patients, and they have more pronounced gene-positive than gene-negative probands [84]. Histologically, intramyocardial microvessels demonstrate a completely abnormal architecture. Figure 16.3 shows histological findings of intimal hyperplasia ("onion skin appearance"), media hypertrophy, and decreased capillary density, all of which leads to reduced microvascular blood flow. In this combination with increased metabolic demands of the hypertrophied myocardium this causes microvascular ischemia and cell death. Therefore, this microvascular ischemia perpetuates fibrosis and as a consequence compensatory hypertrophy and contributes to the pro-arrhythmic substrate. In addition, the presence of microvascular ischemia indicates a worse prognosis in HCM [85]. Ongoing clinical trials are investigating improvements in microvascular ischemia and related arrhythmias from the use of late-current sodium channel blockers [86, 87].

16.1.2.2 Diagnosis of Hypertrophic Cardiomyopathy

Echocardiography is the standard method to screen for HCM because it has a good sensitivity for detecting global or focal hypertrophy. Therefore it is also the test of choice to follow affected individuals, who carry a diagnosis of HCM as well as screening their family members who are at risk for the development of HCM. Furthermore, Doppler echocardiography provides essential hemodynamic data identifying abnormal LV filling, LVOT gradients at rest and during exercise, and mitral regurgitation, which is associated with LVOT gradients and systolic anterior motion of the mitral valve (SAM). Echocardiography is also an essential method to monitor the mechanisms of symptoms, the risk of sudden death, as well as the effects of treatment, and the changes in resting and exertional LVOT gradients, mitral regurgitation, diastolic function, and pulmonary artery systolic pressure. Because of its better resolution and lower inter-study-variability than echocardiography [17, 18], MRI is increasingly being used to evaluate HCM patients; in addition, MRI has better spatial resolution, is less operator dependent, and is not affected by chest wall configuration or body habitus. Furthermore, late gadolinium

enhancement (LGE) can detect the presence, the pattern of distribution, and the extent of myocardial fibrosis, which is a marker for potential ventricular arrhythmias [88]. However, the importance of quantification of cardiac fibrosis as an indication for primary prevention of sudden death with implantable defibrillators is controversial and focus of ongoing research. While MRI has greater sensitivity to detect abnormal wall thickness and provide precise quantification, its high cost and poor tolerability in some patients limit its use for longitudinal follow-up. In addition, echocardiography is superior to MRI for the assessment of mitral regurgitation, quantification of LV outflow tracts, pulmonary artery systolic pressure, and left ventricular filling pressures.

Endomyocardial biopsy with histologic evaluation of myocyte appearance and myofiber orientation is useful for excluding other infiltrative cardiomyopathies which can mimic HCM as detailed in Table 16.1. As previously discussed, genetic testing is helpful to confirm clinical suspicion of HCM and to exclude a known gene defect in family members of an affected individual, which obviates the need for serial long-term follow-up. At present, genetic testing is not a reliable method to predict future development of the disease in phenotypically normal but gene-positive individuals or for the prediction of disease progression and severity in HCM patients [54].

16.1.2.3 Amyloidosis as a Cause of Cardiac Hypertrophy

Cardiac amyloidosis causes a progressive increase in heart wall thickness that is not due to myocardial hypertrophy but rather to extracellular amyloid deposition [89]. This extracellular deposition of amyloid fibrils is composed of an autologous protein which has a beta sheet fibrillar confirmation. While the two main forms of amyloidosis, light chain (AL) and TTR amyloidosis, are the most common, there are more than 30 related amyloidosis proteins capable of forming amyloid fibrils [90, 91]. Cardiac involvement in amyloidosis can be rapidly progressive, and it is the most common cause of death in AL amyloidosis and a major determinant of prognosis. AL amyloid frequently involves the heart, liver, kidney, peripheral and autonomic nervous system, as well as the GI tract [89, 90]. Most patients are diagnosed in the fifth decade of life, and about 50 % have cardiac involvement. CHF augurs a poor prognosis with a survival of only 6 months in untreated patients. Death is usually due to progressive CHF or sudden death due to asystole or electromechanical dissociation.

For TTR amyloidosis, there is a hereditary and nonhereditary form, the latter of which is known as senile amyloid (SA). The hereditary form is autosomal dominant with a 50 % likelihood that the offspring will inherit the disease. TTR generally manifests in the third to fifth decades as cardiac amyloid, neuropathy, or both, depending on the specific molecular abnormality. Senile amyloidosis is related to the breakdown of abnormal TTR. SA generally affects the heart in men in their seventh or eighth decade of life [92]. CHF is often the first manifestation of SA.

Amyloidosis has protean manifestations due to organ infiltration, and symptoms are often nonspecific. Amyloid may present as CHF, progressive wasting, or as a peripheral neuropathy. The finding of low voltage in the electrocardiogram and thick LV walls in the echocardiogram known as voltage-mass discordance is a useful clue to the diagnosis of amyloid in a CHF patient [89]. Cardiac MRI with abnormal gadolinium uptake may also be indicative of cardiac amyloid [93]. Technetium pyrophosphate radionuclide scans may show homogenous uptake of the heart in cases of TTR and SA due to the binding of the P component of the amyloid fibrils [89]. Once there is clinical suspicion of amyloid, a tissue diagnosis should be made. This can be done with a needle biopsy of the abdominal fat or biopsy of another involved tissue. However, in cases with suspected cardiac amyloid, an endomyocardial biopsy may be needed [93]. For AL, amyloid blood and urine are also assessed with immunofixation to detect abnormal proteins which can be quantified by a free light chain assay. In the presence of these abnormal proteins, a bone marrow biopsy should be done to assess the severity of plasma cell dyscrasia [90]. In the absence of AL amyloid, blood testing can be done for a mutation of TTR. If this is negative, SA is the most likely diagnosis. In ambiguous cases, special staining of the biopsy specimens can elucidate the type of amyloid.

Cardiac amyloidosis can be clinically distinguished from HCM by the progressive nature of LVH secondary to progressive amyloid deposition. In HCM the ECG demonstrates LVH, whereas in amyloid, the ECG voltage is low and progressively decreases with amyloid infiltration as wall thickness increases due to the amyloid infiltration [93]. The clinical presentation of cardiac amyloid reflects myocardial infiltration. Initially there is impaired diastolic dysfunction and which generally progresses to systolic dysfunction [89]. Patients often develop right- and left-sided heart failure as well as atrial and ventricular arrhythmias [94, 95]. When CHF is seen in association with other organ involvement suggesting amyloid infiltration such as macroglossia, carpal tunnel syndrome, easy bruising and bleeding, autonomic neuropathy, nephrotic syndrome, and cachexia, amyloid should strongly be considered.

On echocardiography, amyloid may mimic HCM by the presence of asymmetric septal hypertrophy. Cardinal echocardiographic findings in amyloid to suggest the diagnosis are a sparkling appearance of the myocardium, progressive diastolic dysfunction, increased wall thickness of the LV, RV septum in the absence of systemic or pulmonary hypertension, and the intra-atrial septum and bi-atrial dilation. Strain and strain rate imaging show impaired myocardial function which progresses over time [93].

Treatment which is similar for all amyloidosis involving the heart requires management of the cardiac-related complications. Most patients develop CHF with volume overload and thus should be on a low-sodium diet (1–2 G of sodium per day). Patients should monitor their weights daily as well as their edema and ascites. Diuretics are the mainstay of therapy for CHF due to amyloid [89]. In addition certain cardiac drugs such as digoxin and calcium channel blockers are generally contraindicated as they might bind to the P component of the amyloid fibrils which can result in digoxin toxicity and in the case of calcium channel blockers severe and even fatal hypotension. Beta blockers are generally not useful in amyloid as they promote bradycardia as well as hypotension. Afterload reduction is often problematic due to

autonomic dysfunction and systemic or orthostatic hypotension [89]. Chronic oral anticoagulation is warranted in patients with atrial fibrillation to reduce the risk of systemic embolization and stroke. TTR has a proclivity for cardiac conduction disturbances and bradycardia so that pacemaker therapy is useful in this setting. It is unclear if defibrillators are effective in preventing sudden death in these patients as sudden death may be due to asystole or electromechanical dissociation [94, 95].

The most common type of AL amyloid produced by plasma cells in the bone marrow may be treated by autologous bone marrow transplantation or chemotherapy with thalidomide, melphalan, dexamethasone, bortezomib, lenalidomide, and bendamustine or with a combination of these medications [90]. AL amyloid therapy is focused on reducing or eliminating plasma cell production of free light chains. Response to therapy can be in part assessed by reduction in the cardiac biomarker for CHF (BNP). A 30 % reduction in levels is indicative of a positive response; however, progressive renal failure can cause increases in BNP and limit the utility of the BNP level for assessing the response to therapy [91].

Melphalan-dexamethasone is a standard regimen which is generally well-tolerated [96], but its effectiveness in patients with advanced cardiac disease is limited [91], with median survivals being between 10 and 18 months. Recently, bendamustine, an alkylating agent with a unique mechanism of action, has shown potential promise as a therapeutic agent. However, the data is limited on improving survival.

Combination therapy with immunomodulating drug thalidomide with dexamethasone and cyclophosphamide has shown benefits on end-organ responsiveness in 33 % of patients; however, toxicity occurs in up to 60 % of patients. The second-generation drug lenalidomide and third-generation agent pomalidomide in combination with dexamethasone are being assessed [90]. In small studies, 40–50 % of patients appear to be responders. The addition of alkylating agents increases the response rate but also the drug toxicity [91].

Protease inhibitor drugs such as bortezomib, ixazomib, and carfilzomib are being tested [97]. These drugs have been shown to be effective in reducing the production of free fibrillar light chains [98]. The newer protease inhibitors ixazomib and carfilzomib appear to have a greater protease inhibitor effect and less toxicity. These drugs are currently being evaluated in clinical trials [97].

In some patients with AL amyloid combined bone marrow and heart transplant or in patients with TTR, amyloid combined liver and heart transplantation may be effective in eliminating the source of amyloid production and restoring normal cardiac function [89, 93, 99]. A recent study has shown preliminary promising results using a therapeutic approach of RNA interference which reduced the production of transthyretin [92].

16.2 Part II: Management of Hypertrophic Cardiomyopathy

Many individuals affected by HCM are undiagnosed, most will not experience lethal events, and many will not have symptoms. However, those who develop symptoms such as dyspnea, angina, and lightheadedness can experience functional

disability secondary to heart failure and stroke as well as to sudden cardiac death (SCD). The development of atrial fibrillation puts these patients at substantial risk of stroke. Of note, the association of sleep apnea and HCM carries a high risk of atrial fibrillation [100], and thus HCM patients with sleep apnea should be treated for it in an attempt to reduce the risk of developing atrial fibrillation or its recurrence. Therapy of patients with HCM can be classified into medical, interventional/device, and surgical treatments (Chaps. 7 and 53).

16.2.1 Medical Treatment

Most of HCM patients are either asymptomatic or present with only minimal symptoms rendering them to a lower risk of SCD than patients who are symptomatic [101–104]. The majority of HCM patients are treated medically with the initial aim of reducing symptoms along with reducing the risk for SCD.

Currently there is no consensus on the ideal marker for identifying when to initiate therapy and how to appropriately adjust therapeutic goals. Some advocate the use of the LVOT pressure gradient to monitor and tailor therapy; however, these measurements can be quite variable on a daily basis [105]. Moreover, the association between the resting LVOT gradient, symptoms, and the risk of SCD is somewhat inconsistent [106]. BNP may be a useful biomarker to monitor (Chap. 12) and correlate with patients' symptoms and change in therapy.

Pharmacological therapy is the initial approach to treat symptoms related to HCM and can be subclassified into three categories: (1) symptom relief, including exercise intolerance, angina, or syncope; (2) arrhythmia management and prevention of SCD; and (3) prevention of disease progression. Table 16.3 details the different medications available for treatment of patients with HCM. Additional adjunct therapies such as initiation of anticoagulation once atrial fibrillation appears [107], as well as aggressive treatment for obstructive sleep apnea to prevent new onset or recurrence of atrial fibrillation are also recommended and are beyond the scope of this chapter (discussed in Chap. 50). As randomized clinical trials on therapeutic interventions in patients with HCM are scarce, most clinicians rely on their own experience as well as on expert consensus guidelines [107].

16.2.1.1 Medical Therapy for Symptomatic Relief

(a) *Beta-Adrenergic Receptor Blockers* (β-*Blockers*) (*Atenolol*, *Metoprolol*, *Bisoprolol*, *Propranolol*, and *Nadolol*)

β-Blockers are the most studied therapeutic class in patients with HCM and are regarded as the first-line therapy in patients with HCM for symptom relief. Their effectiveness is due to the negative chronotropic and inotropic effects: increase in diastolic filling time and attenuation of adrenergic-induced tachycardia, improving myocardial oxygen supply-demand and reducing myocardial

Table 16.3 Medical therapies for patients with hypertrophic cardiomyopathy

	Main use	Mechanism of action	Prevention of sudden cardiac death	Side effects	Comments
β-Blockers (atenolol; metoprolol; bisoprolol; propranolol; nadolol)	First-line therapy for symptomatic relief	Negative inotropic and chronotropic effect: Heart rate reduction Increase in diastolic filling time Improvement of myocardial oxygen supply-demand and reduction of myocardial ischemia	No (might be if started at younger age [107])	Bradycardia (especially if given in combination with CCBs) Hypotension Fatigue Depression Alopecia Impotence	Can reduce resting LVOT gradients as well as increase exercise-induced LVOT gradients β-Blockers with vasodilatory effects (i.e., carvedilol) should be avoided
Calcium channel blockers (CCBs) (verapamil; diltiazem)	An alternative in those who cannot tolerate β-blockers	Negative inotropic and AV nodal blocking effect Increased LV relaxation Small decrease in LVOT gradient Might reduce myocardial ischemia through coronary artery dilatory effect	No	Bradycardia (especially if given in combination with β-blockers) Hypotension	Should be used with caution in those with elevated PCWP as the can worsen heart failure Vasodilation can cause elevation of the LVOT gradient

(continued)

Table 16.3 (continued)

	Main use	Mechanism of action	Prevention of sudden cardiac death	Side effects	Comments
Disopyramide	Reduction of LVOT gradient and mitral regurgitation related to SAM of the mitral valve	Blunting of the sodium-calcium exchange system, decreasing myocardial inotropy Decrease of heart rate and slowing of conduction through the bundle of his Reduction of the LVOT gradient and mitral regurgitation (when related to systolic anterior motion) Reduction of LV wall stress Improves diastolic dysfunction	A trend toward reduction	Cardiac arrhythmias QT prolongation Urinary retention Dry mouth Exacerbation of glaucoma Side effects can be managed by concomitant use of pyridostigmine	A combination of disopyramide and a β-blocker is most effective for reduction of LVOT gradients Should not be used as monotherapy in patients with AF as it can enhance AV conduction
Amiodarone	Both rate and rhythm control of atrial fibrillation episodes in HCM patients	Class III antiarrhythmic also with β-blocking effects and negative inotropic effects	Controversial—data does not support the administration of amiodarone for reduction of SCD	QT prolongation Pulmonary fibrosis Thyroid dysfunction Liver toxicity Corneal deposits Skin discoloration	Must be stopped prior to initiation of disopyramide due to QT prolongation effect
Angiotensin receptor blockers (losartan; valsartan)	Reversal of interstitial fibrosis	Blockade of the AT_1 receptor, prevents cells form undergoing angiotensin II-induced changes Decrease in LV mass Decreases rest and exercise gradient	No	Growth retardation in children Hypotension	Decrease in blood pressure may increase LVOT gradients

ischemia [107]. β-Blockers can reduce or abolish both resting LVOT gradients as well as the increase in the LVOT gradient that occurs with exertion. This is also attributable to the negative inotropic and chronotropic actions of β-blockers. Slowing of the heart rate causes an increase in the diastolic filling time and thus an increase in LV end-diastolic volume along with a decrease in the end-diastolic pressure [108]. This results in more efficient inactivation of myocardial contractile proteins and improvement in diastolic filling time [107, 109]. β-Blockers also improve isovolumic relaxation in patients with HCM to <50 ms when adequately treated [110], suggesting that β-blockers increase LV compliance and improve diastolic dysfunction [52]. Reduction in heart rate also reduces myocardial scarring and fibrosis [111], which further decreases the substrate for arrhythmia [88, 112]. There is limited evidence suggesting improved survival with β-blocker therapy (when therapy is initiated in young patients) [113] (Chaps. 5 and 8).

Initial studies in HCM patients used propranolol. This drug has largely been replaced by longer-acting drugs (e.g., metoprolol and atenolol) with better tolerance and greater β-1 receptor selectivity. However, carvedilol and other β-blockers, which have vasodilatory effects, should not be used in patients with HCM due to their vasodilatory effects potentially causing an increase in the LVOT gradients, as well as worsening of mitral regurgitation secondary to systolic anterior motion of the mitral valve. β-Blocker therapy, especially when given in high doses, may lead to unwanted effects such as bradycardia, fatigue, hypotension, depression, alopecia, and impotence.

(b) *Calcium Channel Blockers* (*CCBs*) (*Verapamil* and *Diltiazem*)

Non-dihydropyridine CCBs mainly provide an alternative to patients who are unable to tolerate β-blocker therapy such as those with severe chronic obstructive lung disease or asthma. Although, as shown in Table 16.3, there is a difference in their mechanism of action, CCBs possess negative inotropic effects, as well as AV nodal blocking effects, producing a similar clinical effect as that of β-blockers. However, the effect of CCBS on diastolic dysfunction is controversial [107]. Verapamil has been the most commonly used and studied CCB in patients with HCM. CCBs increase LV relaxation through negative inotropic effect and can cause a small decrease in the LVOT gradient, an increase in the cardiac index, and an increase in exercise capacity [114]. Verapamil has also been shown to "normalize" LV diastolic filling and thus prevent hemodynamic compensation associated with the onset of atrial fibrillation in patients with HCM [115] (Chap. 37).

HCM patients show reversible ischemia secondary to an increased demand in the hypertrophied myocardium, intramural coronary artery medial thickening, or endothelial dysfunction [52]. Verapamil reduces and even eliminates perfusion deficits in some patients with HCM, as well as exercise-induced perfusion deficits [116–118]. Diltiazem has also been shown to improve measures of diastolic performance [119] and reduce myocardial ischemia [120] in HCM patients.

Major adverse events of CCBs include bradycardia and hypotension. CCBs should be used cautiously in HCM patients with elevated pulmonary capillary

wedge pressures as they have been associated with an increased risk of worsening CHF and even death in this setting. In patients with borderline blood pressure (systolic blood pressure <90 mmHg), CCBs can cause vasodilation and afterload reduction which can increase the LVOT gradient causing worsening mitral regurgitation and leading to potential hypotension. Administration of both β-blockers and CCBs should be done cautiously as this combination may cause severe bradycardia with or without high degree atrioventricular block. The dihydropyridine class CCBs should not be used in obstructive HCM patients as they cause afterload reduction which can aggravate LVOT gradients, mitral regurgitation, and hypotension [107].

(c) *Disopyramide*

Disopyramide is a class IA antiarrhythmic drug initially used to treat arrhythmias; it acts by blunting the sodium-calcium exchange system, decreasing myocardial inotropy. Its effects are somewhat similar to that of CCBs only without the effect of a lowered systemic blood pressure [121]. Disopyramide reduces the LVOT gradient and mitral regurgitation and may thus also increase forward stroke volume and blood pressure. Since the initial report of its clinical benefit in patients with HCM by Pollick [122], disopyramide has been shown to effectively reduce LVOT gradients, LV wall stress, and MR severity (when related to systolic anterior motion of the mitral valve), along with improving diastolic function in HCM patients. Despite its negative inotropic effects, disopyramide produces favorable hemodynamic effects, maintaining cardiac output, which might reflect a decrease in systolic anterior motion (SAM) and consequently a decrease the severity of resulting mitral regurgitation [123]. Invasive and noninvasive studies have shown that disopyramide improves LV pressure-volume curves and consequently diastolic dysfunction [124, 125] (Chap. 52).

Owing to its negative inotropic effect, disopyramide alone is more effective than β-blockers or CCBs in patients with dynamic LVOT gradients for reducing LVOT gradients [126]. The combination of disopyramide and a β-blocker had the greatest effect on reducing LVOT gradients as well as on improving clinical status [127]. In a large multicenter study evaluating 491 patients with LVOT gradients >30 mmHg, patients who received disopyramide had amelioration of symptoms in about 66 % of cases and a 50 % reduction in the outflow gradient over a period of ≥3 years. Despite initial concerns, disopyramide has not been found to be proarrhythmic in patients with a normal QT interval on ECG nor does it cause an increase in cardiac and sudden cardiac death. Treatment with disopyramide has shown a trend toward reducing SCD as well as all-cause mortality when compared to standard monotherapy [128]. In patients resistant to initial pharmacological therapy with β-blockers or CCBs, substantial symptom relief can be achieved along with low mortality through a stepped management that includes adding disopyramide to selected patients [129]. Thus, disopyramide treatment should be tried in obstructive HCM prior to proceeding to surgical or percutaneous interventions.

Disopyramide also reduces myocardial ischemia in patients with HCM. In patients who were treated with disopyramide, although there was no change in blood flow with the drug, the peak LV pressure and external work markedly decreased, leading to less oxygen demand and reduction in ischemia [130].

Disopyramide can cause QT interval prolongation. As with any antiarrhythmic medication, when initiating disopyramide therapy, monitoring for cardiac arrhythmias is needed as well as monitoring for QT prolongation. Caution should be used in patients receiving other QT prolonging medications, and the drug should not be used in those with a prolonged QTc as well as in patients with sinus node dysfunction (in the absence of a pacemaker) (Chaps. 46 and 49). Disopyramide should not be used as monotherapy in HCM patients without concomitant β-blocker or CCBs that block AV node conduction. If the patient develops atrial fibrillation, disopyramide can enhance AV conduction and dangerously lead to an increase in the ventricular rate [107]. Other adverse events include anticholinergic effects such as urinary retention, dry mouth, and membranes and exacerbation of closed-angle glaucoma. Anticholinergic side effects can be managed by dose reduction [107] or be reversed and prevented with the concomitant use of pyridostigmine [131]. Thus, the occurrence of anticholinergic side effects should not cause immediate cessation of disopyramide but rather initiation of therapy with pyridostigmine.

16.2.1.2 Medical Therapy for Prevention and Treatment of Arrhythmias in Patients with HCM

Amiodarone

Atrial fibrillation can complicate the clinical course of patients with HCM and is frequent when left atrial enlargement is present. The presence of AF generally leads to clinical deterioration of patients with HCM. The loss of atrial contribution to left ventricular filling and the increase in heart rate associated with AF cause a substantial increase in the risk for thromboembolic events. Amiodarone, a class III antiarrhythmic drug which also possesses β-adrenergic receptor antagonist effects and negative inotropic effects, is the only medication for which there is efficacy and safety data regarding treatment of AF in patients with HCM [132]. Amiodarone can control both rate and rhythm in HCM patients effectively by reducing embolic episodes as well as the need for cardioversion [133]. Amiodarone with or without β-blocker therapy is advocated for the treatment of AF and maintenance of rhythm control by the current AHA/ACC guidelines for the management of AF [134] (Chaps. 50 and 52).

While beneficial in the setting of AF, the role of amiodarone in preventing SCD, the most dreaded complication of HCM, is controversial. Amiodarone use for SCD is now less relevant with the advent of use of the automatic implanted cardioverter defibrillator (AICD). Initial reports suggested a protective effect of amiodarone in patients with HCM [135, 136]. However, subsequent studies have shown that amiodarone may actually increase the risk of lethal arrhythmias [137, 138]. In one study, 20 % of patients treated with amiodarone developed delayed conduction in the Hessian and Purkinje systems; of these, 50 % had a lower threshold for inducible ventricular tachycardia upon electrophysiologic testing [138]. Additional studies

have shown that despite therapy with amiodarone, the rate of SCD [139] or appropriate implantable cardioverter defibrillator (ICD) discharge [140] was high. Current data does not support the use of amiodarone to prevent SCD in most HCM patients.

The long-term use of amiodarone can be offset by its numerous side effects which include pulmonary fibrosis, thyroid function abnormalities, liver toxicity, corneal deposits, and skin discoloration. These, along with the potential for QT prolongation, limit the widespread utilization of amiodarone. In addition, because of potential QT prolongation, amiodarone cannot be used in conjunction with disopyramide. When initiating disopyramide therapy, patients need to be off amiodarone for several weeks, due to the long half-life of amiodarone. The QT interval needs to be checked before starting disopyramide and subsequent to its initiation in case the amiodarone effect on the QT interval is still present [128].

16.2.1.3 Medical Therapy for Prevention of Disease Progression

Angiotensin II AT_1 Receptor Blockers (ARBs) (Losartan and Valsartan)

Angiotensin II acts as a growth factor, which can cause hypertrophy of cardiac myocytes and mitogenesis of cardiac fibroblasts. These effects, resembling load-induced hypertrophy, are mediated mainly through the AT_1-R receptor. They may initiate a positive feedback regulation of this hypertrophy by inducing the angiotensin gene and transforming growth factor-beta 1 (TGFβ1) gene [141]. In vitro treatment of myocytes in cell cultures with losartan, an AT_1-R receptor blocker, prevented the cells form undergoing angiotensin II-induced changes. However, treatment with an investigational drug PD 123319, an angiotensin II AT_2 receptor (AT_2-R) blocker, did not have the same protective effect [141, 142]. As opposed to AT_1-R, the AT_2-R is expressed in low levels in the normal heart; however, it is upregulated in pathophysiological conditions including left ventricular hypertrophy (LVH) and plays a functional role in counterbalancing AT_1-R-mediated growth effects [142, 143]. Several studies show that stimulation of AT_2-R exerts an antigrowth effect in various cell types including cardiomyocytes [144], and AT_2-R blockade amplifies cardiac protein synthesis in hypertrophied hearts ex vivo [145]. Others have shown that pressure overload failed to induce LVH in AT_2-R knockout mice, suggesting that AT_2-R is obligatory for a hypertrophic response [146]. The ratio of AT_2-R to AT_1-R increases in failing hearts, suggesting that AT_2-R-related benefits can be further enhanced by drugs with combined AT_1-R blockade and AT_2-R agonist properties.

ARBs primarily act by blocking angiotensin 1 receptors (AT_1-R) which are present throughout the cardiovascular system. ARBs have been shown to be beneficial in patients with CHF, not only through reducing blood pressure but also through blocking the neurohormonal signaling in the heart [52, 147] (see Chap. 36 for discussion on ARBs and ACE-I). As opposed to angiotensin-converting enzyme inhibitors (ACE-I) that cause an overall decrease in the level of stimulating angiotensin II, thus reducing its activity at AT_1-R and AT_2-R sites, ARBs are more specific for blocking the AT_1-R subtype. Thus, it is contemplated that ARBs may have a more beneficial effect than ACE-I in HCM patients. Studies have shown that

the use of ARBs in HCM patients without LVOT gradients reduces symptoms and can also halt and cause reverse remodeling of the left atrium, improvement in LV diastolic function [148], and reduce LV mass [149, 150]. At the molecular level, procollagen alpha1, a precursor protein, which is converted into its active form in cardiac tissue, has been shown to increase cardiac fibrosis and correlate with early mortality through increased risk for SCD [151]. In HCM transgenic mice treated with losartan, significantly lower levels of procollagen alpha 1 and TGF-β1 were found, suggesting that this therapy can reverse interstitial fibrosis in HCM and have salutary effects in HCM patients [151].

16.2.1.4 Procedural/Interventional Treatment

Reduction of Symptoms

Other therapies aimed at reduction of the LVOT gradient, and thus reduction of symptoms includes surgical myectomy, catheter-based alcohol septal ablation, and dual-chamber pacing. Surgery and alcohol septal ablation should optimally be performed by experienced operators and only in patients with symptoms interfering with everyday activity despite optimal medical therapy, have a dynamic LVOT gradient of ≥50 mmHg which is associated with septal hypertrophy and systolic anterior motion of the mitral valve, and a septal thickness sufficient to perform the procedure [107]. Dual-chamber pacing has also been used to reduce LVOT pressure gradients in a small subset of mostly elderly patients. However, pacing has been less validated than septal reduction and should be reserved for those who are refractory to medical therapy and who cannot undergo either myectomy or alcohol septal ablation [107].

Prevention of SCD

Patients with HCM should undergo risk stratification for determination of risk for SCD. Therapy with an AICD has been shown to be effective in treatment of ventricular arrhythmias and preventing SCD in HCM patients [152]. Risk factors for sudden cardiac death are listed in Table 16.4. Absolute indications for defibrillator placement include history of SCD, ventricular fibrillation, or hemodynamically significant ventricular tachycardia, in those with a wall thickness of ≥3 cm and unexplained syncope episodes and in those with an abnormal response to exercise who have additional risk factors or modifiers for SCD [107] (also see Chap. 7).

Heart Transplantation

A recent analysis within a large US transplant cohort demonstrated that the prevalence of transplantation due to HCM was about 1 %/year, similar to patients with restrictive cardiomyopathy, but significantly less than ischemic or dilated

Table 16.4 Risk factors for sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM) [107]

Established risk markers for SCD
Personal history of an episode of either ventricular fibrillation, sustained ventricular tachycardia (VT), or an event of SCD, including appropriate therapy which terminated an episode of SCD
Family history of SCD, including appropriate therapy which terminated an episode of SCD
Unexplained syncope
Documented non-sustained VT: 3 or more beats at greater than or equal to 120 beats per minute
Left ventricular (LV) wall thickness of >3 cm
Inappropriate response to exercise testing: failure to increase the systolic blood pressure by 20 mmHg or a drop of at least 20 mmHg during effort
Other potential risk modifiers for SCD
Late gadolinium enhancement on MRI
Genetic mutations
Marked LVOT obstruction (>30 mmHg)
LV apical aneurysm

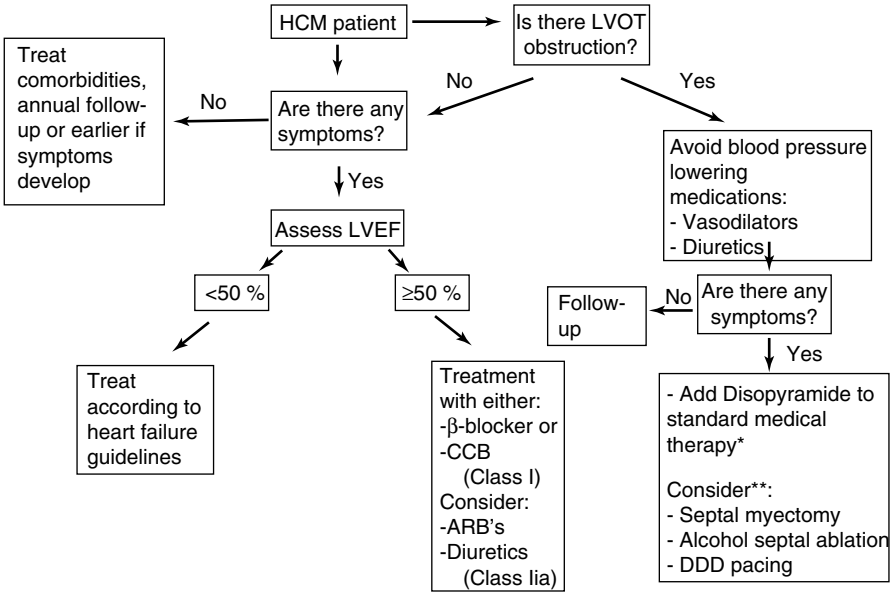

Fig. 16.4 Treatment scheme for patients with hypertrophic cardiomyopathy (HCM). *LVEF* left ventricular ejection fraction. *Maximal medical therapy should be used, including disopyramide, before proceeding with surgery/interventional therapy. Disopyramide should be used in conjunction with β-blocker therapy. **The ideal treatment option will be determined according to the patient's risk for surgery (Adapted with permission from Gersh et al. [107])

cardiomyopathy [153]. HCM patients who underwent transplantation had a 1-, 5-, and 10-year survival of 85 %, 75 %, and 61 %, respectively [153], comparable to other, non-HCM-related cardiac transplantation. Heart transplantation should be reserved as a practical therapeutic option in patients with HCM who develop

advanced CHF despite medical and/or septal reduction therapy (surgical or percutaneous); heart transplant may be the only viable therapeutic option [153].

16.3 Concluding Remarks

Myocardial hypertrophy is a phenotype that is secondary to multiple cardiac disease entities, but it is the primary manifestation of HCM, as it occurs in the absence of LV pressure overload. HCM is an inherited heart disease occurring in 1 in 500 people along with the occurrence of spontaneous variants. It presents with a diverse and complex clinical presentation, which can lead to marked morbidity and mortality if left untreated. As detailed in this chapter and outlined in Fig. 16.4, the current medical options primarily address reduction of symptoms. Patients with the obstructive form of this disease who are symptomatic might also benefit from procedural/interventional treatment. At present with current therapy, the disease-related mortality is <1 %/year. However, there is no evidence that gradient reduction therapy, which frequently improves symptoms, enhances longevity. Ongoing research is directed at developing a more complete understanding of this disease along with improved diagnostic and therapeutic capabilities, which should allow better patient management and improved quality of life.

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Chapter 17
Myocardial Metabolic Abnormalities and Cardiac Dysfunction

Petra C. Kienesberger

Abstract To sustain contractile function, the myocardium has a very high and continuous demand for ATP, which it generates from a variety of carbon sources, including fatty acids, glucose, ketone bodies, pyruvate, and lactate. In the healthy adult heart, most of the ATP is generated via mitochondrial oxidation of fatty acids (50–70 %), and the balance between fatty acid oxidation and other forms of ATP production, such as glucose oxidation and glycolysis, is tightly regulated. In fact, dysregulation or inflexibility of myocardial energy metabolism has been linked to a number of major cardiac diseases including myocardial hypertrophy, heart failure, ischemic heart disease, and obesity and diabetes mellitus-associated cardiomyopathy. Deranged cardiac energy metabolism and impaired cardiac energetics have been suggested to contribute to these pathophysiological states, rendering metabolic modulators an attractive option for the management of various forms of heart disease. This chapter summarizes our current understanding of the role of cardiac energy metabolism in the development and progression of heart failure, pressure overload-induced hypertrophy, and obesity-related cardiomyopathy. In addition, potential therapies to restore metabolic balance and efficiency in the heart and ameliorate cardiac dysfunction are outlined.

Keywords Cardiac metabolism • Cardiac energetics • Heart failure • Cardiomyopathy • Hypertrophy • Obesity • Lipotoxicity

17.1 Introduction

To generate sufficient ATP for contractile function, cardiomyocytes transport energy substrates, mainly fatty acids and glucose, from the circulation across the sarcolemmal membrane. Fatty acids are presented to the cardiomyocytes in the form of "free" fatty acids conjugated to serum albumin or triacylglycerol (TAG)-rich

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very-low-density lipoproteins and chylomicrons [1, 2]. TAGs in lipoproteins are hydrolyzed to fatty acids by lipoprotein lipase in the coronary lumen [3, 4]. Fatty acids then enter cardiomyocytes mainly via transport proteins or carriers including fatty acid translocase (FAT/CD36), plasma membrane fatty acid-binding protein (FABPpm), and fatty acid transport protein 1/6 (FATP1/6) [5–9]. Fatty acid carriers can translocate to the sarcolemma to increase fatty acid uptake into cardiomyocytes [5]. For example, FAT/CD36, which is believed to facilitate approximately 50 % of fatty acid uptake into cardiomyocytes and controls 40–60 % of myocardial fatty acid oxidation in the working mouse heart [9–12], can translocate to the sarcolemma following insulin stimulation, activation of AMP-activated protein kinase (AMPK), and contraction [5]. Upon transport across the sarcolemma, fatty acids are subsequently converted to fatty acyl-coenzyme A esters (fatty acyl-CoA) by long-chain acyl-CoA synthetases (ACSL) in an ATP-dependent manner [1, 13]. This metabolic step traps fatty acids within cardiomyocytes and activates them so that they can be metabolized [13].

In order to be transported across the mitochondrial membrane, fatty acyl-CoAs need to be converted to acylcarnitines by carnitine palmitoyltransferase 1 (CPT1) and are then transferred across the inner mitochondrial membrane via carnitine:acylcarnitine translocase, which exchanges carnitine for acylcarnitine [2]. Upon conversion of acylcarnitine back to long-chain acyl-CoA by CPT2 in the mitochondrial matrix, fatty acids enter β-oxidation, which is catalyzed by the sequential enzymatic action of acyl-CoA dehydrogenase, enoyl-CoA hydratase, hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. This shortens the fatty acyl moiety by two carbons in each cycle and produces reducing equivalents in the form of flavin adenine dinucleotide ($FADH_2$) and nicotinamide adenine dinucleotide (NADH) [14]. The β-oxidation of unsaturated fatty acids, which represent the majority of fatty acids in circulation that enter the cardiomyocyte, involves additional enzymes, 2,4-dienoyl-CoA reductase and enoyl-CoA isomerase, to convert *cis* double bonds to *trans* double bonds [15]. It should be noted that saturated and unsaturated fatty acids are oxidized at comparable rates in the rodent and human heart [16, 17]. Enzymes involved in β-oxidation are under a high degree of transcriptional control by peroxisome proliferator-activated receptor (PPAR) α and β/δ, as well as PPARγ coactivator (PGC) 1α and 1β [18, 19]. The reducing equivalents (NADH and $FADH_2$) generated via β-oxidation and subsequent delivery of acetyl-CoA to the tricarboxylic acid cycle are then converted to ATP through oxidative phosphorylation at the inner mitochondrial membrane. Since ATP cannot cross the mitochondrial membrane, creatine kinase transfers the high-energy phosphate bond in ATP to creatine, which is taken up from the circulation via a creatine transporter [20]. This leads to the formation of phosphocreatine and adenosine diphosphate (ADP) [21]. Phosphocreatine, which is smaller than ATP, can diffuse from the mitochondria to myofibrils, the contractile apparatus of cardiomyocytes [21]. The myofibrillar creatine kinase converts phosphocreatine back to ATP to power contractions and the free creatine diffuses back to the mitochondria [21]. The creatine kinase system functions as an important energy buffer in the myocardium [21]. When energy demand is higher than energy supply, the phosphocreatine pool decreases to

maintain ATP levels [21]. This is an early adaptation to myocardial energy deficiency. Also, under these conditions, ADP levels rise, which can impair a variety of intracellular processes and lead to defective contractile function [21].

Similar to fatty acids, glucose is transported into the cardiomyocyte via proteins embedded in the sarcolemma. Glucose uptake is mediated mainly by two glucose transporters, Glut1 and Glut4 [22]. Glucose transport via Glut1 is insulin independent and accounts for basal glucose uptake. Glut1 expression is reduced following birth but can increase again in pathophysiological states including cardiac hypertrophy [22] (Chap. 16). In contrast to Glut1, the insulin-sensitive glucose transporter Glut4 is abundantly expressed in the adult heart [23]. Glut4 translocation from storage vesicles to the sarcolemma is stimulated by insulin and by contractions [23]. Upon uptake into the cell, glucose is phosphorylated by hexokinase, which commits glucose to further metabolism [24]. Glucose-6-phosphate is then catabolized through glycolysis, and the resulting pyruvate is shuttled into mitochondria, converted to acetyl-CoA, and subjected to oxidation for ATP production. Glucose that is not immediately directed towards glycolysis and mitochondrial oxidation can be converted to glycogen for temporary storage [24]. The following sections outline how energy metabolism is altered in cardiac pathophysiology and highlight potential therapeutic avenues which could be pursued to restore energetic balance in the diseased heart.

17.2 Myocardial Energy Starvation in Heart Failure

Heart failure is a multifactorial disorder that is fairly common – it affects more than 2 % of people in the United States, and 30–40 % of heart failure patients die within 1 year from the diagnosis [21]. Between 1979 and 2004, the United States was confronted with a threefold increase in heart failure hospitalizations, with more than 80 % of patients being at least 65 years old [25]. It is projected that the incidence of heart failure will increase in the future as the population continues to age. Despite the various causes of heart failure, which include hypertension, coronary artery disease, cardiomyopathy, and cardiac arrhythmias, impaired energy metabolism appears to be a fundamental characteristic that contributes to the progression of heart failure [21, 25] (Fig. 17.1) (Chaps. 1 and 3). This concept is not new as it was first described in 1939 by Herrmann and Decherd that the failing heart is essentially energy-starved [26], meaning that there are not enough energy equivalents (ATP and phosphocreatine) to sustain contractile function in end-stage heart failure. Interestingly, the efficacy of beta-blockers, angiotensin II blockers, or angiotensin-converting enzyme inhibitors in ameliorating heart failure is in part attributed to their effect in reducing cardiac energy demand and improving the metabolic balance [21] (Chaps. 8 and 18).

The derangement of cardiac energy metabolism in heart failure occurs at three stages – energy substrate utilization (uptake and oxidation), oxidative phosphorylation in mitochondria, and high-energy phosphate (ATP, phosphocreatine) metabolism, as was evidenced in the rodent and human heart [21]. Previous studies have

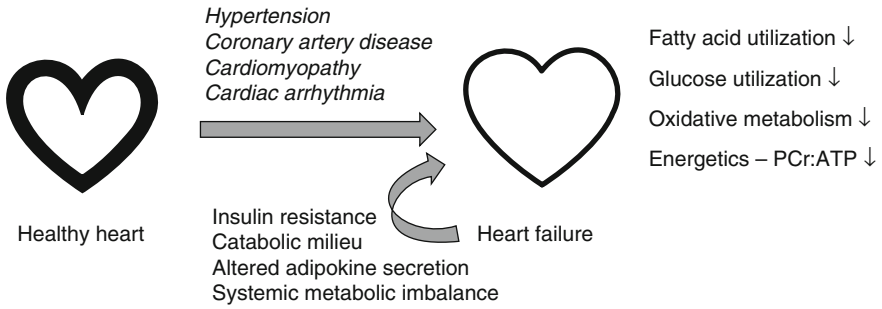

Fig. 17.1 Metabolic changes in advanced heart failure. Cardiovascular diseases such as hypertension, coronary artery disease, cardiomyopathy, and cardiac arrhythmia can lead to heart failure. In end-stage heart failure, typical metabolic changes are decreased fatty acid utilization, glucose utilization, and overall oxidative metabolism, resulting in impaired energetics. Effects of heart failure on systemic metabolism include insulin resistance, increased catabolism, and altered adipokine secretion, which contribute to the progression of heart failure and further impair myocardial energy metabolism. PCr:ATP is phosphocreatine:adenosine triphosphate

generally shown that while fatty acid utilization is not substantially altered in early stages of heart failure [27, 28], it drops substantially in advanced heart failure [29] (Fig. 17.1). Glucose utilization has been reported to increase in early stages of heart failure [30] and decrease along with the development of insulin resistance in advanced heart failure [21, 31–33] (Fig. 17.1). Since the systemic metabolic milieu is drastically altered in heart failure with commonly increased circulating fatty acids, glucose, and insulin, and catabolic over activity, these results need to be viewed with caution as it is difficult to distinguish between the inherent impairment of substrate metabolism in the myocardium and metabolic adaptations due to altered substrate availability [21, 25]. Impaired structure and function of mitochondria are also commonly observed in failing hearts [34, 35], leading to reduced oxidative phosphorylation, oxygen consumption, and ATP/phosphocreatine production.

In addition, the creatine kinase system is substantially altered in heart failure [21, 36, 37], which causes a drastic decline in ATP transfer and ATP starvation of myofibrils. Interestingly, ATP concentrations are sustained in a normal range in earlier stages of heart failure and only decline by approximately 30–40 % in advanced heart failure [21, 38–40]. However, the decline in intracellular creatine and phosphocreatine due to impaired creatine transporter function precedes and is greater than the decline in ATP concentrations (30–70 %), representing an early sign of deranged cardiac energetics in heart failure [36, 39, 41, 42]. Hence, phosphocreatine-to-ATP ratios are reduced in heart failure and correlate with heart failure classes according to the New York Heart Association [43] (Fig. 17.1). These changes in high-energy phosphate metabolism drastically limit the energetic reserve of the myocardium. For example, when failing hearts are challenged with high workload (e.g., by stimulation with catecholamines), free ADP increases to concentrations that are double compared to those in the healthy heart [44], thereby reducing the contractile reserve [21]. Given that impaired energy metabolism critically contributes

to heart failure development and/or progression, modulators that improve the energetic reserve of the heart may become attractive options for the treatment of heart failure.

At present, there is no approved therapy available that specifically targets energy metabolism in heart failure [25]. Experimental metabolic therapies that are aimed at improving metabolic balance and efficiency in the myocardium generally decrease fatty acid utilization and increase glucose oxidation [25]. For example, the piperazine derivative, trimetazidine, is an experimental drug that selectively inhibits mitochondrial long-chain 3-ketoacyl-CoA thiolase, thereby decreasing fatty acid oxidation and increasing glucose utilization via secondary activation of pyruvate dehydrogenase [45]. Trimetazidine restores coupling between glycolysis and glucose oxidation and leads to ATP production with less demand for oxygen [45]. While the results from clinical trials are promising [45–47], more clinical studies are required to demonstrate the efficacy of this drug in ameliorating heart failure and angina (Chap. 22).

Heart failure not only affects myocardial energy metabolism but whole body metabolism via endocrine communication of the heart with other organs [25, 48, 49]. For example, systemic insulin resistance is a characteristic feature of heart failure [48]. It develops in response to neurohormonal stimuli (catecholamines), inflammatory cytokine release, oxidative stress, and tissue hypoperfusion as a consequence of heart failure [25, 50]. Moreover, insulin resistance appears to predict severity of heart failure and reduced survival [25]. In addition, resistance to the anabolic hormone insulin, among other factors, leads to an overall catabolic environment that contributes to muscle cachexia in heart failure patients [25, 49]. Overstimulation of adipose tissue lipolysis via increased catecholamines, inflammatory cytokines, natriuretic peptides, and pressure overload also leads to a rise in circulating fatty acids and changes in adipokine secretion and thereby contributes to the systemic and cardiac metabolic imbalance in heart failure [25, 50, 51]. Therefore, therapies that target not only cardiac metabolism but whole body metabolism, for those individuals in heart failure, could hold promise in treating this debilitating disease (Chaps. 3 and 18).

17.3 Metabolic Remodeling in Myocardial Hypertrophy

Cardiac hypertrophy is an initially adaptive response to cellular stress leading to cardiomyocyte enlargement, increased protein synthesis, re-induction of the so-called fetal gene program, and heightened sarcomeric organization [52, 53]. Chronically, cardiac hypertrophy can become maladaptive and trigger heart failure and malignant arrhythmia due to perturbations of cellular calcium homeostasis and ionic currents [52, 53]. Significant morphological changes following long-term cardiac hypertrophy include increased rates of programmed cell death, fibrosis, and cardiac chamber dilatation [52, 53]. Common stressors that lead to hypertrophic remodeling in cardiomyocytes are pressure or volume overload, mutations of

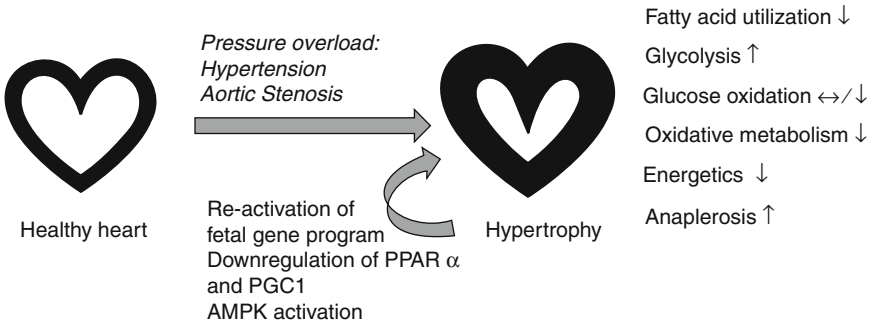

Fig. 17.2 Metabolic changes in pressure overload-induced cardiac hypertrophy. Pressure overload-induced hypertrophy, triggered by hypertension or aortic stenosis, is associated with a decrease in fatty acid oxidation and overall oxidative metabolism and energetics, while anaerobic glucose metabolism (glycolysis) is increased. Glycolysis is uncoupled from glucose oxidation, and excess pyruvate is shuttled towards alternative pathways, such as anaplerosis. The decrease in fatty acid utilization is mostly due to the reactivation of the fetal gene program and downregulation of transcriptional regulators of fatty acid oxidation and mitochondrial biogenesis and function. AMPK activation has been suggested to underlie the increase in glucose uptake and glycolysis in cardiac hypertrophy

sarcomeric or other proteins, and loss of contractile mass from prior infarction [52, 53]. The following section describes metabolic changes following pressure overload hypertrophy as this type of hypertrophy is increasingly common due to the increasing prevalence of hypertension (Chap. 16).

One of the metabolic hallmarks of pressure overload-induced cardiac hypertrophy is that cardiac energy metabolism reverts to a fetal-like profile, which is due to a decrease in fatty acid oxidation and increased reliance on carbohydrates for ATP production with an overall decrease in oxidative metabolism [54, 55] (Fig. 17.2). This substrate shift has been suggested to contribute to the progression of cardiac hypertrophy to overt heart failure [56], although it still remains elusive to what extent metabolic remodeling influences the development and progression of pressure overload-induced cardiac hypertrophy. The reduction in fatty acid oxidation is attributed to a decrease in the expression of genes involved in β-oxidation and oxidative phosphorylation [55]. A number of studies using animal models have shown that this is due to the downregulation of the transcriptional master regulators PPARα and PGC1 [55, 57–60] (Fig. 17.2). In addition, a reduction in membrane-bound fatty acid transporters and carnitine has also been observed in the hypertrophic heart [61–64]. The resulting energy insufficiency leads to the activation of the energy-sensing kinase, AMPK, which contributes to an increase in glucose uptake and glycolysis by promoting translocation of glucose transporters to the sarcolemma and stimulating the glycolytic enzyme, phosphofructokinase 2 [55, 65–67] (Fig. 17.2). Interestingly, the increase in glucose uptake is insulin-independent, and changes in glucose metabolism in the hypertrophic heart are not accompanied by marked changes in proteins involved in glucose transport or glycolysis [33, 55, 68]. In contrast to the increased glycolysis, many studies have reported that glucose

oxidation is either unchanged or decreased in the hypertrophied heart, suggesting that glucose oxidation and glycolysis are uncoupled in cardiac hypertrophy [55, 69–71] (Fig. 17.2). As a result of this uncoupling in glucose metabolism, lactate dehydrogenase, which converts pyruvate into lactate, is activated to process the excess pyruvate. Consequently, increased secretion of lactate from the hypertrophied myocardium has been reported [55, 72, 73].

The excess pyruvate can also be shuttled towards anaplerosis, which refers to metabolic processes that replenish tricarboxylic acid (TCA) cycle intermediates that are removed from the TCA cycle for biosynthetic pathways to produce glucose, fatty acids, and amino acids [74]. In this process, pyruvate is converted to oxaloacetate and malate through its carboxylation via pyruvate carboxylase and malic enzyme, respectively [74]. Consistent with this notion, an 80–90 % increase in anaplerotic flux has been reported in the hypertrophied heart [75, 76] (Fig. 17.2). Although pyruvate can replenish TCA cycle substrates via anaplerosis, it is an energetically costly process as it reduces the efficiency of ATP production from pyruvate [55]. Changes in other glucose metabolism pathways were also observed in the hypertrophied heart, including pentose-phosphate pathway [77–79] and hexosamine pathway [80, 81]. To date, it remains unclear whether and to what extent these "alternative" glucose metabolism pathways contribute to the pathophysiology of cardiac hypertrophy.

The increase in the reliance on glucose utilization in the hypertrophic heart appears to be an adaptive process, at least in earlier stages of hypertrophic remodeling. This notion is inferred from studies with mutant mice where the expression of glucose transporters has been altered. For example, mice overexpressing the insulin-independent glucose transporter Glut1, specifically in the heart, exhibit increased glucose uptake and glycolysis that is partially uncoupled from glucose oxidation, as well as decreased fatty acid oxidation [82]. Importantly, these mice were protected from pressure overload-induced cardiac dysfunction [82]. In contrast, mice with cardiac deficiency of the insulin-sensitive glucose transporter Glut4 exhibit reduced contractile function and cardiomyocyte hypertrophy [83]. Prevention of metabolic remodeling in pressure overload hypertrophy via cardiac-specific deletion of acetyl-CoA carboxylase 2, which produces the fatty acid oxidation inhibitor malonyl-CoA, attenuated cardiac hypertrophy, protected against fibrosis, and improved cardiac function [84]. These findings suggest that metabolic remodeling contributes to the pathophysiology of cardiac hypertrophy.

Interestingly, cardiac-specific overexpression of PGC1α and the associated increase in mitochondrial size did not protect from cardiac remodeling induced by transverse aortic constriction [85]. Instead, it led to a greater impairment in contractile function and increase in left ventricular chamber dimension [85]. These data suggest that attempts to stimulate master regulators of mitochondrial biogenesis and size in cardiac hypertrophy to improve oxidative metabolism may in fact worsen outcomes following pressure overload-induced hypertrophy. Dietary and pharmacological strategies have also been pursued to ameliorate outcomes in pressure overload-induced hypertrophy [54, 86, 87]. Interestingly, feeding rats with a diet low in carbohydrates and high in fat attenuated cardiac hypertrophy and remodeling [86]. In contrast, activation of fatty acid metabolism via PPARα agonist (WY-14643) treatment augmented pressure overload-induced contractile dysfunction,

despite the prevention of substrate switching [87]. Since these interventions drastically influence whole body metabolism in addition to cardiac metabolism, their direct effects on metabolism and function in the hypertrophic heart remain unclear.

17.4 Metabolic (Mal)adaptation of the Heart in Obesity

Obesity, defined as excess accumulation of body fat, and associated type 2 diabetes mellitus, is a significant risk factor for the development of heart failure [88, 89]. Although the onset of heart failure in obesity is likely multifactorial, obesity-associated cardiomyopathy appears to be a major initiating factor and contributes to the increased morbidity and mortality among obese individuals [88]. This is exemplified by the finding that even after correcting for hypertension and other common obesity-related risk factors, the presence of obesity still approximately doubles the risk of developing heart failure [90]. Chronic obesity commonly leads to systemic metabolic perturbances including insulin resistance and type 2 diabetes with concomitant hyperglycemia and hyperlipidemia. It has been hypothesized that this oversupply of energy substrates to the heart initially leads to adaptive changes and ultimately precipitates contractile dysfunction [90]. Specifically, the increased availability of fatty acids resulting in augmented fatty acid uptake, in conjunction with inadequate activation of fatty acid oxidation, gives rise to excess accumulation of toxic lipid metabolites in the myocardium and a general increase in cardiac fat content [88, 90]. High fatty acid oxidation rates in obesity, as have been observed in both animal models and humans, inhibit cardiac glucose utilization via substrate competition, hence contributing to decreases in glycolysis and glucose oxidation as well as insulin resistance [19, 91] (Fig. 17.3). These metabolic changes also lead to a decrease in mechanical efficiency [19, 91]. It has been suggested that the metabolic

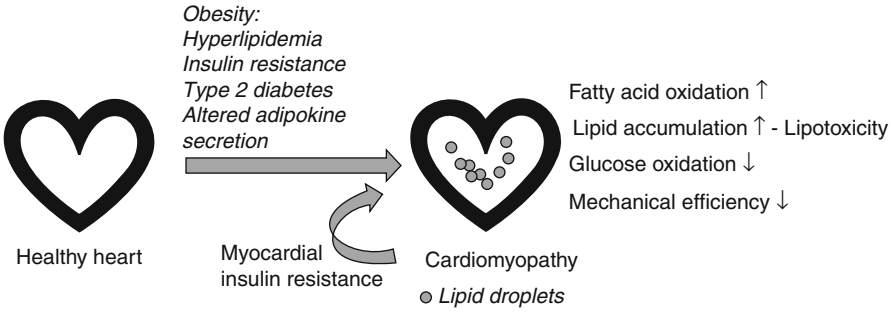

Fig. 17.3 Metabolic changes in obesity-associated cardiomyopathy. Obesity and obesity-associated systemic changes in energy metabolism (hyperlipidemia, insulin resistance, type 2 diabetes) and adipokine secretion lead to increased cardiac fatty acid oxidation, lipid accumulation, and lipotoxicity, which are paralleled by reduced glucose oxidation and mechanical efficiency. Myocardial insulin resistance further promotes metabolic dysregulation in the heart

remodeling of the myocardium observed in obesity not only precedes but contributes to overt functional and structural changes of the heart in obesity [90, 92].

Increased accumulation of toxic lipid metabolites, a process that is also termed as "lipotoxicity," has also been suggested to contribute to cardiac dysfunction during obesity [93–95] (Fig. 17.3). Examples for toxic lipid metabolites are long-chain acyl-CoAs, ceramides, diacylglycerols, and acylcarnitines [96]. Lipotoxicity may lead to cardiac dysfunction by means of activating apoptosis, impairing insulin signaling, promoting endoplasmic reticulum stress, activating protein kinase C and mitogen-activated protein kinase, as well as modulating PPAR signaling [96]. Studies using nonobese transgenic mice and obese-diabetic rat models show that accumulation of lipids in cardiomyocytes corresponds with a decrease in systolic and diastolic function and cardiac hypertrophy [4, 19, 93, 97–101]. However, the individual contribution of lipid subspecies to cardiac pathophysiology is unclear. Mechanisms for the lipotoxicity-induced insulin resistance in the heart have been suggested to involve diacylglycerol-mediated activation of protein kinase C, resulting in increased serine phosphorylation of insulin receptor substrate 1 and decreased activation of downstream insulin signaling mediators, such as phosphatidylinositol 3-kinase and Akt [19]. The implication of increased TAG accumulation in the obese heart is less understood, but it may impair cardiac function by fueling the production of "toxic" lipid species [1]. Myocardial TAG content positively correlates with body mass index, suggesting that cardiac TAG deposition increases gradually with increased adiposity [102]. Elevated myocardial TAG content was also observed in individuals with impaired glucose tolerance and type 2 diabetes [1, 103, 104]. Moreover, the increase in cardiac TAG accumulation preceded the development of overt cardiac dysfunction, suggesting a causal relationship between elevated TAG levels in the heart and obesity/type 2 diabetes-associated myocardial dysfunction [1, 103].

To date, drugs used to treat metabolic disturbances in obesity are mainly aimed at lowering circulating lipid levels and ameliorating insulin resistance. For example, there are two classes of PPAR agonists used to achieve this effect. These are ligands for PPARα and PPARγ, respectively. Both PPARα and PPARγ agonists lower circulating lipid levels either by increasing fat storage in adipocytes or increasing fatty acid oxidation in the muscle and liver [19]. Despite the beneficial systemic effect of PPARα and PPARγ agonists, their direct effect on the heart may not always be desirable. For example, cardiac-specific overexpression of PPARα induced a cardiac phenotype similar to diabetic cardiomyopathy [105]. Myocardial fatty acid oxidation rates were increased in these transgenic mice, while glucose uptake and oxidation were decreased, concomitant with the development of pathological cardiac hypertrophy, increased lipid accumulation, and cardiac dysfunction [105]. Similarly, cardiomyocyte-specific overexpression of PPARγ led to cardiac dysfunction in mice that was associated with increased myocardial lipid accumulation and expression of enzymes involved in fatty acid utilization [106]. In humans, PPARγ agonist treatment is also associated with peripheral edema and heart failure [106, 107]. These findings suggest that PPAR agonist treatment in obesity may have adverse effects on the heart by increasing cardiac lipid deposition. Interestingly, recent studies showed that inhibition of mitochondrial β-oxidation with trimetazidine,

which is widely used for the treatment of angina, can improve obesity-related cardiac dysfunction [108]. Trimetazidine not only improves contractile efficiency in obese humans but protects against obesity-induced systolic and diastolic dysfunction in mice without altering insulin sensitivity or exacerbating obesity-induced insulin resistance [108]. This suggests that trimetazidine, by improving the metabolic balance in the heart, may be a viable therapy for the treatment of obesity-related cardiomyopathy.

Metabolic disturbances in adipose tissue initiate obesity-associated morbidity and cardiovascular disease [109, 110]. Besides fueling the systemic and cardiac lipid oversupply in obesity, the hypertrophic obese adipose tissue also changes its secretory profile of hormones and cytokines, so-called adipokines, which promotes not only insulin resistance and inflammation but likely has a direct effect on cardiac energy metabolism [19, 90, 111] (Fig. 17.3). However, more studies are required to better understand the direct effects of changes in circulating adipokines such as adiponectin, leptin, resistin, and retinol-binding protein 4 on cardiac metabolism and function during obesity in both animal models and humans.

17.5 Concluding Remarks

Cardiac energy metabolism is tightly regulated to meet the high energy demands of myocardial contraction and to adapt to short-term fluctuations in energy substrate supply and workload. When challenged by chronic stressors, including pressure overload and obesity, myocardial energy metabolism can initially adapt to counter-regulate but is eventually locked into a dysregulated and inflexible state with a major shift in substrate utilization and/or cardiac energetics and efficiency. Many studies have shown that this impairment in cardiac energy metabolism can promote the development of heart failure with a significant drop in the heart's energetics and premature death. Since there is evidence that maladaptive changes in cardiac energy metabolism contribute at least in part to multiple forms of heart disease, drugs that aim to restore a balanced substrate utilization in the heart have the potential to become attractive options to treat these diseases and prevent their progression to overt heart failure.

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Chapter 18
Molecular Targets in the Treatment of Cardiac Hypertrophy

Christian Kuhn, Susanne Hille, and Norbert Frey

Abstract Cardiac hypertrophy is associated with a variety of widespread disorders such as ischemic, valvular, and hypertensive heart disease. It has been identified as an independent risk factor for heart failure and mortality. Therefore, prevention as well as reversal of cardiac hypertrophy represents an obvious goal in the treatment of these patients. So far, established drug therapies target mainly α- and β-adrenergic receptors as well as the renin-angiotensin-aldosterone system. However, many other molecular pathways have been found to contribute in the pathogenesis of pathological hypertrophy. Hypertrophic signaling is controlled on transcriptional and post-transcriptional level. The recent discovery of several noncoding RNA species has added another layer of complexity to the regulation of posttranscriptional gene expression. Furthermore, posttranslational modifications such as phosphorylation influence the activity of hypertrophic signaling. Finally, protein degradation mechanisms affect hypertrophic pathways. With growing knowledge about the molecular regulation of cardiac hypertrophy, novel targets will arise for medical therapy. In this chapter, we will provide a brief overview over selected pathways and highlight the impact of general mechanisms on hypertrophic signaling.

Keywords Heart • Hypertrophy • Calcineurin • Autophagy • MicroRNA • G protein-coupled receptor • Long noncoding RNAs • Circular RNAs • Wnt/Frizzled signaling • Small G proteins • Histone deacetylases • LCZ696 • Angiotensin • AT_1R • NFAT signaling

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18.1 Introduction

During intrauterine development, the heart grows by hyperplasia of cardiomyocytes and other cell types building the extracellular matrix. Shortly after birth, cardiomyocytes exit cell cycle undergoing a final round of DNA duplication without cell division [1]. Cardiac growth then switches from hyperplasia to hypertrophy. Nevertheless, the heart remains a flexible organ and is able to respond to environmental changes by atrophy or hypertrophy [2]. While pregnancy and exercise evoke so-called physiological hypertrophy, stimuli that cause biomechanical stress due to increased afterload, volume overload, or mutations in genes encoding for sarcomeric proteins result in pathological hypertrophy. Thus, a variety of cardiovascular disorders like valvular heart disease, hypertension, myocardial infarction, or hypertrophic cardiomyopathy are accompanied by cardiac hypertrophy. Initially hypertrophy is considered to be compensatory in order to decrease wall stress [3]. In the long run however, hypertrophy can be maladaptive and is associated with an increased risk for heart failure [4], arrhythmias [5], and mortality [6]. Therefore, the direct treatment of hypertrophy seems to be a reasonable goal. However, the underlying mechanisms are multifaceted and complex (Chap. 16). In this chapter, we overview established therapies for cardiac hypertrophy. Furthermore, we discuss molecular pathways containing potential targets for the treatment of hypertrophy in the future.

18.2 Molecular Pathways as Targets

18.2.1 G Protein-Coupled Receptors

Up-to-date standard pharmacotherapy of hypertension and heart failure targets α- and β-adrenergic as well as angiotensin II-AT_1 receptors. All of them belong to a large receptor family of G protein-coupled receptors (GPCRs) with more than 800 members [7]. They share a typical structure with seven transmembrane helices. The receptors are coupled to a class of heterotrimeric proteins, the G proteins. Activation of GPCRs leads to dissociation of G proteins into Gα and Gβγ subunits that mediate GPCR signaling. Depending on the respective isoform, the effects can be stimulatory (G_s) or inhibitory (G_i) (for more details, readers may refer to Chaps. 5, 34, 35, and 36).

18.2.1.1 β-Adrenergic Signaling

In the heart, β_1 and β_2 are the two major isoforms of adrenergic receptors [8]. They are coupled to G_s proteins. Stimulation of β_1- and β_2-adrenergic receptors by their ligands epinephrine and norepinephrine leads to increased cAMP levels via

adenylyl cyclase finally resulting in activation of protein kinase A (PKA). Interestingly, β_2- and the more recently identified β_3-receptor also couple to G_i proteins [9]. To clarify the role of β-adrenergic receptors in vivo, several mouse models have been developed. The majority of genetically engineered mice that are deficient for the β_1-receptor die in utero. The surviving animals show normal heart rates under basal conditions but lack the positive chronotropic and inotropic response to isoproterenol [10]. Cardiac-specific overexpression of β_1-receptors in mice causes cardiomyocyte hypertrophy, apoptosis, fibrosis, and heart failure [11, 12]. However, the consequences of overexpression of β_2-receptors are more complex. A 200-fold overexpression of β_2-receptors in the murine heart is accompanied by increased heart rate and left ventricular contractility that are comparable to isoproterenol stimulation [13]. These animals develop severe heart failure following transverse aortic constriction [14], but display improved contractility compared to wild-type mice after myocardial infarction [15]. Using higher and lower overexpression levels (60-fold to 350-fold) in mouse models revealed that higher overexpression levels are associated with dilated cardiomyopathy, heart failure, and mortality, while 60-fold overexpression of β_2-receptors does not have an impact on survival [16]. Homozygous β_2-receptor knockout mice are viable and do not develop an overt cardiac phenotype under baseline conditions. The increase in heart rate following stimulation by isoproterenol and epinephrine is comparable to wild-type mice, but β_2-receptor knockout mice show higher blood pressure [17]. The lack of β_3-receptors causes an increase in total body fat with no overt cardiac phenotype [18]. Of note, heart-specific overexpression of the human β_3-receptor in mice is accompanied by increased cardiac contractility under simultaneous stimulation with isoproterenol or a specific agonist and β_1-/β_2-receptor blockade by propranolol [19].

A decade ago when activation of the adrenergic nervous system was recognized to be maladaptive, β-blockers were first used in the treatment of chronic heart failure which proved to be beneficial [20]. They reverse left ventricular remodeling and reduce the risk of arrhythmias and mortality [21]. Furthermore, β-blockers are also widely prescribed drugs in the treatment of hypertension. It has been shown that treatment with β-blockers causes regression of left ventricular hypertrophy [22]. In contrast, there is evidence that treatment of uncomplicated hypertension with β-blockers as monotherapy is associated with an increase in stroke risk with no clear benefit concerning mortality or cardiovascular morbidity (reviewed in [23]). However, β-blockers are efficacious agents in the management of heart failure and hypertrophic obstructive cardiomyopathy [23] (Chaps. 5 and 8).

A hallmark of prolonged β-receptor stimulation is desensitization via phosphorylation by GPCR kinases (GRK) [24], PKA, or protein kinase C (PKC) leading to uncoupling, internalization, and finally downregulation of the receptors. The phosphorylated GPCR has a high affinity to β-arrestins that cause the uncoupling of the receptor from the G protein. So far, seven mammalian isoforms of these serine/threonine kinases (GRK1–GRK7) have been identified. GRK2 (βARK1) and GRK5 are the predominantly expressed isoforms in the heart. Interestingly, GRK2 is induced in human failing hearts [25]. The global knockout of GRK2 results in embryonic lethality due to hypoplasia of the myocardium and heart failure [26].

Surprisingly, cardiac-specific ablation of GRK2 is not embryonically lethal, indicating essential noncardiac functions during development. The animals exhibited higher cardiac contractility under baseline as well as under stimulation conditions [27]. Furthermore, the homozygous loss of GRK2 could improve the deleterious effects of experimental myocardial infarction in mice [28]. Interestingly, a peptide that contains the carboxyl terminus of GRK2 acts as an inhibitor due to competitive binding of Gβγ. Cardiac overexpression of this inhibitor (βARKct) reverses heart failure in a well-established mouse model of dilated cardiomyopathy [29]. Moreover, overexpression of βARKct effectively prevents hypertrophy in mice that carry a mutation in the myosin heavy-chain gene that causes hypertrophic cardiomyopathy [30]. The therapeutic potential of βARKct overexpression has already been analyzed in a large animal trial. Pigs that had undergone myocardial infarction received an adeno-associated virus serotype 6 (AAV6) encoding for βARKct via retrograde injection into the coronary sinus resulting in improved cardiac contractility parameters [31]. Another promising substance, the small-molecule inhibitor of Gβγ binding, M119, blunted hypertrophy and cardiac dysfunction in murine models as well [32].

18.2.1.2 Renin-Angiotensin-Aldosterone System (RAAS)

Another pathway that signals via a G protein-coupled receptor is the renin-angiotensin-aldosterone system (RAAS). Today, numerous pharmaceutical agents inhibit cardiac hypertrophy by targeting systemic or tissue RAAS via renin inhibition, angiotensin-converting enzyme (ACE) inhibition, angiotensin II-AT_1 receptor blockade, or aldosterone receptor blockade. The classical view of the RAAS is that circulating angiotensin II and aldosterone tightly regulate fluid balance as well as blood pressure. Angiotensinogen that is synthesized in the liver is cleaved by renin. The product angiotensin I is again cleaved by ACE that is expressed in the endothelium. The resulting angiotensin II binds to the receptors AT_1R and AT_2R, members of the GPCR family, and stimulates aldosterone secretion. Moreover, the concept of tissue RAAS within the heart has been established [33], suggesting that RAAS inhibition confers direct antihypertrophic effects beyond mere reduction of blood pressure [34]. Interestingly, the combination of the neprilysin inhibitor sacubitril with the AT_1 receptor blocker valsartan (LCZ696) reduced blood pressure in patients with hypertension more efficiently than valsartan alone [35]. Furthermore, administration of LCZ696 reduced mortality in heart failure compared to ACE inhibitor enalapril [36]. Neprilysin, also known as neutral endopeptidase, enkephalinase, common acute lymphoblastic leukemia antigen, and CD10, cleaves the natriuretic peptides ANP, BNP, and CNP as well as other peptides like angiotensin II [37]. So far, regression of hypertrophy by this substance has not been examined in patients, but data from the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) study exhibit a greater reduction of NT-proBNP in patients with heart failure with preserved ejection fraction compared to the treatment with valsartan [38] (also see Chap. 36).

18.2.2 Calcineurin/NFAT Signaling

Calcineurin is a calcium/calmodulin-dependent serine/threonine phosphatase that plays a central role in the pathogenesis of cardiac hypertrophy. High intracellular calcium levels activate calcineurin via calmodulin. Calcineurin consists of a 57–61 kDa catalytic subunit (CnA) and a 19 kDa regulatory subunit (CnB). There are three genes that encode the catalytic subunit: CnAα, CnAβ, and CnAγ. Furthermore, two genes exist that encode for the regulatory subunit: CnB1 and CnB2. Only CnAα, CnAβ, and CnB1 are expressed ubiquitously and therefore in the heart [39]. Activated calcineurin dephosphorylates transcription factors of the NFAT family leading to their translocation from the cytoplasm to the nucleus where they induce the so-called hypertrophic gene program [40]. Two mouse models highlighted that calcineurin is both necessary and sufficient to produce cardiac hypertrophy. Cardiac overexpression of a constitutively active mutant of calcineurin produced massive hypertrophy finally resulting in heart failure and sudden death [41]. Of note, calcineurin activity is also significantly increased in hearts from patients suffering from terminal heart failure [42], implying that the calcineurin/NFAT pathway plays an important role in human cardiac disease as well. The homozygous knockout of CnAβ in mice renders the animals resistant to pro-hypertrophic stimuli such as angiotensin II or isoproterenol infusion and aortic banding [43]. While CnAα knockout mice are viable [44], the loss of CnB1 by a tissue-specific deletion results in perinatal or adolescent lethality depending on the promoter that drives the Cre recombinase [45] (Chap. 4).

There are five isoforms of the "nuclear factor of activated T-cells" (NFAT) transcription factors that may act as downstream effectors of calcineurin: NFATc1 (NFAT2), NFATc2 (NFAT1), NFATc3 (NFAT4), NFATc4 (NFAT3), and NFAT5. However, engineered mouse models revealed important differences depending on the isoform investigated. The homozygous deletion of NFATc1 is embryonically lethal due to heart valve malformation. Mice that are deficient for NFATc2 [46] or NFATc3 [47] exhibit an attenuated hypertrophic response to overexpression of calcineurin, angiotensin II infusion, or aortic banding. The homozygous deletion of NFATc4 did not affect hypertrophy due to angiotensin II infusion, aortic constriction, and calcineurin overexpression [47].

The drugs cyclosporine A (CSA) and FK506 inhibit calcineurin and are widely used for immunosuppression. Numerous studies tried to solve if these two substances might be used as potent inhibitors not only of the immune system but also of cardiac hypertrophy (reviewed in [39]). The results were partially contradictory, probably due to different doses used in these studies and the pleiotropic effects of these drugs on several organs, e.g., the kidney. Unfortunately, cyclosporine A and FK506 turned out to be inappropriate for clinical use, since the doses to inhibit cardiac hypertrophy are nephrotoxic.

In search for other modulating factors of the calcineurin/NFAT pathway, a number of endogenous proteins has been identified. They either directly interact with calcineurin depending on its subcellular compartmentalization [48] or act as antagonists of calcineurin by phosphorylating NFATs.

At the cardiac Z-disc, calcineurin interacts with calsarcin-1 (myozenin-2) that belongs to a family of calsarcins with two other members (calsarcin-2 and calsarcin-3) [49, 50]. Calsarcin-1 serves as an inhibitor of calcineurin in the heart. Homozygous deletion of calsarcin-1 results in an exaggerated hypertrophy upon calcineurin overexpression and aortic banding [51]. Conversely, its cardiac-specific overexpression blunted hypertrophy after chronic angiotensin II infusion [52]. Interestingly, a recent report has shown that calsarcin-1 can shuttle to the nucleus [53], which is also true for calcineurin itself [54], implying an additional layer of regulation.

Another interacting partner of calcineurin that can be found at the Z-disc, in the cytoplasm, as well as in the nucleus is the "muscle LIM protein" (MLP) [55]. The role of MLP in cardiac hypertrophy is controversial. While MLP-deficient mice suffer from a dilated cardiomyopathy phenotype [56], animals that overexpress MLP do not show an altered hypertrophic response after aortic banding or angiotensin II infusion [57]. However, MLP is upregulated in hypertrophic models such as pressure overload [58]. Interestingly, disruption of the interaction of calcineurin with MLP by overexpression of "protein kinase C-interacting cousin of thioredoxin" (PICOT) prevents cardiac hypertrophy due to competitive binding of PICOT to MLP [59].

The Z-disc protein Lmcd1 (LIM and cysteine-rich domain 1/dyxin) induces cardiac hypertrophy via the calcineurin/NFAT pathway [60]. Overexpression of Lmcd1 causes hypertrophy in cell culture, while an effective knockdown prevented the hypertrophic response. Cardiac-specific overexpression of Lmcd1 produced a phenotype with mild hypertrophy that was significantly exaggerated by calcineurin overexpression in vivo. In contrast, CIB1 (calcium and integrin binding1/calmyrin) links calcineurin to the L-type calcium channel at the sarcolemma via a direct interaction of CIB1 with the CnB subunit of calcineurin [61]. The deletion of CIB1 in a mouse model prevented hypertrophy after aortic banding. Cardiac overexpression of CIB1 in mice did not cause a hypertrophic phenotype under baseline conditions, but exaggerated the effects of pressure overload.

The proteins Cain/Cabin-1 and A-kinase anchoring protein 79 (AKAP79) harbor a domain that inhibits calcineurin activity. Overexpression of the inhibitory domain of Cain and AKAP79, respectively, prevents cardiomyocyte hypertrophy induced by phenylephrine and angiotensin II in vitro [62]. Moreover, the cardiac-specific overexpression of these inhibitory domains was sufficient to attenuate hypertrophy evoked by isoproterenol infusion and aortic constriction [63].

Similarly, RCAN1 (regulator of calcineurin, MCIP1) interacts with calcineurin [64] and inhibits calcineurin-mediated hypertrophy in vivo due to pressure overload [65] or due to overexpression of constitutively active calcineurin [66]. The transcription of the isoforms RCAN1-1 and RCAN1-4 is driven by different promoters [67]. The promoter of RCAN1-4 carries multiple NFAT-binding sites and is thus highly responsive to calcineurin signaling, thereby establishing a negative feedback loop for the regulation of calcineurin activity [68]. However, the genetic deletion of RCAN1 in a knockout mouse model revealed a more complex function of RCAN1. RCAN1-deficient mice that overexpressed active calcineurin suffered from exacerbated hypertrophy. Surprisingly, the RCAN1 knockout animals were

protected from hypertrophy after aortic banding or isoproterenol infusion [69] implying a facilitating role of RCAN1 in calcineurin signaling. These apparent discrepancies may be resolved by the notion that the context-specific action of RCAN1 depends on its expression level [70, 71] as well as posttranslational modifications [72, 71]. Interestingly, RCAN1 is encoded by a gene that is located in the Down syndrome critical region where the gene of another inhibitor of calcineurin, the dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 1A (Dyrk1a), is located as well. Dyrk1a, predominantly localized to the nucleus, catalyzes its own phosphorylation at an YXY motif [73], while all other substrates are phosphorylated at serine/threonine residues. Besides other transcription factors, Dyrk1a phosphorylates NFATs leading to their nuclear export [74]. Thus, the overexpression of Dyrk1a in cardiomyocytes blunts the hypertrophic response upon stimulation by phenylephrine or overexpression of calcineurin [75]. While a complete loss of Dyrk1a results in embryonic lethality [76], haploinsufficiency of Dyrk1a in mice sensitizes the heart to pressure overload and results in excessive hypertrophy after aortic banding caused by exaggerated NFAT activity [77]. However, there is evidence that the overexpression on Dyrk1a in vivo might not be useful in the prevention of cardiac hypertrophy [78].

Several other kinases have been identified to phosphorylate NFATs, thereby antagonizing calcineurin, including glycogen synthase kinase 3 (GSK3), c-Jun N-terminal kinase (JNK), and p38 MAP kinases [39], which emphasizes the role of NFAT transcription factors as integrators of multiple signaling pathways. Of note, GSK3 needs a priming phosphorylation reaction to phosphorylate serine/threonine residues [79]. Dyrk1a might represent a physiological priming kinase for GSK3. Interestingly, overexpression of GSK3β inhibits hypertrophy in cardiomyocytes after stimulation with phenylephrine and endothelin-1 [80]. Likewise, the overexpression of constitutively active GSK3β prevents cardiac hypertrophy induced by adrenergic stimulation or pressure overload [81].

In summary, calcineurin signaling is an important mediator of pathologic hypertrophy. The inhibition of this pathway might be a useful tool to prevent or attenuate hypertrophy (Fig. 18.1). Unfortunately, the identification of multiple modifiers of calcineurin activity has not yet generated a specific therapy for cardiac hypertrophy, which will be the goal for future research.

18.2.3 Histone Deacetylases (HDAC)

Lysine-(K)-deacetylases (KDACs) are important tools in eukaryotic posttranslational regulation as these enzymes control protein function by removing acetyl groups from modified lysine residues in a variety of nuclear and cytoplasmic target proteins [82]. Because lysine deacetylation was initially identified [83] and is best characterized in histones, eukaryotic KDACs are often referred to as histone deacetylases (HDACs). By removing acetyl groups from the N-terminal tails of histones and interacting with other chromatin regulators, HDACs promote nucleosome

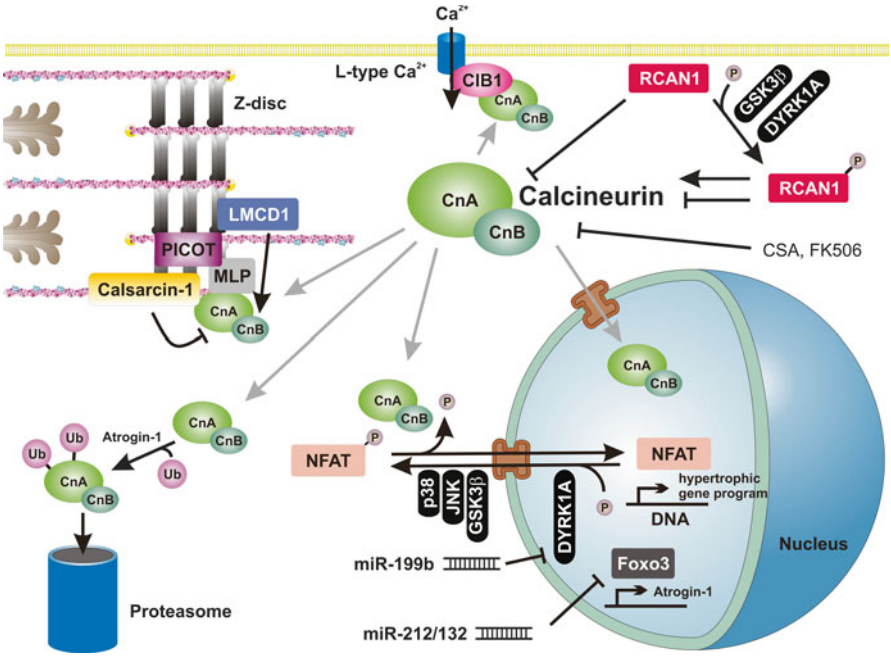

Fig. 18.1 Calcineurin/NFAT signaling plays a central role in the development of pathological cardiac hypertrophy. This pathway is an excellent example to illustrate how numerous molecules can act as modifiers and affect calcineurin/NFAT activity. These modifiers represent interesting targets in the treatment of cardiac hypertrophy

formation and chromatin condensation, which usually results in transcriptional repression of the targeted chromosomal region [84, 85]. Aside from gene regulation, HDACs have been shown to be associated with a multitude of other cellular processes, as they can as well act on nonhistone substrates, like transcription factors, signal transducers, hormone receptors, cytoskeletal proteins, and chaperones [82, 86].

Currently, 18 different and distinctly encoded HDACs have been identified in mammalian cells. These are divided into four classes: class I (HDACs 1, 2, 3, 8), subclass IIa (HDACs 4, 5, 7, 9), subclass IIb (HDACs 6, 10), class III (sirtuins), and class IV (HDAC 11) [87]. While class III HDACs require the NAD^+ cofactor for activity, HDACs from the classes I, II, and IV are dependent upon Zn^{2+} for deacetylase activity.

Due to the fact that many redundant pathways converge on HDACs and their role as epigenetic regulators of gene expression, these enzymes represent interesting targets for therapeutic strategies. Especially since it was discovered that HDACs play an important role in cancer development and maintenance, several small-molecule HDAC inhibitors have been developed to counter tumor growth and tumor survival [88]. The first HDAC inhibitor approved by the FDA in 2006 for the treatment of cutaneous T-cell lymphoma was a pan-inhibitor of zinc-dependent

HDACs called SAHA (vorinostat) [89]. When it became apparent that class IIa HDACs interact with the myocyte enhancer factor-2 (MEF2) transcription factor family and subsequently influence calcium/calmodulin-dependent protein kinase (CaMK)-and mitogen-activated protein kinase (MAPK)-mediated signaling [90], several studies focused on the role of HDACs in the heart.

The cardiac-specific transcription factor MEF2 is known to be a common endpoint of various hypertrophic signaling pathways. Interestingly, the posttranslational (in)activity of MEF2 is at least in part dependent upon its association with class IIa HDACs, which function as nuclear repressors of the transcription factor and silence the expression of MEF2 target genes [91, 92]. Consequently, it was shown that the overexpression or constant activation through signal-resistant mutants of class IIa HDACs 4 [93], 5 [94, 95], and 9 [95] suppresses MEF2-dependent gene expression and agonist-induced hypertrophic growth in primary cardiomyocytes. Consistently, the targeted deletion of HDAC 5 [96] or HDAC 9 [95] in mice results in spontaneous hypertrophy with advanced age. Furthermore, these knockout mice are sensitized to cardiac hypertrophy due to pressure overload. Additionally, transgenic mice displaying a moderate cardiac-specific overexpression of the class III HDAC Sirt1 show resistance to oxidative stress and apoptosis [97], whereas the chemical inhibition of Sirt1 in cardiomyocytes enhances apoptosis [98]. However, high-level overexpression of Sirt1 causes hypertrophy, which might be a result of mitochondrial dysfunction. Mice deficient for Sirt7 develop hypertrophy with extensive fibrosis and inflammatory cardiomyopathy [99]. Therefore, class IIa and III HDACs are generally seen as cardiac protectors.

In class I HDACs, redundancy of the different family members leads to conflicting assumptions of their function in the heart. In mice, the simultaneous cardiac-specific deletion of HDAC1 and HDAC2 results in neonatal lethality that is characterized by arrhythmias, dilated cardiomyopathy, and heart failure, whereas the cardiac-specific inactivation of either HDAC1 or HDAC2 has no apparent effect on the phenotype [100]. Inconsistently, different groups demonstrated that the knockout of HDAC2 is either insufficient to block hypertrophy in response to chronic administration of the β-adrenergic receptor agonist isoproterenol and pressure overload [100] or blunt the hypertrophic response to these stimuli [101]. On the other hand, transgenic mice that are overexpressing HDAC2 in the heart show severe cardiac hypertrophy [101]. Interestingly, heart-specific overexpression of HDAC3 results in increased cardiomyocyte proliferation and cardiac hyperplasia without hypertrophy [102]. The isoproterenol-induced hypertrophy was neither exacerbated nor inhibited by overexpression of HDAC3 in vivo.

As the class I HDACs seem especially detrimental to cardiac function, the emerging HDAC inhibitors represent potentially important tools in the treatment of cardiomyopathy. HDAC inhibitors are divided into four structurally distinctive groups, hydroxamic acids (e.g., trichostatin A [TSA], suberoylanilide hydroxamic acid [SAHA]/vorinostat), benzamides (e.g., MS-275), short-chain fatty acids (e.g., phenylbutyrate, valproic acid), and cyclic peptides (e.g., depsipeptides). The selectivity for different HDACs and the inhibitory potentials differ greatly among and within these groups [103]. Indeed, it was demonstrated that in mice, TSA attenuates

ventricular hypertrophy that is induced by continuous infusion of isoproterenol [104], angiotensin II [105], or aortic banding [105, 106]. Of even greater significance is the fact that TSA is able to cause regression of a preestablished aortic constriction-induced cardiac hypertrophy [105]. Similarly, the hydroxamic acid scriptaid is able to reduce hypertrophy in the aortic banding model, which is accompanied by reduced cardiomyocyte size and preservation of systolic function [106]. Furthermore, both TSA and valproic acid blunted the development of cardiac hypertrophy in transgenic mice overexpressing the HDAC2-dependent SRF inhibitor Hop [104]. Of note, some of the observed effects could be due to a role of HDACs in the regulation of blood pressure, as valproic acid was, e.g., shown to affect the mean arterial pressure in spontaneously hypertensive rats [107].

HDAC inhibitors offer a novel therapeutic strategy to counter pathological cardiac hypertrophy and remodeling. Although HDAC inhibitors such as vorinostat or romidepsin are already approved by the FDA and are well tolerated in cancer treatment, little is known about long-term side effects. Interestingly, SAHA was recently tested in a mouse and in a rabbit model of ischemia/reperfusion [108]. In rabbits, treatment with SAHA before ischemia and at the time of reperfusion decreased infarction size and partially rescued cardiac function. Of note, SAHA seems to mediate its cardioprotective effects via an increased autophagic flux.

18.2.4 Small G Proteins

The family of small G proteins consists of numerous members that can be classified as Ras, Rho, Arf, Ran, Rab, and other proteins [109]. All of these proteins are monomeric GTPases that can either exist in an active form if bound to GTP or in an inactive form if bound to GDP. The switch between these two states is regulated by guanine dissociation inhibitors (GDI) and guanine nucleotide exchange factors (GEF). Furthermore, the GTPase activity can be enhanced by GTPase-activating proteins (GAP) [110].

18.2.4.1 Ras

Harvey-Ras (H-Ras), Kirsten-Ras (K-Ras), and neuroblastoma-Ras (N-Ras) are classical members of the Ras (rat sarcoma virus) family. Active Ras initiates MAPK signaling via Raf1, MEK1/MEK2, and ERK1/ERK2 (reviewed in [111]). In humans, mutations in genes of this particular pathway cause congenital disorders such as Costello, LEOPARD, and Noonan syndrome that are associated with hypertrophic cardiomyopathy [112]. Moreover, overexpression of Ras in the heart results in cardiac hypertrophy with myofibrillar disarray and diastolic dysfunction [113]. Consistently, mice that are deficient for the cardiac GAP Nf1 develop hypertrophy due to sustained activity of Ras finally resulting in heart failure and increased mortality [114]. Accordingly, cardiac-specific overexpression of a dominant negative

isoform of Raf1 prevented transgenic mice from MAPK activation and hypertrophy after aortic banding [115]. However, transgenic animals showed increased mortality following pressure overload probably due to increased apoptosis of cardiomyocytes. In line with this notion, the cardiac-specific knockout of Raf1 was associated with an increase of apoptosis as well. These mice developed cardiac dysfunction and dilation but no hypertrophy [116]. Interestingly, elevated phosphorylation levels of p38 and JNK could be detected in the mutant hearts indicating activation of important hypertrophic pathways that are discussed elsewhere [117].

18.2.4.2 Rho

The small G protein RhoA induces ANP and MLC-2 expression as well as increased myofibrillar organization in cardiomyocytes in vitro [118, 119]. Although the overexpression of RhoA produces characteristic features of cardiomyocyte hypertrophy in cell culture, the cardiac-specific overexpression of RhoA did not result in a hypertrophic phenotype in vivo. Transgenic mice that overexpressed either a wild-type or a constitutively active form of RhoA did not develop cardiac hypertrophy [120], but left ventricular dilation and heart failure. Interestingly, these animals also exhibited bradycardia, atrioventricular blocks, and atrial fibrillation. The Rho-associated kinases ROCK1 and ROCK2 are effectors of RhoA. The homozygous deletion of ROCK1 in mice resulted in embryonic or postnatal lethality in most of the mice [121]. The heterozygous animals showed a significant reduction of ROCK1 and were analyzed after hypertrophic stimulation by chronic angiotensin II infusion and aortic banding. The hypertrophic response did not differ between wild-type and knockout mice. However, mutant animals developed less fibrosis. A ROCK1 knockout mouse model generated by a different group presented a similar phenotype. The analysis of homozygous ROCK1-deficient animals produced comparable results with less fibrosis upon transverse aortic constriction but no changes in cardiac hypertrophy. Consistently, the cardiac-specific overexpression of a constitutively active ROCK1 that lacks the inhibitory C-terminus caused fibrosis without hypertrophy [122]. The extent of fibrosis was exaggerated after treatment with angiotensin II compared to control mice.

The examples of the small G protein family outlined above emphasize the complexity of hypertrophic signaling. Still, little is known about the regulation and the effectors of these GTPases as well as potential targets for therapy.

18.2.5 Wnt/Frizzled Signaling

Frizzled receptors belong to the family of GPCRs that are discussed above. The function of Frizzled receptors however does not solely depend on the action of G proteins. Wnt proteins serve as ligands to activate Frizzled. Downstream intracellular signaling is mediated either via β-catenin, the so-called canonical pathway, or

via noncanonical pathways [123]. In canonical signaling, Wnt stimulation results in recruitment of the coreceptors LRP5 and LRP6 to Frizzled, translocation of Axin and Dishevelled-1 to the receptor complex at the plasma membrane, and finally release of β-catenin from the destruction complex and translocation to the nucleus where it induces Wnt-dependent gene expression together with the transcription factors TCF/Lef (T-cell factor/lymphoid enhancer factor).

Without binding of Wnt ligands to Frizzled, β-catenin is incorporated into a destruction complex consisting of Axin, APC (adenomatous polyposis), GSK3β, and CK1 (casein kinase 1). CK1 acts as a priming kinase and phosphorylates β-catenin followed by phosphorylation of β-catenin by GSK3β. Phosphorylated β-catenin is ubiquitinated by the E3 ligase β-TrCP (β-transducin repeat-containing protein) and then degraded in the proteasome. In the absence of β-catenin, TCF/Lef is bound to transcriptional repressors of the HDAC family and Groucho [124].

The noncanonical pathways include activation of Rho/ROCK or Rac/JNK via Dishevelled-1 and phospholipase C via G proteins finally resulting in increased calcineurin and protein kinase C activity [124].

Since β-catenin serves as an integrator of canonical Wnt signaling, its role in cardiac hypertrophy is of special interest. Stimulation of cardiomyocytes with phenylephrine and endothelin-1 leads to accumulation of β-catenin. Furthermore, β-catenin levels increase after aortic constriction in rats [125]. The overexpression of a β-catenin mutant that lacks phosphorylation sites for GSK3β in cardiomyocytes causes hypertrophy [125]. The deletion of β-catenin in a constitutive knockout mouse model was lethal during embryogenesis [126]. Similarly, the heart-specific loss of β-catenin was embryonically lethal as well [127]. Heterozygous mice survived though and developed less cardiac hypertrophy following aortic banding [127]. Consistently, an inducible cardiomyocyte-specific knockout caused reduced hypertrophy due to pressure overload in mice [128]. Of note, analysis of the hypertrophic gene program revealed that the attenuated hypertrophic response was not associated with reduction of ANP and BNP expression in either of these models. Another model of inducible β-catenin deletion in the heart however did not alter hypertrophy induced by angiotensin II infusion [129]. Moreover, mutant mice that express a stabilized β-catenin by deletion of exon 3, which protects β-catenin from degradation, did neither develop hypertrophy under baseline conditions nor under stimulation with angiotensin II [129].

Experimental modulation of Wnt signaling upstream of β-catenin includes the deletion of Dishevelled-1 in mice [130]. Dishevelled-1 knockout mice exhibited blunted hypertrophy after aortic banding accompanied by reduced β-catenin levels. In line with these results, cardiac-specific overexpression of Dishevelled-1 in transgenic mice caused hypertrophy, cardiac dysfunction, and increased mortality [131].

Due to the partially contradictory studies analyzing the role of β-catenin in cardiac hypertrophy, the therapeutic exploitation of canonical Wnt signaling seems to be out of reach presently. Though, exploration of regulatory proteins that act upstream of β-catenin such as secreted Frizzled-related protein (sFRP), Dickkopf (DKK), and Wnt inhibitory factor 1 (WIF-1) might be useful. In line with this

notion, it has been shown that DKK3 knockout mice are sensitized to pressure overload. These animals developed exaggerated hypertrophy following aortic constriction, while transgenic mice that overexpress DKK3 were protected after aortic banding [132].

18.3 Other Signaling Targets

18.3.1 Autophagy

Autophagy is a lysosome-dependent degradation mechanism that is responsible for recycling of intracellular components ranging from long-lived proteins to organelles such as mitochondria [133]. There are three major types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy [134]. Macroautophagy describes the event of engulfment of cytosolic material into emerging double-membrane vesicles, the so-called phagophores. The complete vesicles termed autophagosomes finally fuse with lysosomes where their cargo is degraded [133]. During microautophagy, the membranes of lysosomes invaginate and include cytosolic material directly. In contrast, chaperone-mediated autophagy describes the internalization of proteins into lysosomes via binding of targeted proteins to a chaperone.

Recently, it has been appreciated that autophagy plays a central role in the heart under physiological as well as under pathophysiological conditions. An excellent example is provided by the early postnatal period that is associated with starvation. Newborn mice exhibited a significant increase of the autophagic flux due to starvation [135]. Furthermore, autophagy was largely activated in mice that were subjected to experimental starvation for 1–3 days [136, 137]. Blocking autophagy in mouse models by deletion of genes encoding for central proteins of this degradation pathway such as beclin-1 [138], Atg5 [135], or Atg7 [139] resulted in embryonic or neonatal lethality. Interestingly, the pharmacological inhibition of autophagy by systemic application of bafilomycin A1, which prevents the fusion of autophagosomes with lysosomes, caused heart failure in mice [137]. Similarly, the inducible, heart-specific knockout of Atg5 in adult mice was associated with cardiac dilation and dysfunction. On the other hand, mice with an embryonic heart-specific deletion of Atg5 did not develop a heart failure phenotype, but were sensitized to pressure overload by aortic banding resulting in aggravated left ventricular dysfunction [140]. Induction of autophagy has been documented under hypertrophic conditions following aortic constriction [141]. However, reduction of the autophagic flux by haploinsufficiency of beclin-1 in heterozygous knockout mice improved cardiac function after aortic banding, while hypertrophy was similar to banded control animals [141]. The overexpression of beclin-1 in turn exacerbated hypertrophy upon pressure overload and was associated with diminished fractional shortening. Taken together, the published data so far do not resolve the function of autophagy in

hypertrophy. Complete inhibition of autophagy is obviously detrimental. Excessive activation of autophagy seems to be a maladaptive mechanism as well though. Since it has been shown that autophagy plays a role in human cardiac disease as well, such as dilated cardiomyopathy [142], blocking autophagy in a controlled fashion might, thus, be an attractive target in the therapy of hypertrophy.

18.3.2 Noncoding RNAs in Cardiac Hypertrophy

18.3.2.1 MicroRNAs

In contrast to the well-known protein-coding messenger RNAs (mRNAs), there is an emerging world of noncoding RNAs (reviewed in [143]), providing a previously unrecognized layer of regulation of gene expression. Noncoding RNAs are divided into short (<200 bp) and long RNAs (>200 bp) due to technical reasons of RNA isolation. MicroRNAs are short RNAs (19–25 bp) that typically directly regulate posttranscriptional gene expression. Precursors of a mature microRNA, the so-called pri-miRNAs, are transcribed by RNA polymerase II. The pri-miRNAs form hairpin structures that are further processed by Drosha and DGCR8 into pre-miRNAs in the nucleus. After nuclear export into the cytoplasm, Dicer cleaves pre-miRNAs resulting in a double-stranded microRNA. One strand is incorporated into the RNA-induced silencing complex (RISC) as a mature microRNA [144]. Complimentary binding of the so-called seed region of the microRNA with the mRNA is sufficient to cause significant repression by degradation or translation inhibition of mRNAs. The binding sites are usually located at the 3′ untranslated region of mRNAs. Therefore, it is not surprising that a single microRNA can regulate many targets. Conversely, a single mRNA has several potential binding sites for different microRNAs. Presumably, different cardiac disorders are associated with the induction or repression of a distinct subset of microRNAs. During the past decade, attempts have been made to establish a signature of microRNAs that is associated with cardiac hypertrophy not only in mouse models [145, 146], but also in humans [147]. Of note, microRNAs are not present in cells only but can also be detected in plasma. These circulating microRNAs are surprisingly stable, because they are packaged in exosomes [148] and microvesicles [149] or carried by proteins such as Argonaute 2 (Ago2) [150] and high-density lipoproteins (HDL) [151]. Circulating microRNAs are currently evaluated as a novel group of biomarkers in clinical medicine. With respect to cardiovascular disorders, microRNAs have been analyzed as biomarkers in acute myocardial infarction, heart failure, and coronary artery disease [152] (Chap. 13).

Several mouse models have been generated that underline the importance of microRNAs in the pathogenesis of cardiac hypertrophy. One of the first microRNAs that has been implicated in hypertrophic growth was miR-208. miR-208a is located in intron 27 of the murine α-MHC (myosin heavy-chain, *Myh6*) gene. It is co-transcribed with α-MHC. The homozygous deletion of miR-208a resulted in viable

mice that developed normally. Under stress conditions due to aortic constriction however, they lacked a hypertrophic response and the isoform switch from α- to β-MHC (*Myh7*) [153]. Conversely, cardiac overexpression of miR-208a causes hypertrophy and elevated β-MHC levels [154]. The main underlying mechanism is that miR-208 targets the thyroid hormone receptor-associated protein 1 (THRAP1). Thyroid hormone (T3) signaling induces the expression of α-MHC but represses the expression of β-MHC [155]. The T3-dependent regulation of MHC isoforms is disturbed in miR-208a knockout mice. A second and a third member of the miR-208 family, miR-208b [154] and miR-499 [156], have been identified within the β-MHC gene (*Myh7*/*Myh7b*) and have also been implicated in the pathogenesis of cardiac hypertrophy and heart failure [157, 158]. Subsequently, the therapeutic potential was tested with an anti-miR against miR-208a in a rat model of salt-sensitive hypertension [159]. Its systemic administration reduced cardiomyocyte hypertrophy and improved survival. The role of miR-499 is still controversial in the context of hypertrophy. A transgenic mouse model with overexpression of miR-499 exhibited cardiac hypertrophy and fibrosis [157]. Yet, another model of miR-499 did not develop spontaneous hypertrophy. The transgenic mice were even protected from the effects of ischemia and reperfusion [160]. Of note, in this study, calcineurin was identified as a direct molecular target of miR-499.

The muscle-specific microRNA miR-1 belongs to a cluster of microRNA genes consisting of miR-1-1/133a-2, miR-1-2/133a-1, and miR-206/133b [144]. miR-1 as well as miR-133 is downregulated in several models of hypertrophy. The genetic ablation of miR-1-2 results in embryonic lethality in 50 % probably due to ventricular septal defects (VSD) [161]. The surviving animals display ECG abnormalities and arrhythmias. Although the overexpression of miR-1 could mitigate hypertrophy in neonatal rat cardiomyocytes and blunt hypertrophy after injection of miR-1 into the heart of isoproterenol-stimulated animals [162], the overexpression of miR-1 in transgenic mice caused heart failure and hypertrophy [163]. The homozygous knockout of either identical microRNA miR-133a-1 or miR-133a-2 did not result in an obvious phenotype. The double knockout however caused increased embryonic lethality with animals displaying chamber dilation, wall thinning, and VSDs [164]. Only one-fourth of the double knockout mice survived and exhibited reduced cardiac function but no hypertrophy. However, adult mice that received an antagomir against miR-133 developed cardiac hypertrophy [165]. Interestingly, calcineurin also seems to be a target of miR-133 and in turn regulates the expression of miR-133 [166].

Besides the abovementioned microRNAs, also miR-199b modulates calcineurin/NFAT signaling [77]. The cardiac overexpression of miR-199b targets the kinase Dyrk1a, thereby causing exaggerated hypertrophy upon calcineurin overexpression in vivo or transverse aortic constriction. Overexpression of the miR-212/132 family causes cardiac hypertrophy and heart failure [167]. Conversely, a homozygous deletion blunted the effects of the pro-hypertrophic stimulus due to transverse aortic constriction. Again, the calcineurin/NFAT pathway seems to be the target of these microRNAs. miR-212/132 represses the transcription factor Foxo3 that modulates calcineurin activity [168] by regulating the expression of atrogin-1, an F-box

protein. Atrogin-1 binds to Skp1, Cul1, and Roc1 assembling an SCF ubiquitin ligase complex that promotes ubiquitination of calcineurin and subsequent degradation [169]. Of note, the application of an anti-miR against miR-132 could prevent hypertrophy due to aortic constriction in vivo [167].

The outlined above examples show that microRNAs are promising targets of pharmacologic intervention by administering either microRNA mimics that amplify the effects of microRNAs or anti-miRs that inhibit gene regulation of microRNAs. For further information, we recommend excellent review articles about the role of microRNAs in the heart [170–172] and also see Chaps. 14, 15, and 62.

18.3.2.2 Long Noncoding RNAs

More recently, the focus on noncoding RNAs in cardiac biology has broadened from microRNAs to long noncoding RNAs. Long noncoding RNAs (lncRNA) are a heterogeneous group of RNAs with diverse functions. lncRNAs participate in transcriptional regulation by, e.g., chromatin modifications and posttranscriptional gene regulation by binding RNAs as well as by serving as scaffolds in macromolecular complexes [173]. So far, the lncRNA Fendrr has been implicated in heart development [174]. Moreover, another lncRNA termed braveheart seems to regulate cardiomyocyte differentiation [175]. Recently, lncRNAs were also connected to cardiac hypertrophy (Chap. 13). First attempts have been made to identify lncRNAs that are expressed or even enriched in the heart, but only a few were regulated during hypertrophy [176]. The specific lncRNA CHRF (AK048451) modulates hypertrophy by binding miR-489. The overexpression of miR-489 in a transgenic mouse model blunts hypertrophy and fibrosis due to chronic angiotensin II infusion. Myd88 (myeloid differentiation primary response gene 88) was identified as the target of miR-489. Consistently, Myd88 knockout mice were resistant to hypertrophy caused by angiotensin II as well. Mechanistically, CHRF seems to act as a sponge binding miR-489, thereby reducing miR-489 levels available for the regulation of gene expression [177].

Another cluster of lncRNAs is located within the *Myh7* gene. These lncRNAs were named myosin heavy-chain-associated RNA transcripts (Myheart, or Mhrt) [178]. They are expressed in a heart-specific fashion and are enriched in the adult myocardium. In that study, Mhrts were repressed under hypertrophic conditions after aortic banding. The transgenic overexpression of a single lncRNA reduced cardiac hypertrophy and improved heart function in mice that were subjected to pressure overload. Mhrt inhibited hypertrophy by antagonizing BRG1, a member of chromatin-modifying enzymatic complexes. Of note, BRG1 itself regulates the transcription of Mhrt.

Although the field of lncRNA in cardiac biology and hypertrophy is very young, the above outlined examples highlight the importance of lncRNAs in the gene regulation network and emphasize the potential of lncRNAs as therapeutic targets.

18.3.2.3 Circular RNAs

Although circular RNAs were first described in eukaryotic cells in 1979 [179], their biological significance has been unknown. Originally, the formation of circular RNAs was thought to be an uncommon and rare event. However, RNA sequencing enabled the identification of numerous circRNAs [180]. Two recent studies discovered an important function of circRNAs in posttranscriptional gene regulation. It has been shown before that transcripts of the sex-determining region Y (*Sry*) gene form circRNAs. Interestingly, more than 90 % of the transcripts in adult mouse testes are circular [181]. Now, there is evidence that Sry serves as a "sponge" for miR-138 [182] due to multiple binding sites for miR-138. Moreover, the antisense transcript of cerebellar degeneration-related protein 1 (CDR1) termed CDR1as or ciRS-7 binds miR-7 like a sponge as well [182, 183]. Sponge RNAs inhibit the function of microRNAs merely by complementary binding. Accordingly, the expression level of target genes of miR-7 was affected by CDR1as/ciRS-7. Knockdown of CDR1as/ciRS-7 caused downregulation of target genes [182, 183]. Interestingly, the morpholino-mediated knockdown of miR-7 reduced the size of the midbrain in zebrafish. A similar phenotype was produced by injection of CDR1as/ciRS-7 [183]. The novel function of circRNAs adds another layer of complexity to posttranscriptional gene regulation and may provide further opportunities for therapeutic interventions also in the context of cardiac hypertrophy and heart failure.

18.4 Concluding Remarks

Cardiac hypertrophy predisposes toward increased mortality as an independent risk factor. Therefore, inhibition or regression of hypertrophy appears to be an attractive target for medical intervention. In line with this notion, multiple trials have shown that regression of left ventricular hypertrophy is associated with improved survival. The HOPE ("Heart Outcomes Prevention Evaluation") study indicated that treatment with the ACE inhibitor ramipril reduced cardiovascular events such as myocardial infarction and stroke as well as mortality [184] associated with attenuation or regression of left ventricular hypertrophy as assessed by ECG [185]. Consistently, a subgroup analysis of the LIFE ("Losartan Intervention For Endpoint reduction in hypertension") trial showed that reduction of the left ventricular mass measured by echocardiography decreases the risk for myocardial infarction, stroke, and mortality independent of blood pressure reduction [186].

Beyond the established inhibition of α- and β-adrenergic and angiotensin receptors, the discovery of additional intracellular pathways underlying pathological hypertrophy made it possible to consider specific molecular therapies. For example, several inhibitors of hypertrophy (as outlined above) might be delivered by a gene therapy approach in the future (Chap. 15). In order to achieve cardiac gene delivery, adeno-associated viruses (AAV) have been successfully employed in a number of

animal models [187]. Recently, overexpression of SERCA2a via AAV1 in heart failure has been examined in a phase 2 trial [188]. However, due to remaining immunological issues that are associated with application of AAVs, the direct administration of RNA species as regulators of gene expression might be an interesting alternative. Dependent on the function of a specific microRNA, therapeutics can enhance or blunt the effect of microRNAs by using mimics or anti-miRs. Extensive work has been done on chemical modifications of microRNAs to enhance stability and binding affinity [172]. Furthermore, the therapeutic use of RNA sponges might be useful to negatively modulate microRNA effects.

Extensive molecular research has provided a variety of interventional opportunities. Upcoming therapies will have to be carefully evaluated not only with respect to efficacy but also with respect to patient safety. Additionally, new approaches will have to compete with the existing therapies. Nevertheless, there is a hope that patients will benefit from specific antihypertrophic therapies in the future.

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Part III
Coronary Heart Disease

Chapter 19
Acute Coronary Syndromes: Introduction and Pathophysiologic Classification

Kjell Nikus and Yochai Birnbaum

Abstract Several different classifications of acute coronary syndromes (ACS) exist, and most of them are based on the electrocardiogram (ECG). Based on differences in pathophysiology, treatment, and outcome, ACS are classified as ST-elevation myocardial infarction (STEMI), non-ST-elevation MI, and unstable angina. STEMI is the most urgent subtype of ACS, because it is believed to reflect acute ongoing transmural myocardial ischemia caused by acute coronary occlusion. Based on changes in the different parts of the ECG, ACS patients may be classified according to the extent of the ischemic process or myocardial injury, the acuteness of the disease process, and the severity of myocardial ischemia. In the majority of patients, ACS classification is rather straightforward, but some controversial issues remain to be solved in the future. The role of different ACS subtypes regarding choice of medication also needs to be explored more in detail. This chapter reviews pathophysiological mechanisms explaining the different ECG patterns encountered in ACS; the different ECG manifestations are also presented by illustrative figures. Both established guidelines and ECG-based expert reports for the classification of ACS are presented. Unresolved, controversial issues regarding ECG manifestations of ACS are discussed.

Keywords Electrocardiogram • Acute coronary syndrome • ST-elevation myocardial infarction • Non-ST-elevation myocardial infarction • Coronary artery disease • Acute myocardial ischemia

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19.1 Introduction

The term acute coronary syndrome (ACS), originally defined as myocardial infarction (MI), unstable angina, or ischemic sudden death, was introduced in the early 1990s [1]. The paradigm that these three clinical entities are part of a spectrum of manifestation of the same atherosclerotic coronary artery process was introduced. In the consensus document of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC) Committee for the Redefinition of MI, ACS was defined as unstable angina or MI [2]. Cardiovascular disease is the most common cause of mortality worldwide. The majority of cardiovascular deaths are caused by coronary artery disease [3]. ACS is the most ominous manifestation of coronary artery disease.

The widespread use of cardiac troponin (cTn) assays in ACS diagnosis, beginning in the 1980s, has made a significant impact on the clinical diagnoses of ACS. Current generation cTn assays are extremely sensitive for diagnosing myocardial injury (for more details, readers may refer to Chaps. 10 and 11). As a result, there has been a progressive reclassification in that patients previously diagnosed with unstable angina now are classified as non-ST-elevation MI (NSTEMI) [4]. The 2012 Joint Task Force for the definition of MI recommended the classification of MI into subgroups based on pathological, clinical, and prognostic differences, along with different treatment strategies [5]. *MI type 1* represents the classical scenario with a clinical event initiated by a plaque rupture, ulceration, fissuring, erosion, or dissection with resultant intraluminal thrombosis leading to various degrees of flow disturbance in the affected coronary artery. Distal embolization of thrombotic material and platelet aggregates and/or diminished blood flow results in myocardial necrosis.

In *MI type 2*, a condition other than coronary artery disease contributes to an imbalance between myocardial oxygen supply and demand. A direct toxic effect of endogenous or exogenous high circulating catecholamine levels, in addition to coronary vasospasm and/or endothelial dysfunction, is considered as etiologic factors. Potential causative factors are tachy- or bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension.

Perioperative MI is not an infrequent complication in major noncardiac surgery. Typically, the episodes are asymptomatic. Nevertheless, asymptomatic perioperative MI is as strongly associated with 30-day mortality, as is symptomatic MI. Studies of patients undergoing major noncardiac surgery indicate that many of these infarctions are caused by a prolonged imbalance between myocardial oxygen supply and demand (type 2 MI). However, plaque rupture and platelet aggregation, leading to thrombus formation (type 1 MI), were found in approximately half of subjects with fatal postoperative outcome. The role of antithrombotic therapy in type 2 MI is unclear because of the different pathophysiologic mechanisms involved and also because of lack of data from prospective randomized trials.

MI type 3 is defined as sudden cardiac death with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic electrocardiographic

(ECG) changes or new left bundle branch bloc (LBBB), but without biomarker evidence of myocardial necrosis. According to the Task Force statement, a diagnosis of MI can be established in these cases, although biomarker analyses were not done, or the analyses were done early, before elevated values can be observed.

Periprocedural myocardial injury after percutaneous coronary intervention (PCI) is classified as *MI type 4a*. Elevated cTn values are frequently observed after cardiac procedures, but the level of biomarker elevation that could affect patient outcome is debatable. In addition, (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic ECG changes, (iii) angiographic findings consistent with a procedural complication, or (iv) imaging test demonstrating a new loss of viable myocardium or new regional wall motion abnormality are required. *Type 4b MI* is caused by stent thrombosis.

Finally, coronary artery bypass grafting (CABG)-related MI (*type 5*) is defined by elevation of cardiac biomarker values and either (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Due to the complexity of mechanisms causing plaque instability, it is unlikely to be able to identify a common cause for the phenotype of ACS. Recently, a pathogenetic classification into three homogenous groups was proposed: (i) obstructive atherosclerosis with systemic inflammation, (ii) obstructive atherosclerosis without systemic inflammation, and (iii) patients without obstructive atherosclerosis [6] (Chap. 25). The authors speculated that this classification might help in the search of new diagnostic algorithms and therapeutic targets. There are practically no genetic data differentially associated with the clinical entities of ACS.

19.2 Pathophysiologic Background of Myocardial Ischemia

In the vessel wall, two principal mechanisms precipitate ACS: rupture of the fibrous cap of a plaque in the coronary artery wall and superficial erosion of the vessel intima. Inflammation contributes both to plaque rupture and to erosion that lead to ACS [7]. Type 1 MI is nearly always caused by luminal thrombus or a sudden plaque hemorrhage imposed on an atherosclerotic plaque with or without concomitant vasospasm [8]. In STEMI, the thrombus is mostly occlusive, whereas in unstable angina and NSTEMI, the thrombus is usually incomplete and dynamic, or even absent. According to autopsy studies, the majority of fatal coronary thrombi are associated with plaque rupture regardless of the clinical presentation [9]. Also in patients who survive, plaque rupture is the most common substrate for thrombi causing MI [8].

In type 1 MI, acute reduction of blood flow, caused by an occlusive blood clot that is formed on a ruptured atherosclerotic plaque, leads to complete or almost complete obliteration of the vessel lumen. The resultant impairment of blood flow leads to acute transmural ischemia that involves all layers of the myocardium.

Necrosis of the involved myocardial region occurs rapidly, if coronary flow is not reestablished spontaneously or by reperfusion therapy. ST elevation in the ECG leads facing the involved zones is the typical ECG manifestation in these cases, resulting in a clinical diagnosis of ST-elevation MI (STEMI) (Chap. 20).

Acute total occlusion of an epicardial coronary artery does not always result in transmural myocardial ischemia. Preexisting severe stenosis of the occluded artery may result in the formation of collateral channels that provide residual blood flow. In many instances, the blood clot overlying the ruptured plaque does not completely occlude the artery. Cyclic flow variations with repeat episodes of subendocardial ischemia may result from dynamic changes in the size of the thrombus with distal embolization of platelet aggregates and clots or secretion of vasoactive substances. Typically, this pathophysiologic scenario results in myocardial injury, and the clinical diagnosis is NSTEMI. In case of intermittent, mild impairment of blood flow without large distal emboli, there may be no rise in the troponin levels; these patients are classified as unstable angina (Chap. 23).

It is obvious that severe ischemia leading to ongoing myocardial necrosis should be rapidly diagnosed, as these patients may benefit from urgent reperfusion therapy preferably by primary PCI or alternatively by thrombolytic therapy. On the other hand, most patients with incomplete occlusion of a coronary artery may be stabilized first with medical therapy before a decision is made to refer them for coronary angiography and revascularization.

19.3 Acute Myocardial Ischemia and the ECG

The ECG has a very important role in the clinical classification of ACS, and for that reason, ECG-based classifications in ACS are discussed below.

Acute myocardial ischemia may affect all components of the electrical activation of the heart, including the P wave, the PR interval, the QRS complex, the ST segment, and the T and U waves. Many methods have been developed to identify electrical alterations induced by acute myocardial ischemia. In the clinical practice, the surface 12-lead ECG is the most widely used diagnostic tool, along with patient history and physical examination. All patients evaluated for ACS should be placed on a cardiac monitor and a 12-lead ECG obtained within 10 min of presentation (to compare with a previous ECG if available) and repeated if the chest discomfort changes.

Acute occlusion of a coronary artery induces, within seconds, transmural myocardial ischemia, expressed in the ECG as prominent, *positive T waves* [10] (Fig. 19.1). This stage is typically short lasting, and ST elevations ensue within seconds to minutes. The phenomenon is easily demonstrated with ECG recording during PCI, where the coronary artery is totally occluded for a short time, but due to the short duration of the phase with prominent T waves, it is seen only in a minority of ACS patients.

ST elevation is the most dramatic ECG manifestation of acute transmural myocardial ischemia in the leads facing the ischemic zone. In the leads facing to the

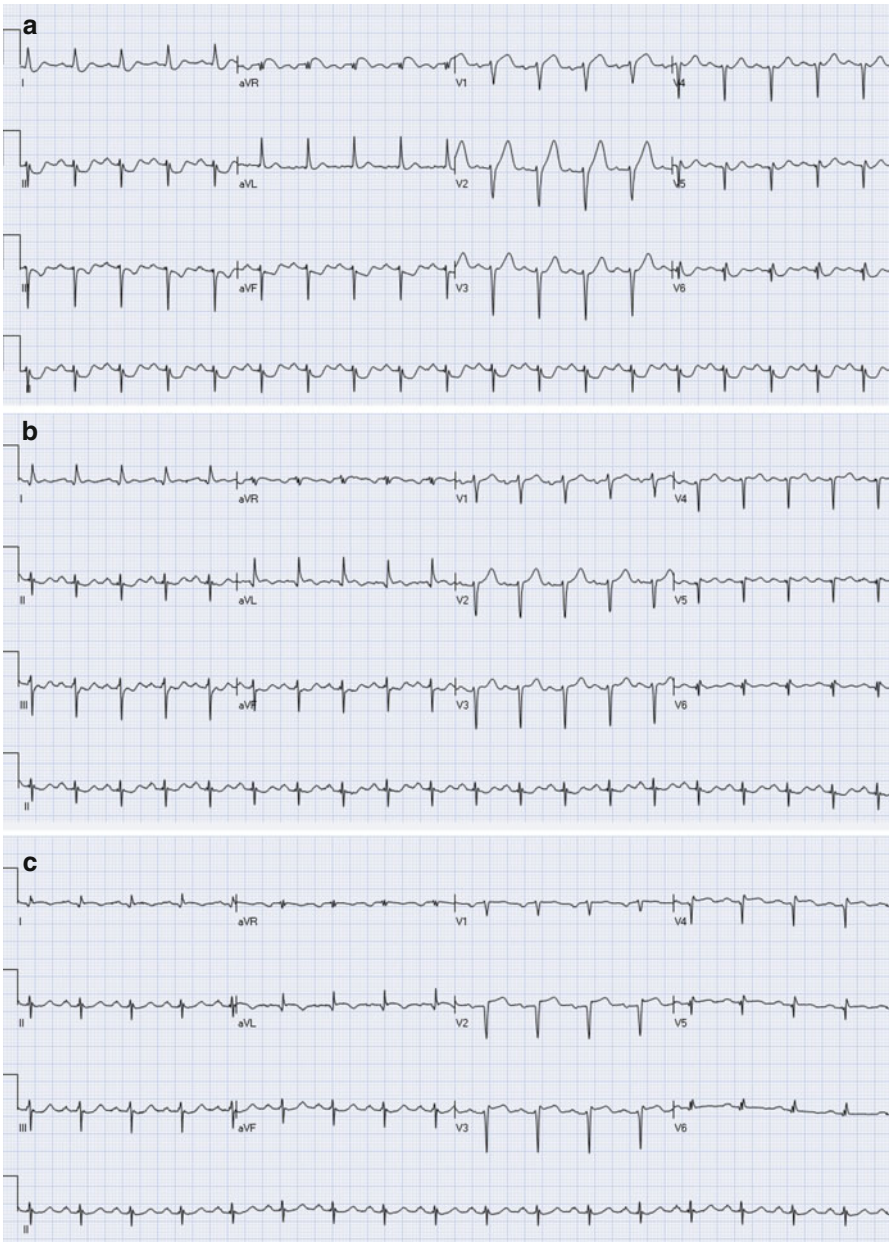

Fig. 19.1 (**a**) Sinus tachycardia with poor R-wave progression in the precordial leads, suggesting old anterior myocardial infarction. There is ST depression in the leads I, II, III, aVF, and V6. Therefore, there is reciprocal ST elevation in lead aVR. There is minimal ST elevation in lead V1, and the T wave in lead V2 is tall and positive, suggesting ischemia (Grade 1 of myocardial ischemia). (**b**) Several hours later, after resolution of symptoms, there is less ST depression in the inferior and lateral leads. ST elevation in leads aVR and V1 resolved, and the T-wave amplitude in V2 decreased. In addition, the T waves in aVL are now negative, suggestive of resolution of ischemia. (**c**) The next day, a QS wave is seen in lead V2, and there is now ST elevation in leads V2–V3, suggestive of an anterior myocardial infarction

anatomically opposite myocardial segments, reciprocal ST depressions can be detected. These ST depressions do not represent additional subendocardial ischemia, but rather is a pure electrical phenomenon of reciprocal changes. Based on the distribution and morphology of ST changes in the ECG leads and the presence of coexistent QRS- or T-wave changes, different ECG classifications were developed. These are regarded as markers of severity of myocardial ischemia and extent of the ischemic process; they also reflect temporal differences during the disease process.

When ischemia is confined primarily to the subendocardium, the overall ST vector typically faces the inner ventricular layer and the ventricular cavity such that the surface ECG leads show *ST depression* [11]. This subendocardial ischemic pattern is a frequent finding during spontaneous episodes of rest angina such as appears during ischemic imbalance. In severe extensive subendocardial ischemia, as in acute subtotal or even total occlusion of the left main coronary artery, the ECG shows ST depression in the majority of the ECG leads and ST elevation in lead aVR [12].

19.4 Historical Aspects of ACS Classification

The association between abnormally wide Q waves and MI was established by historical works in the 1930s–1940s [13, 14]. Originally, Q-wave MI was considered strongly associated with transmural infarction. Later on, moderate sensitivity and good specificity for Q waves to detect myocardial necrosis at autopsy in patients with a narrow QRS complex was reported [15]. Adverse post-MI outcome was evident from studies conducted before the introduction of reperfusion therapy – fibrinolysis or PCI. Q-wave duration, Q/R ratio, and Q waves in multiple infarct locations were associated with worse long-term outcome [16].

In the chronic phase of MI, Q waves are regarded as a sign of irreversible necrosis. However, about 50 % of patients presenting within 1 h of onset of ST-elevation acute coronary syndrome (STE-ACS) already have Q waves in the leads with ST elevations, especially in the anterior leads. These Q waves may be transient and not necessarily represent irreversible damage. It is believed that intense ischemia may cause a transient loss of electrical activity in the region at risk. Thus, Q waves on presentation may reflect either irreversible damage and/or a large ischemic zone and thus portend a large final infarction. On the other hand, in inferior STE-ACS, preexisting Q waves may disappear during acute ischemia – the Q waves may be "pulled up" by the injury current – and reappear during reperfusion.

The traditional view that Q waves represent transmural MI, while subendocardial MI is reflected by ECG changes other than Q waves, was questioned in the 1980s [17]. It was evident from autopsy studies that about half of subendocardial MIs caused pathological Q waves, while about half of transmural MIs did not [18]. Accordingly, the terms Q-wave and non-Q-wave MI replaced the former designations. The most recent golden standard of myocardial injury, cardiac magnetic resonance imaging (CMR), has shown that the Q-wave/non-Q-wave distinction is determined by the total size rather than by the transmural extent of the underlying scar [19].

Braunwald's group introduced the concept of reduction of infarct size by pharmacologic agents in the late 1960s–1970s, and that resulted in a need for refinement of the classification of acute coronary events [20]. The term unstable angina (acute ischemia without resultant detectable necrosis) was introduced in the early 1970s and was classified according to severity by Braunwald in the late 1980s [21, 22].

19.5 ACS Classification of MI Based on Location

After the introduction of the three original ECG leads, I, II and III, by Einthoven in 1912, investigators began to classify MIs based on changes in the QRS complex according to their location into anteroapical and posterobasal MI. With the development of the unipolar leads and multiple chest lead technique, additional locations were introduced. Monumental work with systematic autopsy studies in the 1930s and 1940s established the theoretical and empirical basis for the association between different ECG patterns and the location of myocardial necrosis [14]. Based on pathological correlation, a relationship between the location of infarcted areas and Q waves on the ECG was, until recently, accepted and, with minor modifications, implemented in scientific statements and textbooks.

Already in the 1930s, studies showed different premortal ECG patterns depending on the MI location at autopsy. In patients, who survived the acute infarction, coronary angiography enabled the correlation of ECG signs of myocardial necrosis with this new technique. Reperfusion therapy, initially by intracoronary thrombolysis in the 1980s, resulted in a clear need to improve the ECG diagnosis to be able to predict the culprit artery and the estimated size of the area at risk by observing changes from the acute occlusive phase (ST/T changes). Since then, many ECG algorithms for the prediction of the culprit artery and the level of vessel occlusion have been introduced. The results of the studies evaluating these algorithms vary; they are dependent on factors such as time from ECG recording to angiography, individual variation of coronary artery anatomy, and coronary artery dominance.

More recently, the correlation between Q waves in various ECG leads and the affected myocardium has been studied by CMR. Based on these findings, a new terminology for LV walls and location of Q-wave MIs was proposed [23]. The consensus group recommended to classify the different MI locations based on the following six most commonly occurring patterns of abnormal Q waves and Q-wave equivalents (Fig. 19.2). In *septal* MI, the septal wall and often a small part of the adjacent anterior wall are involved, and the ECG shows Q waves in leads V1 and V2 [24]. The term *mid-anterior* was recommended for MIs located especially in the mid-low segments of the anterior wall. This MI subtype is typically caused by occlusion of the first diagonal branch, and in the ECG Q waves are present in leads aVL (I) and sometimes V2. Compared with septal infarction, in *apical-anterior* MI, the abnormal Q waves extend into the more leftward precordial leads – typically V3 and V4 and sometimes V5 and V6. There are no abnormal Q waves in leads aVL and I. E*xtensive anterior* infarction is essentially a combination of the three previously

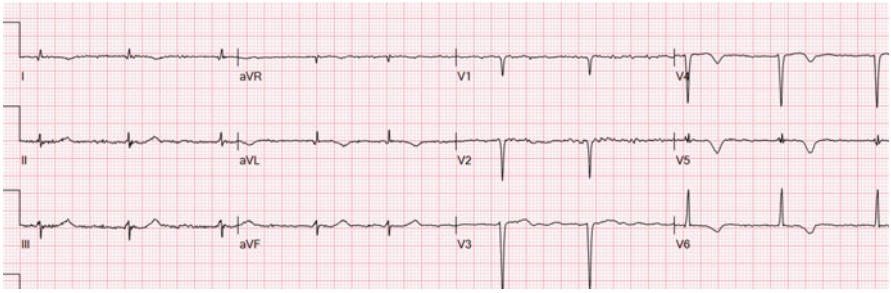

Fig. 19.2 Old anterior myocardial infarction with Q-wave equivalent small R waves in the leads V2–V5 and Q waves in the leads aVL and V1. There are no signs of acute myocardial ischemia; there are no ST elevations, and the T waves are inverted in the leads I, aVL, and V4–V6 (postischemic changes)

mentioned types. Consequently, the ECG shows abnormal Q waves in the precordial leads and lead aVL (sometimes also in lead I). In *lateral* MI, the ECG may produce the Q-wave equivalents of abnormally prominent R waves in leads V1 and V2. There may also be abnormal Q waves in lead I, aVL, and/or V5 and V6. Finally, *inferior* MIs produce Q waves in leads II, III, and aVF, but without increased R waves in leads V1 and V2. When the infarct-related artery (right coronary or left circumflex artery) is very dominant and the occlusion is proximal, the infarction encompasses both the inferior and the lateral wall, and then the ECG pattern is the association of criteria of inferior and lateral MI (inferolateral MI).

19.5.1 EGG Coding and Scoring Systems

The Minnesota Code was developed in the late 1950s in response to the need for reporting ECG findings in objective, uniform, and clearly defined terms [25]. In clinical trials and epidemiologic studies, this coding system is the most widely used ECG classification system. Changes in the QRS complex, the ST segment, and the T wave are included in the system; these ECG parameters are typically altered in ACS. With the introduction of the concept of myocardial salvage by Braunwald's group in the 1960s and 1970s, there was a need for universally available diagnostic methods to assess infarct size [20].

19.5.1.1 Estimates of the Extent of Myocardial Ischemia/Infarction

In the mid-1980s, the Selvester QRS scoring system was developed for the estimation of the total percentage of the left ventricle that is infarcted by using a weighted scoring system [26]. Originally, studies confirmed the agreement between the Selvester QRS score and MI size determined by postmortem histopathology in

patients with non-reperfused MI. More recently, the agreement with CMR-determined MI size in reperfused STEMI has proven to be poor [27].

Later on, the Aldrich score was developed for estimating the extent of myocardium at risk for infarction by quantitating initial ST changes on the presenting ECG [28]. This score is expressed as % myocardium at risk of infarction. The Aldrich ST score has been shown to underestimate myocardium at risk when compared with single-photon emission computed tomography (SPECT) imaging [29]. In a recent study, the score did not provide a stable estimate of myocardium at risk between prehospital and hospital ECGs [30]. Theoretically, an ECG score to estimate area at risk should include quantitative measurements of both the ST-segment and QRS-complex abnormalities.

It is commonly accepted that the absolute amplitude of ST deviation and/or extent of ST deviation (as reflected in the number of leads with threshold ST elevation) correlates with the size of the myocardial injury. It has been suggested that the magnitude of ST elevation in the inferior leads in inferior STEMI and the number of leads with ST elevation in the precordial leads in anterior STEMI (Aldrich score) correlate with the predischarge Selvester QRS score [31]. However, the correlation between the Aldrich score and the size of the ischemic area at risk (assessed by pretreatment technetium Tc 99 m sestamibi scan or CMR) in patients undergoing reperfusion therapy was weak. The existence of opposite ischemic vectors with cancellation and attenuation of ST deviations could be a plausible explanation for the weak correlation. Another possible explanation for the attenuation of ST elevation is preconditioning by either ischemia or pharmacological agents.

19.5.1.2 Estimation of Acuteness

In animal models, the amount of irreversibly injured myocardium increases with longer duration of ischemia, whereby the extent of salvageable myocardium logically decreases. Due to the dynamic nature of thrombosis formation and spontaneous fibrinolysis with resultant varying degrees of coronary flow, exact ischemic time (time from occlusion to reperfusion of the infarct-related artery) is often difficult to establish in clinical settings. Nevertheless, time from symptom onset to reperfusion (treatment delay) has been used as a proxy for total ischemic time [32]. This time interval is divided into different fragments, such as time from first medical contact to balloon inflation, door-to-balloon time, etc., and are used as measures of assurance for quality standards in health care and also as outcome predictors. Controversy exists regarding the ability of time measures to predict myocardial salvage, final infarct size, and mortality, all of which are important prognostic factors.

Anderson-Wilkins and colleagues developed an ECG acuteness score to augment historical timing of the acute symptom onset or, alternatively, to estimate viability [33]. This score is provided as a continuous scale from 4.0 (hyperacute) to 1.0 (subacute) based on the comparative hyperacute T waves versus abnormal Q waves in each of the leads with ST elevation. However, the independent significance of the T-wave amplitude apart from the presence of Q waves has not been tested. The ECG

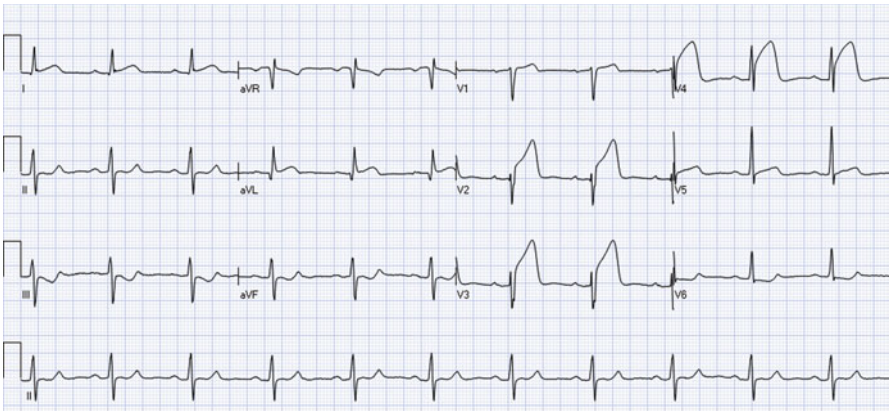

Fig. 19.3 Anterior ST elevations: the ECG shows ST elevations in leads I, aVL, and V1–V5. Reciprocal ST depressions are present in leads III, aVF, and V6. Preinfarction syndrome: ST elevations without Q waves or inverted T waves in the leads with ST elevations. Grade 2 ischemia: ST elevations without changes in the QRS complex

method of acuteness score was superior to historical timing in predicting myocardial salvage and prognosis after reperfusion therapy, suggesting that ECG-estimated duration of ischemia might provide a better and objective means to select acute reperfusion therapy rather than the subjective patient history, which could potentially preclude proper reperfusion in some patients with salvageable myocardium presenting late [34]. In general, it could be questioned, whether these ECG parameters reflect timing or if it would be more appropriate to refer to them as an estimate of viability, as the rate of progression of myocardial necrosis over time varies considerably.

Sclarovsky introduced a simple method, without the need for counting scores, to estimate acuteness of the infarct process in STEMI [35]. In this classification, ST elevation without T-wave inversions or Q waves is defined as the "preinfarction syndrome" (Fig. 19.3), while ST elevations accompanied by inverted T waves and/or Q waves are referred to as evolving MI (Fig. 19.4). The hypothesis is that the preinfarction syndrome represents the window of opportunity for reperfusion therapy, while evolving MI indicates a later stage of the process with irreversible myocardial injury. Preliminary, retrospective data showed differences in outcome in STEMI patients depending on this classification [36]. Especially in patients with anterior STEMI and evolving MI without reperfusion (no inverted T waves), primary PCI was superior to fibrinolysis.

19.5.1.3 Grade of Ischemia

Shortly following an occlusion of an epicardial coronary artery, the T waves become positive, tall, and symmetrical in leads with their positive poles facing the ischemic zone, and later on ST elevations develop. In some patients, changes in the terminal portion of the QRS may also be detected if myocardial ischemia continues.

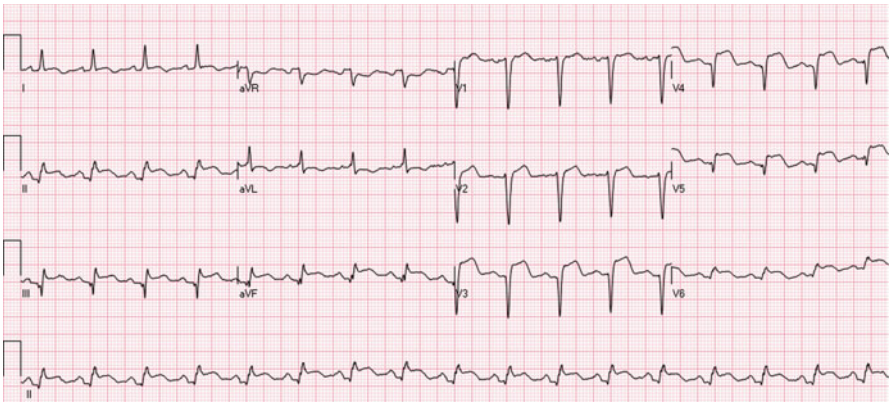

Fig. 19.4 Anterior and inferior ST elevations: the ECG shows ST elevations in leads I, II, III, aVF, and V1–V6. Evolving MI: Q waves are present in leads V3–V5, and there are minor terminal T-wave inversions in V4–V6

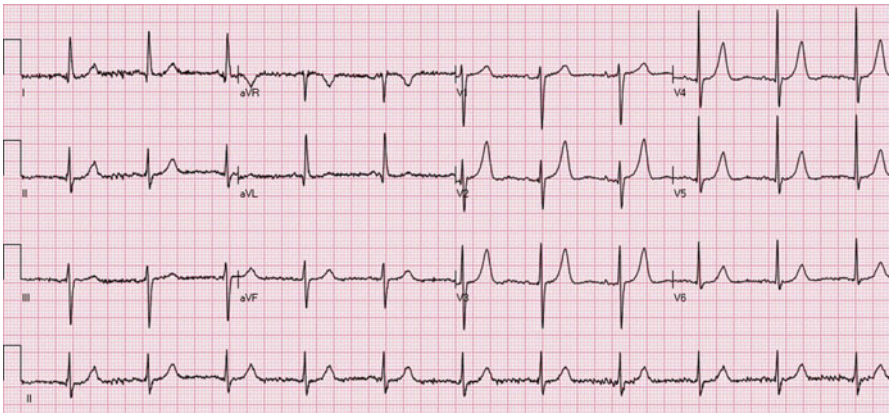

Fig 19.5 Tall T waves in the precordial leads represent Grade 1 ischemia

Myocardial protection has been proposed as the underlying physiological factor in this classification system, named the Sclarovsky-Birnbaum grading of ischemia [10]. According to the prevailing hypothesis, the changes in the terminal portion of the QRS complex reflect severe ischemia and are believed to be caused by prolongation of the electrical conduction in either the Purkinje fibers or the myocardium in the ischemic zone. For practical purposes, Sclarovsky categorized these changes into three grades of ischemia: Grade 1, tall symmetrical T waves without STE (Fig. 19.5); Grade 2, STE with tall T waves without terminal QRS distortion (Fig. 19.3); and Grade 3, STE with positive T waves with distortion of the terminal portion of the QRS (disappearance of the S waves below the isoelectric lines in leads with Rs configuration (usually V1–V3) or emergence of the J-point >50 % of the R waves in leads with qR configuration) (Fig. 19.6).

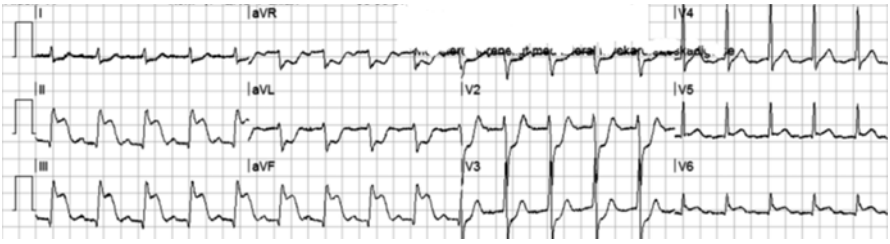

Fig. 19.6 Inferior and lateral ST elevations: the ECG shows ST elevations in the leads II, III, aVF, and V5–V6 and reciprocal ST depressions in I, aVR, aVL, and V1–V4. Grade 3 ischemia: the J-point is elevated >50 % of the height of the R wave in leads II, III, and aVF

A small percentage of patients presenting with ongoing chest pain due to coronary artery occlusion present with only Grade 1 of ischemia (tall T waves without ST elevation) [37]. Continuous ECG recording showed that without reperfusion therapy, these patients may develop Q-wave MI in the subsequent days. The patients tend to have collateral circulation to the infarcted zone, probably secondary to preexisting subtotal occlusion of the artery, suggesting partial protection by ischemic preconditioning or residual perfusion via the collateral circulation.

Studies performed by several independent groups clearly showed that a Grade 3 ischemia pattern on the presenting ECG is associated with larger final infarct size, less myocardial salvage, and poorer clinical outcomes, especially in patients presenting relatively late (>2–3 h after onset of symptoms), despite prompt reperfusion by fibrinolysis or primary PCI [38]. The Sclarovsky-Birnbaum score is an empiric practical tool to categorize ECG findings for better risk assessment. However, no prospective studies randomizing patients to different treatment groups based on the grade of ischemia have been published. Hence, we have no data to support different therapeutic strategies in patients with Grade 3 compared with Grade 2 ischemia, although patients with the former have worse outcome.

19.5.2 Standard ECG Criteria in the Diagnosis of Myocardial Infarction

The World Health Organization (WHO) has played a leading role in the formulation and application of standard criteria for the diagnosis of MI. The WHO Expert Committee in 1959 established the ECG criteria for "very probable" MI, which was mainly based on Q waves with concomitant T-wave changes [39]. In the Joint International Society and Federation of Cardiology/World Health Organization Task Force statement of 1979, unequivocal ECG findings were the development of abnormal, persistent Q or QS waves and evolving "injury current" lasting longer than 1 day [40]. The joint ESC/ACC committee consensus document published in 2000 highlighted the need for classification into STEMI and NSTEMI instead of Q-wave and non-Q-wave MI in the acute phase, mainly because of the importance of reperfusion therapy in STEMI [2].

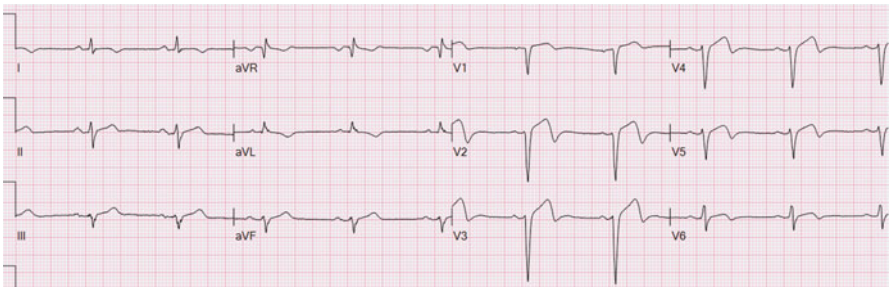

Fig 19.7 Recent myocardial infarction. The ST elevations in leads II, III, and aVF and V1–V6 are borderline for the established thresholds for STEMI. There are T-wave inversions in leads I, aVL, and V1–V6

The Universal definition of MI, published in 2007, introduced different cut points for ST elevation in men and women in leads V2–V3 [41]. Population studies have clearly shown gender differences especially in these leads. In the most recent universal definition of MI, an additional factor – patient age – was introduced [5]. Importantly, the authors pointed out that lesser degrees of ST displacement or T-wave inversion do not exclude acute myocardial ischemia or evolving MI, since a single static recording may miss the more dynamic ECG changes that might be detected with serial recordings. They also recommended to use supplemental leads such as V3R and V4R (reflecting the free wall of the right ventricle) and V7–V9 (reflecting the basal inferolateral wall), as well as serial ECG recordings, in patients who present with ischemic chest pain and a nondiagnostic initial ECG.

19.5.2.1 Proposal for a New ECG-Based Classification of ACS

A recent working group statement questioned the definitions in the prevailing ECG classification of STE- and non-STE-ACS [12]. The statement recommended a classification based on the pathophysiologic/electrophysiologic processes involved instead of strict classification based on the ECG findings per se. The time point of patient presentation and the recording of the ECG with relation to the pathological processes taking place in the coronary artery and the myocardium is a critical aspect determining the classification of ACS. If the presenting ECG is recorded during the acute occlusive stage, ST elevations are present in the ECG leads overlying the ischemic area. Then the initial diagnosis will be STE-ACS. However, if spontaneous fibrinolysis is effective or if the patient has received antithrombotic medication and the coronary artery has opened before the initial ECG is recorded, inverted T waves without ST elevations may be present. This will result in an initial diagnosis of NSTE-ACS (Fig. 19.7). The classification does not state that all ECG patterns classified as STE-ACS should necessarily indicate the need for emergent reperfusion therapy. Instead, by adding pathophysiological aspects into the ECG classification, the authors wanted to correct some prevailing misunderstandings. One of these is related to the underlying mechanisms of inverted T waves without ST depression in ACS (see below).

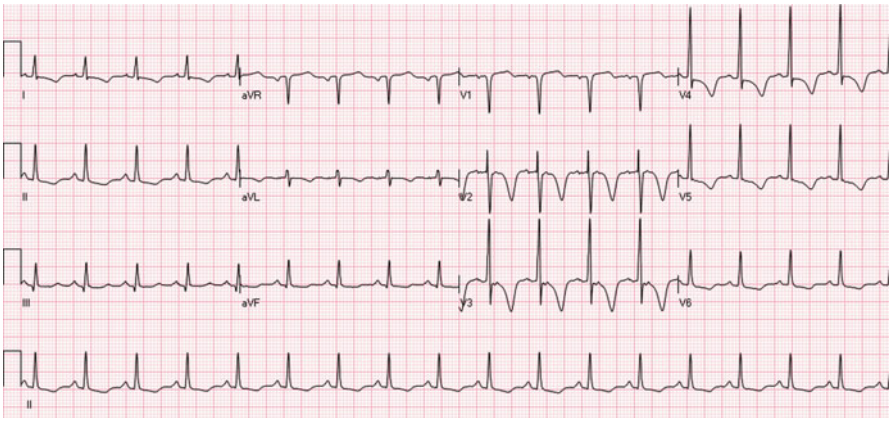

Fig. 19.8 The "Wellens' sign": inverted T waves without significant ST elevations in the precordial leads, maximal in leads V2–V4

T-Wave Changes and STE-ACS

In the working group statement, some of the ECG patterns restricted to the T waves could be considered as STE-ACS. This is the case for prominent positive T waves, both as a transient phenomenon during coronary artery occlusion, and for the persistent T wave classified as Grade 1 of ischemia (Fig. 19.5). CMR has shown that the changes observed in case of precordial "persistent prominent T waves" were similar to those in anterior STEMI. However, it must be stressed that there is no absolute cutoff for T-wave amplitudes indicating myocardial ischemia. Also, other causative factors, such as hyperkalemia, early repolarization, and ventricular hypertrophy, should be considered. The ACC federation (ACCF)/American Heart Association (AHA) STEMI guidelines from 2013 mention the hyperacute T waves in the early stage of coronary occlusion [42]. The guidelines recommend transthoracic echocardiography to facilitate triage in situations, where the ECG is difficult to interpret, and also mention that referral for immediate angiography may be necessary "if doubt exists."

In transmural ischemia of ACS, T-wave inversion usually follows the ST-elevation stage. Prevailing criteria recommend using NSTE-ACS as the initial diagnosis in patients with inverted T waves in their admission ECG. However, T-wave inversion without concomitant ST depression is not a sign of ongoing myocardial ischemia but appears in the "postischemic" reperfusion phase [12]. Accordingly, in the working group statement, isolated T-wave inversion, without ST depression, is considered as representing STE-ACS, but without ongoing acute ischemia. They are actually located in the same ECG leads as ST elevations and can be considered as "finger prints" of preexistent transmural ischemia (Fig. 19.8). In patients with inverted T waves, there is a risk for reocclusion of the artery before the unstable coronary lesion has been stabilized by coronary intervention and antithrombotic therapy. Before the introduction of modern antithrombotic therapy and invasive

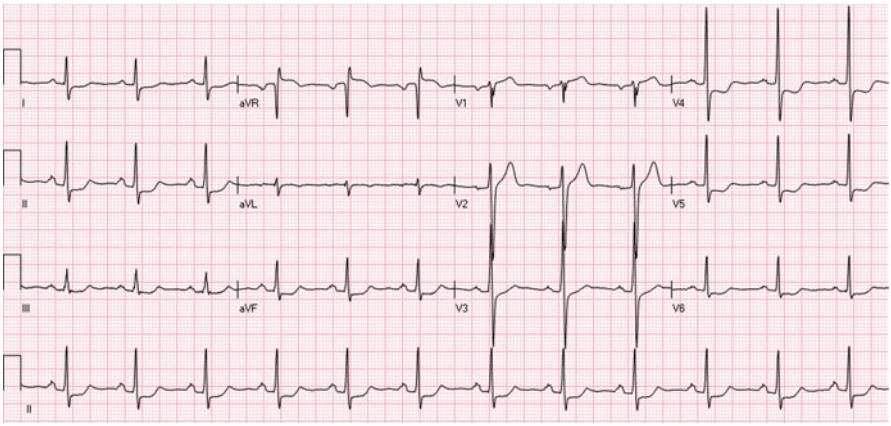

Fig. 19.9 Circumferential subendocardial ischemia: ST depressions in ≥6 leads with accompanying ST elevation in lead aVR

procedures in ACS, three out of four patients with inverted T waves, with no or minor ST deviations in the precordial leads (the "Wellens' sign"), developed Q-wave MI within weeks or months after the acute stage [43]. After thrombolysis or primary PCI, inverted T waves are considered a sign of successful reperfusion. Again, despite the recommendation by the working group to classify inverted T waves as STE-ACS without ongoing ischemia, emergent reperfusion therapy should be considered in these patients only if ST elevations develop or if there are signs of ongoing ischemia with pseudonormalization of the T waves.

Non-ST-Elevation ACS

The working group statement also highlighted subgroups presenting with NSTE-ACS. Acute subendocardial ischemia due to partial reduction of flow and/or increase of demand causes ST depression in leads facing the ischemic myocardial region. ST depression in ≥6 ECG leads during symptoms compatible with ACS often accompanied by T-wave inversion has been associated with left main, left main equivalent, or severe three-vessel disease [12]. This ECG pattern of circumferential subendocardial ischemia also encompasses ST elevation in lead aVR and was present in 8 % of consecutive patients with ACS admitted to a university hospital [44] (Fig. 19.9). In ACS patients with the ECG pattern of circumferential subendocardial ischemia and hemodynamic compromise, urgent invasive evaluation should be considered. The probability for severe coronary artery disease is higher if the patient's baseline ECG is normal and the changes are dynamic, because an identical ECG pattern may be present as a chronic pattern in patients with structural heart disease with left ventricular remodeling, such as valve disease and cardiomyopathy. The ESC STEMI guidelines state: "Left main coronary obstruction—lead aVR ST elevation and inferolateral ST depression: The presence of ST-depression >0.1 mV in eight or

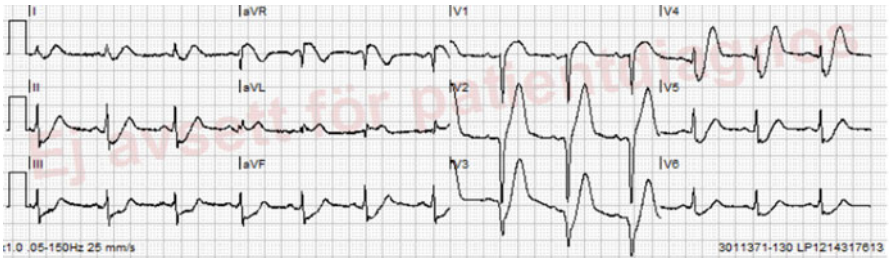

Fig 19.10 J-point depression with upsloping ST depression in leads I, II, III, aVF, and V3–V6. ST elevation in non-consecutive leads aVR, aVL, and V1. Prominent T waves in leads V2–V4

more surface leads, coupled with ST elevation in aVR and/or V1 but an otherwise unremarkable ECG, suggests ischemia due to multivessel or left main coronary artery obstruction, particularly if the patient presents with hemodynamic compromise" [45].

Upsloping ST depression with positive T waves is commonly seen during tachycardia, even in persons without coronary artery disease, and the ECG pattern has usually not been considered a pattern indicating ischemia (Fig. 19.10). This ECG manifestation may be present in patients with NSTE-ACS at slower heart rates and is increasingly recognized as a sign of regional subendocardial ischemia. It has been associated with subtotal or even total occlusion of the LAD or total occlusion of a side branch, when present in the precordial leads [46, 47].

19.6 Debatable and Unresolved Issues in the Classification of ACS

Universally agreed cutoffs for ST elevations in STEMI patients have been established for emergent reperfusion therapy to open an occluded coronary artery. The degree of ST elevation in leads V2 and V3 varies according to gender. Based on epidemiologic data, the ACC/AHA and ESC STEMI guidelines have recommended absolute cutoffs of 0.2 mV in men and 0.15 mV in women without LBBB or left ventricular hypertrophy (LVH) [42, 45]. Both guidelines quote the Third Universal Definition of Myocardial Infarction document [5]. However, these documents also use age to define the cutoff for significant ST elevation: leads V2–V3: 0.2 mV in men 40 years or older, 0.25 mV in men younger than 40 years, and 0.15 mV in women. Moreover, the restriction to patients without LBBB or LVH was omitted in this document. There is data indicating that the level of ST elevations in healthy individuals also may vary with ethnicity. Macfarlane et al. [48] described a higher magnitude of "normal" ST elevation in Nigerian healthy men. These criteria have been adopted as rigid rules by many "quality assurance" programs.

ST elevation in patients presenting with typical symptoms is highly predictive of coronary artery occlusion, but ST elevation per se is not equivalent to STEMI. ST

elevation secondary to nonischemic etiologies is very common, and these are real diagnostic challenges in clinical practice [49]. The clinician should be aware of the most common patterns of nonischemic ST elevation, such as early repolarization, normal pattern, left ventricular hypertrophy, Brugada syndrome (Chaps. 48 and 52), and acute pericarditis. False activation of the catheterization laboratory and, especially, fibrinolytic therapy could be harmful in these patients. Many patients with structural heart disease, such as cardiomyopathy, have baseline ST deviation secondary to bundle branch block, nonspecific intraventricular conduction delay, preexisting aneurysm, hypertrophy, etc. Comparison with previous ECG and repeated ECG recording may help, because ischemic changes are typically dynamic. However, the magnitude of ST elevation may vary also in the case of structural heart disease, for example, due to significant changes in heart rate. On the other hand, patients with baseline nonischemic ST elevation may present with superimposed STEMI. The ECG should be analyzed in the context of the clinical picture always when possible.

Some patients with true transmural ischemia secondary to an acute occlusion of an epicardial artery present with ST elevation less than the recommended threshold due to established collateral circulation, pulmonary disease, pericardial effusion, or fluid retention due to heart failure, which decrease the amplitude of the QRST complexes. Probably, adjusting the magnitude of ST deviation to the total QRS amplitude could be more predictive than the current recommendation for absolute ST-elevation amplitude.

LVH commonly causes ST elevation in leads V1–V3 along with ST depression in the lateral leads. Currently, the ACC/AHA and ESC STEMI guidelines do not give any threshold for ST elevation for leads V1–V3 in patients with LVH, whereas the Third Universal Definition of Myocardial Infarction document does not address this issue [5, 42]. Currently, there are no recommended thresholds for ST elevation in patients with nonspecific intraventricular conduction delay.

The diagnostic criteria of the "mirror-image" STEMI, when there is minimal or no ST elevation in the inferior leads, are not straightforward. The ECG manifestation of ischemia will be reciprocal ST depression in leads V1–V3 (Fig. 19.11). In many patients recording leads V7–V9 (posterior chest leads) may reveal ST elevation, and reperfusion therapy is indicated. The guidelines give slightly different messages; they state that patients presenting with ST depression in leads V1–V3 [45] or V1–V4 should be considered as having STE-ACS equivalent and referred for emergent revascularization. According to the Universal Definition of MI, "ST depression in leads V1–V3 may be suggestive of infero-basal myocardial ischaemia (posterior infarction), especially when the terminal T wave is positive (ST elevation equivalent), however this is non-specific" [5]. As discussed earlier, CMR studies have shown that the infarction is localized to the inferolateral segments, and not to the basal inferior segment [23]. Therefore, the term "inferolateral" STEMI is more appropriate, and it confirms with the Universal Definitions of the LV segments [49, 50]. In addition, the mirror image of the acute phase of STE-ACS (STE with positive T waves) is ST depression with negative T waves; thus early on most cases present with ST depression and negative T waves. It is also unclear whether in cases

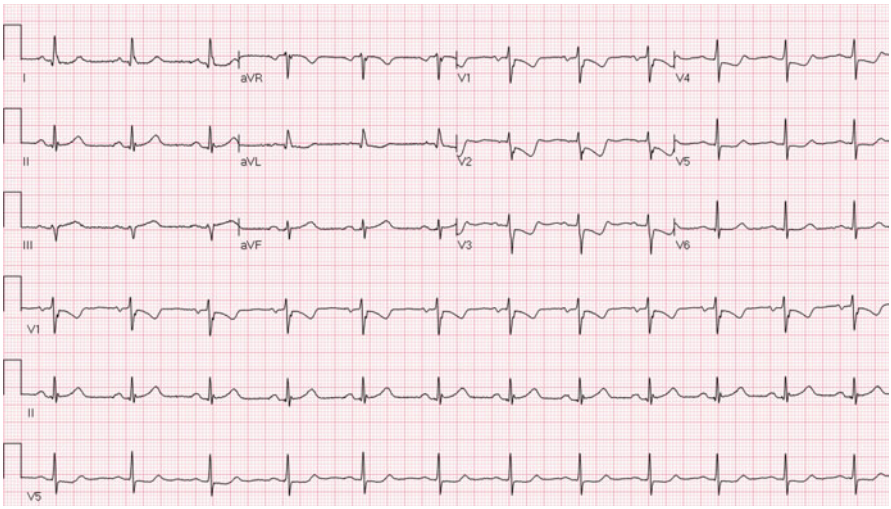

Fig. 19.11 "Mirror-image" STEMI: the ST elevations in the inferior leads do not fulfill STEMI criteria, reciprocal ST depression in leads V1–V5

with ST depression extending beyond lead V4 (V5–V6) true inferolateral STE-ACS equivalent can be excluded (Fig. 19.11). Moreover, we are lacking consensus in patients with right bundle branch block, where ST depression in leads V1–V3 is common – we have no criteria how to diagnose or exclude acute inferolateral STE-ACS equivalent in patients with complete or incomplete right bundle branch block in these patients.

19.7 Concluding Remarks

The ECG is the most commonly used method to classify ACS. In addition to the classical division based on ST elevation and non-ST-elevation myocardial infarction, other clinically important ECG-based classification systems have been used. They give information about the severity of myocardial ischemia, acuteness of the disease process and extent of the area at risk, and infarct size. Still, there are unresolved issues that need to better defined:

- Is it possible to distinguish ischemic ST elevation caused by acute MI from non-ischemic ST elevation induced by nonischemic etiologies, such as pericarditis and early repolarization?
- How to recognize ischemia-induced ST elevation in patients with an acutely occluded coronary artery, when the amount of ST elevation is less than the established thresholds?
- What are the ECG criteria for significant ST elevation in patients with LVH?

- What is "mirror-image" STEMI: ST elevation in V1–V3 or V1–V4? What about ST depression extending beyond leads V3–V4?
- What are the role of previous ECG for comparison in patients with persistent ST depressions due to structural heart disease and a suspicion of ACS?
- How to diagnose acute ischemia and especially STEMI in patients with LBBB, nonspecific intraventricular conduction delay, and electronic right ventricular pacing?

In the future, there will probably also be more non-ECG-based pathogenetic classification systems based on the disease process in the vessel wall and blood circulation.

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Chapter 20
Pathophysiology and Management of Myocardial Infarction

Mahmoud H. Abdou, Niels Engberding, and Nanette K. Wenger

Abstract Acute obstruction of a coronary artery is the most common cause of ST-segment elevation myocardial infarction (STEMI). The most common clinical presentation of myocardial infarction is acute chest pain. It is essential that initial assessment and management be rapid but methodical and evidence based focusing on distinguishing between chest pain secondary to acute coronary syndrome and that caused by nonischemic etiologies. Early revascularization is the mainstay of improving outcomes. Primary percutaneous coronary intervention (PCI) supported by appropriate antithrombotic therapy is the preferred approach when rapidly available. Guideline-directed medical therapy, secondary prevention, and lifestyle modification complement successful long-term management. In this chapter, we will discuss the management of acute STEMI, highlighting some important key elements in the pathophysiology of and mechanisms by which STEMI can develop.

Keywords Myocardial infarction • Plaque rupture • Fibrinolytics • Primary percutaneous coronary intervention • STEMI • Statins • Thrombin inhibitors • Nitrates • Glycoprotein IIb/IIIa inhibitors

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20.1 Introduction

The understanding of the sequence of biological events involved in the pathophysiology and mechanism by which myocardial infarction (MI) occurs has witnessed a significant change over the past decades. The early theory of progressive worsening of severe coronary lesions leading to coronary lumen compromise along with successive vascular spasm and intracoronary thrombosis was heavily supported as the key mechanism by which acute coronary syndromes (ACS) including unstable angina and MI occur. However, extensive angiographic studies following fibrinolysis revealed that the majority of plaques leading to ACS were not sufficiently angiographically severe to fully explain the underlying pathology.

Further detailed vascular biology studies have led to the conclusion that ACS occurs because of acute rupture or disruption of a plaque, known as the thin-capped fibroatheroma, which is different in composition and character from the stable benign plaque (Chap. 19).

In this chapter, we will discuss further the mechanism and pathophysiology by which acute myocardial infarction occurs. We will also highlight the management and pharmacotherapy of treating ST-segment elevation myocardial infarction (STEMI). The management of the remainder of the ACS spectrum (unstable angina and non-ST-segment elevation myocardial infarction) is discussed in Chap. 23.

20.2 Pathophysiology of Myocardial Infarction

20.2.1 Myocardial Injury and Myocardial Cell Death

The constantly pumping heart muscle needs a steady supply of oxygen and fuel to contract. Balance between myocardial oxygen supply and demand is the prime determinant of normal cardiac function. Energy demand is determined by the cardiac workload, which primarily depends on wall stress, heart rate, and inotropic state. Supply is provided by regulation of coronary blood flow through epicardial coronary arteries, resistance arteries, precapillary arterioles, and capillaries. If myocardial oxygen demand exceeds its supply, ischemia-induced contractile dysfunction leads to hypotension and further myocardial ischemia. Under normal physiological conditions, the myocardium gets its supply from aerobic metabolism of glucose, lactate, and free fatty acids via the Krebs citrate cycle into the production of adenosine triphosphate (ATP). In acute myocardial infarction, a sudden cessation of blood supply to a region of the myocardium results in decreased oxidative ATP synthesis, eventually leading to stimulation of anaerobic glycolysis and glycogen breakdown, and inhibition of Na^+/K^+ ATPase resulting in cell swelling. Low cytosolic ATP concentration reduces the contractile ability of the myocardium and, when coupled with increased cytosolic Ca^{2+} from disrupted transport systems in the sarcolemma and sarcoplasmic reticulum, promotes alteration in contractile proteins.

After a variable duration of ischemia, irreversible myocardial injury ensues. Phospholipase activation promotes accumulation of lysophospholipids and free fatty acids within the cell, and development of free radicals and toxic reactive oxygen species (ROS) occurs via different mechanisms including xanthine oxidase, activated neutrophils, electron leakage from ischemic mitochondria, and catecholamine oxidation, in addition to cyclooxygenase and lipoxygenase enzymes. The end result is breaking of cytoskeletal anchoring proteins and progressive membrane permeability of the sarcolemma, resulting in physical and structural disruption, impairment of contractile function, and cardiomyocyte cell death [1–3].

20.2.2 Evolution of Myocardial Infarction

The initial ischemic cellular changes in the myocardium begin almost immediately at the onset of ischemia. Severe loss of myocardial contractility occurs within 60 s. Depending on metabolic state and collateral blood flow, total cessation of blood supply can cause irreversible injury and loss of cellular viability within 20–40 min and up to several hours. At autopsy, hearts with acute myocardial infarction show two zones of myocardial damage: a zone with no flow or very low flow, a *central zone*, surrounded by a *marginal zone* with supply from collateral vessels. One important determinant of infarct size is the extent of collateral coronary circulation that sustains survival of the marginal zone. The presence of collaterals is therefore critically related to survival and development of future congestive heart failure [4]. Irreversible cell death occurs first in the subendocardial zone of the myocardium and then extends as a wave front toward the subepicardium; by 6–24 h, necrosis becomes transmural [5]. Other factors that influence infarct size are ischemic preconditioning and reperfusion.

20.2.3 Ischemic Pre- and Postconditioning

Brief repetitive episodes of transient ischemia separated by periods of reperfusion appear to protect the myocardium against subsequent prolonged ischemia; this has been termed ischemic preconditioning. Two phases of preconditioning have been described: the initial phase, known as the classical or early preconditioning operative for up to 3 h before sustained coronary occlusion, and the delayed phase, operative 24 h after the precondition, known as the second window of protection (SWOP) [6].

The exact mechanism by which ischemic preconditioning-mediated cardioprotection occurs is not fully understood; however, the classical or early phase has been associated with the activation of adenosine (A_1/A_3) receptors, activation of protein kinase C (PKC) coupled to G proteins, opening of ATP-sensitive potassium (K_{ATP}) channels, and closure of mitochondrial permeability transition pore

(MPTP). The mechanism of how SWOP occurs remains even less clear but is believed to be triggered by a spectrum of chemical stimuli including adenosine receptor agonists, cyclooxygenase-2 (COX-2), bradykinin, opioid-κ receptor agonists, nitric oxide donors, cytokines, ROS, and endotoxin derivatives (e.g., monophosphoryl lipid A); these trigger complex signal transduction pathways via kinase cascades, including mitogen-activated protein kinases, tyrosine protein kinases, and nuclear factor kappa B (NFκB). Furthermore, it has been proposed that some nonchemical triggers of SWOP are ischemia, heat stress, rapid ventricular pacing, and exercise [7, 8].

Data from animal models have suggested that ischemic postconditioning can reduce reperfusion-induced myocardial injury by brief repetitive episodes of reperfusion and reocclusion in the affected coronary artery applied at the beginning of reperfusion therapy. It appears that this strategy has similar benefits as ischemic preconditioning and invokes similar protein kinase pathways in animal models [9]. Particularly, the activation of the reperfusion injury salvage kinase (RISK) pathway including prosurvival kinases, such as PI3K-Akt, eNOS, and p70S6K, appears to play a prominent role in protecting the myocardium [10]. However, a clinical trial in STEMI patients did not show ischemic postconditioning to be effective [11].

20.2.4 Ischemia Reperfusion Injury

If ischemic myocardium is reperfused early, there is the potential for nearly complete recovery of the ischemic territory. Frequently, however, the myocardium remains dysfunctional despite successful reperfusion. Sometimes ischemic cellular damage even appears exaggerated and accelerated after successful restoration of blood flow. This paradoxical reperfusion injury occurs after sudden reperfusion of severely ischemic myocardium and has been linked to damage from free radicals and calcium. This manifests as reduction in myocardial contractility and systolic function, lowering of the threshold for fatal arrhythmias, conversion of reversible to irreversible myocyte injury, and microvascular dysfunction. Reperfusion thus may have a paradoxical effect on the myocardium, reducing its beneficial actions [12]. Reactive oxygen species (ROS), sudden increases in intracellular Ca^{2+}, rapid restoration of physiologic pH, and inflammation are mediators of this process. The release of ROS leads to reduction in the bioavailability of nitric oxide. Nitric oxide (endothelium-derived relaxing factor), a cardioprotective vasodilatory molecule, inactivates superoxide radicals and improves coronary flow.

The sudden and rapid release of intracellular Ca^{2+} induces cell death by stimulating myofibril contraction, leading to opening of the MPTP and uncoupled oxidative phosphorylation, rapid ATP depletion, and cell death. Reperfusion injury can be reduced by hypothermia when initiated late during ischemia in animal models, but this has been difficult to demonstrate in clinical trials [13]. Despite improved

understanding of the underlying pathways mediating reperfusion injury, there are currently no specific therapies to prevent it.

20.2.5 Microembolization

Embolization of small fragments of fibrin-platelet thrombus and necrotic core can occur with acute coronary thrombosis. This phenomenon may play a role in some complications of acute myocardial infarction, such as arrhythmias, contractile dysfunction, microinfarcts, and reduced coronary reserve [14]. Other proposed mechanisms of microembolization include primary percutaneous coronary intervention (PCI), PCI of saphenous vein grafts, and coronary thrombolysis.

20.2.6 Stunned and Hibernating Myocardium

Abnormal regional left ventricular wall motion due to total or subtotal coronary occlusion for a brief period of time (5–15 min) results in a condition termed – *myocardial stunning*. Typically, in myocardial stunning, despite reestablishment of coronary blood flow, left ventricular dysfunction may persist for hours or days following reperfusion. Another possible cause for episodes of stunned myocardium is a sudden increase in oxygen demand in the setting of a fixed coronary stenosis, for instance, in patients with stable coronary disease.

If the myocardium is exposed to prolonged ischemia, its contractile function is persistently impaired but may partially or completely recover by improvement of blood flow or reduced oxygen demand; the myocardium is termed to be in a state of – *myocardial hibernation*. The chronicity of underperfusion determines the rate of functional recovery after restoration of normal flow. Acutely hibernating myocardial segments typically recover rapidly while chronically hibernating myocardium has very slow recovery rates after restoration of coronary blood flow, usually weeks to months. Myocardial hibernation can occur in patients with chronic stable angina, unstable angina, or acute myocardial infarction. Revascularization of viable myocardium may improve ventricular dysfunction, inhibit the progression of congestive heart failure, and improve survival [15].

While hibernation describes contractile dysfunction during ischemia, stunning describes abnormal myocardium after ischemia. Moreover, despite these differences, both stunned and hibernating myocardium can be differentiated from irreversibly injured tissue by imaging techniques, such as response to inotropic agents (demonstrated by dobutamine stress echocardiography), improvement of wall motion abnormality after restoration of flow, and shifting metabolism from utilization of free fatty acids to glucose as a source of energy (utilization of radionuclide myocardial perfusion imaging).

20.2.7 Ventricular Remodeling

During the postinfarction period, healing of transmural infarcts takes weeks and months after the initial event, involving an early inflammatory response, myocardial hypertrophy in the infarct border zone, and eventual scar formation. These mechanisms promote architectural changes of the left ventricle such as ventricular dilatation and a change to a more spherical shape of the ventricle, a process known as ventricular remodeling [16]. The extent of transmural necrosis is perhaps the major determinant of remodeling; islands of viable myocardium in the subepicardial necrotic regions are associated with decreased remodeling. Furthermore, microvascular integrity and baseline ventricular compliance also play a major role in reduction of remodeling. The more viable zones of myocardium there are after successful reperfusion in myocardial infarction, the less the degree of remodeling [17].

20.2.8 Coronary Anatomy and Location of Infarction

STEMI with transmural necrosis typically occurs distal to an acutely occluded coronary artery, with thrombus superimposed on a ruptured plaque. However, a coronary occlusion that has developed slowly over time may be silent clinically and evident only on electrocardiogram.

Right ventricular infarction. Approximately 50 % of patients with inferior infarction have some involvement of the right ventricle. Transmural infarction involving the inferoposterior wall and posterior portion of the septum is seen. Isolated infarction of the right ventricle (RV) is seen in 3–5 % of autopsies with MI. The right ventricle can sustain long periods of ischemia but demonstrate excellent recovery of contractile function after reperfusion. The RV is thin walled and receives significant blood supply from endocardial perfusion; therefore, ischemia is less likely to induce RV dysfunction.

Atrial infarction. This occurs in up to 10 % of patients with STEMI, usually in conjunction with ventricular infraction, and can result in rupture of the atrial wall. Rarely isolated atrial infarction has been reported in 3.5 % of autopsies of patients with STEMI. The right atrium is more commonly involved than the left, and infarction is more frequent in the atrial appendage than the lateral or posterior atrial walls. Atrial infarction is frequently associated with atrial arrhythmias [18, 19].

20.2.9 Non-atherosclerotic Causes of Acute Myocardial Infarction

Only a small number of patients with STEMI have normal coronary arteries. In these patients, a lysed embolus, a transiently occlusive platelet aggregate, or a prolonged episode of severe coronary spasm may have been the underlying cause of the infarct. Numerous pathologic processes other than atherosclerosis can lead to sudden occlusion of a coronary artery and result in STEMI (see Table 20.1).

Table 20.1 Causes of non-atherosclerosis myocardial infarction

Coronary artery disease other than atherosclerosis	Arteritis
	Luetic
	Granulomatous (Takayasu disease)
	Polyarteritis nodosa
	Mucocutaneous lymph node (Kawasaki) syndrome
	Disseminated lupus erythematosus
	Rheumatoid spondylitis
	Ankylosing spondylitis
	Trauma to coronary arteries
	Laceration
	Thrombosis
	Iatrogenic
	Radiation (radiation therapy for neoplasia)
	Coronary mural thickening with metabolic disease or intimal proliferative disease
	Mucopolysaccharidoses (Hurler disease)
	Mucopolysaccharidoses
	Fabry disease
	Amyloidosis
	Juvenile intimal sclerosis (idiopathic arterial calcification of infancy)
	Intimal hyperplasia associated with contraceptive steroids or with the postpartum period
	Pseudoxanthoma elasticum
	Coronary fibrosis caused by radiation therapy
	Luminal narrowing by other mechanisms
	Spasm of coronary arteries (Prinzmetal angina with normal coronary arteries)
	Spasm after nitroglycerin withdrawal
	Dissection of the aorta
	Dissection of the coronary artery
Emboli to coronary arteries	Infective endocarditis
	Nonbacterial thrombotic endocarditis
	Prolapse of mitral valve
	Mural thrombus from left atrium, left ventricle, or pulmonary veins
	Prosthetic valve emboli
	Cardiac myxoma
	Associated with cardiopulmonary bypass surgery and coronary arteriography
	Paradoxical emboli
	Papillary fibroelastoma of the aortic valve (fixed embolus)
	Thrombi from intracardiac catheters or guide wires
Congenital coronary artery anomalies	Anomalous origin of left coronary artery from pulmonary artery
	Left coronary artery from anterior sinus of Valsalva
	Coronary arteriovenous and arteriocameral fistulas
	Coronary artery aneurysms

(continued)

Table 20.1 (continued)

Myocardial oxygen demand-supply disproportion	Aortic stenosis, all forms
	Incomplete differentiation of the aortic valve
	Aortic insufficiency
	Carbon monoxide poisoning
	Thyrotoxicosis
	Prolonged hypotension
	Takotsubo cardiomyopathy
Hematologic (in situ thrombosis)	Polycythemia vera
	Thrombocytosis
	Disseminated intravascular coagulation
	Hypercoagulability, thrombosis, thrombocytopenic purpura
Miscellaneous	Cocaine abuse
	Myocardial contusion
	Myocardial infarction with normal coronary arteries
	Complication of cardiac catheterization

Modified from Cheitlin et al. [66]

20.3 Plaque Morphology

Acute myocardial infarction in the majority of cases is believed to result from disruption of the endothelium covering an atherosclerotic plaque – type 1 myocardial infarction; this occurs with plaque rupture or erosion, allowing blood to come in contact with the highly thrombogenic contents of the necrotic core of the plaque, leading to luminal thrombosis. Another mechanism for acute myocardial infarctions is supply-demand mismatch – type 2 myocardial infarction [20].

20.3.1 Composition of Plaques

Acute myocardial infarction related to atherosclerosis is a dynamic process with multiple stages: intimal thickening, fibrous cap atheroma (fibroatheroma) formation, thin-cap fibroatheroma (vulnerable plaque) formation, and plaque rupture.

Intimal thickening can be observed soon after birth. While some plaques may begin as fatty streaks, intimal thickening may be the precursor to symptomatic atherosclerotic disease since these lesions occur in children at similar locations as advanced plaques occur in adults. Histologically, intimal thickening consists mainly of smooth muscle cells and proteoglycan-collagen matrix with little or no infiltrating inflammatory cells [21].

Fibrous cap atheroma is characterized by a lipid-rich necrotic core encapsulated by fibrous tissue and is considered the earliest stage of advanced coronary disease. Early progression of the fibrous cap atheroma involves necrosis with macrophage infiltration of the lipid pool. Later, localized areas of cellular debris, increased free

cholesterol, and near-complete depletion of extracellular matrix are seen. Eventually, a lesion develops with significant luminal narrowing after episodes of hemorrhage with or without calcium deposition and surface disruption [22].

Thin-cap fibroatheroma (*vulnerable plaque*) has a large necrotic core comprising approximately 25 % of plaque area, separated from the lumen by a thin fibrous cap, less than 65 μm in thickness. The fibrous cap is heavily infiltrated by macrophages and T lymphocytes and typically is devoid of smooth muscle cells, enabling it to be more vulnerable to rupture.

20.3.2 Plaque Rupture

Although the precise mechanism of plaque rupture is poorly understood, the disruption is believed to occur at the site of the fibrous cap which is heavily infiltrated by macrophages and T lymphocytes where the underlying necrotic core is typically large. Fibrillar collagens, especially type I collagen, provide most of the tensile strength to the fibrous cap. Collagen synthesis is inhibited by interferon gamma secreted by activated T-cells with the expression of CD40 ligands (CD40L/CD154), which bind to CD40 receptors on the macrophages, B lymphocytes, and other cells including endothelial and smooth muscle cells. This promotes tissue proteolysis through the release of matrix metalloproteinases (MMPs) leading to fibrous cap thinning. Plaque rupture sites typically are deficient in smooth muscle cells, which play an essential role in maintaining the fibrous cap. In vitro studies have shown that smooth muscle apoptosis is promoted and mediated by secretion of interferon gamma, Fas ligand, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and reactive oxygen species by macrophages and T lymphocytes, as well as oxidized LDL. This may be responsible for the decrease in smooth muscle cells in thin-cap fibroatheroma and ruptured plaques [23].

Blood flow-induced shear stress may also influence processes that lead to plaque rupture, where increased peak circumferential stress is greater in thinner fibrous caps. Regions with high shear stress typically exhibit high strain; these combined mechanical stressors, when applied to the weakened fibrous cap, may precipitate rupture, particularly in the presence of microcalcification [24].

20.3.3 Plaque Erosion

Plaque erosion represents the second most common lesion in acute coronary thrombosis. Erosions differ from rupture lesions, as there is absence of fibrous cap disruption. The characteristics of plaque erosion, unlike plaque rupture, include an abundance of smooth muscle cells and proteoglycan matrix and absence of surface endothelium, without a prominent lipid core. There is no communication between the necrotic core and the lumen. Either no or few macrophages and T

lymphocytes are close to the lumen. The luminal surface of erosion is separated from flowing blood by a platelet-rich thrombus adherent to the proteoglycan-rich intima. The absence of endothelium, secondary to apoptotic loss of endothelial cells, allows flowing blood to come in contact with collagen and induces thrombus formation [25].

20.4 Management of ST-Segment Elevation Myocardial Infarction

Prompt recognition is the first step in management of patients with ST-segment elevation myocardial infarction (STEMI) and is a complex, multidisciplinary, and staged process. Typical ST-segment elevations on ECG in a patient with angina-type chest pain most commonly reflect the acute occlusion of an epicardial coronary artery. Cardiomyocytes quickly die if exposed to hypoxia and do not regenerate. Therefore, the most important goal in the care of a patient with STEMI is to reopen promptly the affected coronary artery. Currently, the most reliable method is PCI. This section deals with prehospital care, management in the emergency department, hospital management, and complications.

20.4.1 Prehospital and Initial Management

Once STEMI is suspected, a key element is early initiation of care prior to presenting to the hospital, which raises the likelihood of survival. Most STEMI deaths occur within the first hour of onset, with ventricular fibrillation as the most common cause of mortality. Thus, an approach that enables definitive resuscitative efforts and transport to a hospital is pivotal. Major components of the delay from the onset of symptoms to reperfusion include (1) the time for the patient to recognize the seriousness of the problem and seek medical attention; (2) the time for prehospital evaluation, treatment, and transportation; (3) the time for diagnostic measures and initiation of treatment in the hospital (e.g., door-to-needle time for patients receiving a fibrinolytic agent and door-to-balloon time for patients undergoing a catheter-based reperfusion strategy); and (4) the time from initiation of treatment to restoration of coronary blood flow [26].

Because the vast majority of STEMIs occur outside the hospital, it is essential to implement systems to minimize delay in presenting to a health-care facility equipped to manage STEMI. Some patient-related factors associated with longer time to present to a hospital or seek medical attention include older age, female gender, ethnic and racial minorities, low socioeconomic and literacy status, history of diabetes, and consulting a family relative or a physician [27, 28]. Health-care professionals and especially primary care providers must emphasize and reinforce with patients and families the necessity of urgent medical care for symptoms of an acute coronary

syndrome including chest discomfort, extreme fatigue, and dyspnea, especially if accompanied by diaphoresis, lightheadedness, palpitations, or a sense of impending doom. Counseling on timely activation of emergency services for ischemic-type chest pain is key for prompt access to a health-care facility for proper diagnosis and initiation of management.

Communities should maintain regional systems for management of STEMI that embrace assessment and continuous quality improvement of Emergency Medical Services Systems (EMS) to expand the capability to perform a 12-lead electrocardiogram (ECG), transmit it, and activate the STEMI care team prior to hospital arrival [29]. Improvement of door-to-intervention time and improvement of STEMI outcomes rely on improvement of EMS dispatch and response.

In rural settings or communities without quick and timely access to a PCI-capable medical facility, an alternative approach is prehospital fibrinolysis, demonstrated in multiple randomized controlled trials as safe and effective in reducing ischemia time in STEMI patients. Although none of the individual trials showed a significant reduction in mortality with prehospital fibrinolytic therapy, a meta-analysis of the highest quality trials showed a 17 % reduction in mortality. The greatest reduction in mortality was seen with reperfusion initiated within 60–90 min after the onset of symptoms [30]. This approach requires experienced and well-trained personnel, utilization of computer-assisted ECG with capability of rapid transmission to a central station, and equipping ambulances with the appropriate medicine kits and supplies. These resources are frequently lacking in rural areas, and therefore prehospital fibrinolysis is not available in many US communities.

20.4.2 Management in the Emergency Department

20.4.2.1 Triage and Evaluation

Accurate diagnosis and exclusion of alternate diagnoses are crucial for successful STEMI management in the emergency room. All patients presenting with symptoms suggestive of an acute MI should be rapidly triaged and a 12-lead ECG performed and shown to an experienced physician within 10 min of arrival. A targeted history and focused physical examination should be quickly performed. Five baseline parameters account for >90 % of the prognostic predictors of 30-day mortality from acute MI: age, systolic blood pressure on presentation, the Killip classification (Table 20.2), heart rate, and location of MI [31].

20.4.2.2 Initial Management

In definitive STEMI, time in the emergency department should be minimal, and the patient should be taken directly to the catheterization laboratory while supportive measures are undertaken.

Table 20.2 30-day mortality based on hemodynamic (Killip) classification

	Killip class I	Killip class II	Killip class III	Killip class IV
Clinical presentation	No evidence of CHF	Rales (involving less than half of the posterior lung fields), elevated JVD or S_3	Pulmonary edema	Cardiogenic shock
% of patients	85 %	13 %	1 %	1 %
Mortality rate (%)	5.1	13.6	32.2	57.8

Modified from Lee et al. [31]
CHF congestive heart failure, *JVD* jugular venous distension, *S3* third heart sound

Oxygen

Supplemental oxygen by a nasal cannula is indicated only for hypoxic patients with suspected MI. Oxygen should be administered only if there is evidence of hypoxemia (oxygen saturation <90 %), as the potential harm from hyperoxia can worsen outcomes [32]. Supplemental oxygen should be used with caution in patients with chronic obstructive pulmonary disease and carbon dioxide retention [30].

Aspirin

Unless there is a clear history of aspirin allergy (not intolerance), the immediate use of aspirin in doses of at least 162–325 mg significantly reduces mortality. To achieve therapeutic levels in the blood faster, aspirin is usually chewed to promote buccal absorption.

Reduction of Cardiac Pain

Nitrates

Nitrates enhance coronary flow by coronary vasodilation and reduce ventricular preload by systemic venodilation. The venodilation diminishes venous return to the heart, reducing ventricular volume and pressure, and thus a reduction in ventricular preload occurs. The use of nitrates is not associated with reduction in mortality.

Nitrates are initially administered sublingually (0.4 mg nitroglycerin sublingual tablet) followed by close observation for improvement in symptoms or change in hemodynamics. If an initial dose is well tolerated and appears of benefit, further nitrates should be administered, with monitoring of vital signs. Marked hypotension (systolic blood pressure <90 mmHg), bradycardia, and suspected right ventricular infarction are contraindications to nitroglycerin [33].

If chest pain persists or recurs, intravenous nitroglycerin may help to control ischemic pain; this requires close monitoring of blood pressure. Intravenous nitroglycerin should be initiated at 5–10 μg/min and gradually increased with a goal of 10–30 % reduction of systolic blood pressure and/or relief of chest pain. Long-acting nitrate preparations should not be used. Moreover, nitrates should not be given within 24 h of use of phosphodiesterase (PDE) inhibitors (e.g., sildenafil) because the combination may result in severe systemic vasodilation and life-threatening hypotension.

Another important aspect in the use of nitrates is nitrate tolerance. Although this is most commonly observed with chronic nitrate therapy for chronic angina, it remains a characteristic of nitrate therapy in general. The mechanism by which nitrate tolerance occurs is not fully understood. One proposed mechanism is thought to be by reduction of nitric oxide availability via inhibiting conversion of nitroglycerin to 1,2-glyceryl dinitrate by directly impairing the function of mitochondrial aldehyde dehydrogenase-2 (mtALDH) enzyme [34]. Another theory postulates that nitrate tolerance is secondary to the reduced bioactivity of nitric oxide, supported by findings in animal models that exhibited tolerance to nitrates despite high levels of nitric oxide [35].

Analgesia

Morphine is the drug of choice to treat pain not relieved by maximally tolerated anti-ischemic therapy associated with STEMI. An initial dose of 2–4 mg as an intravenous bolus is given with increments of 2–4 mg repeated at 5–10 min intervals. Morphine may cause hypotension and respiratory depression; these side effects preclude further use of the drug.

Morphine acts by decreasing anxiety and restlessness triggered by activation of the autonomic nervous system, suppression of which results in reduction of myocardial oxygen demand. In patients with pulmonary edema, morphine has additional benefits of peripheral arterial and venous dilatation, reduced work of breathing, and slowing of heart rate due to increased vagal tone. Nausea and vomiting may be troublesome side effects of large doses of morphine and can be treated with a phenothiazine. In high doses, morphine overdose may be problematic, and classic signs of opioid intoxication may develop including depressed mental status, decreased respiratory rate, decreased bowel sounds, and pinpoint miotic constricted pupils.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with increased risk of adverse cardiovascular events in patients with STEMI and should be avoided throughout the hospitalization for STEMI [36, 37].

Anticoagulation

Thrombin (Factor IIa) is the central mediator of clot formation as it induces platelet activation, conversion of fibrinogen to fibrin, and activation of factor XIII, leading to fibrin cross-linking and clot stabilization. Research over the past three decades has resulted in the development of various antithrombotic agents and combination

strategies with the intention to promote culprit artery patency, prevent thrombotic reocclusion after pharmacologic or mechanical reperfusion, and reduce bleeding complications. Several strategies are available and accepted in practice guidelines. Local hospital systems are encouraged to generate their most feasible treatment algorithm that complies with the latest practice guidelines.

Anticoagulant agents used in the management of STEMI can be divided into two major groups:

1. Antithrombin (anti-factor IIa) agents:
   (a) Indirect thrombin inhibitors, e.g., unfractionated heparin and low-molecular-weight heparin
   (b) Direct thrombin inhibitors, e.g., bivalirudin
2. Anti-factor Xa agents:

   For example, fondaparinux

Table 20.3 outlines different clinical characteristics of anticoagulants used in management of STEMI (also see Chap. 23).

Table 20.3 Anticoagulant agents used in management of acute STEMI

	UFH	LMWH (enoxaparin)	Bivalirudin	Fondaparinux
Mechanism of action	Indirect antithrombin (anti-factor IIa)	Indirect antithrombin (anti-factor IIa)	Direct antithrombin (anti-factor IIa)	Anti-factor Xa
Activity on clotting factors	Factor IIa = factor Xa activity	Factor Xa > factor IIa activity	Factor IIa > factor Xa activity	Factor Xa activity only
Molecular weight	12,000–30,000	4,500	2,100	1,700
Half-life	1–2 h	4–6 h	25 min	16–24 h
Antidote	Protamine	Protamine	Factor VII and/or dialysis	Factor VII and/or dialysis
Risk of HIT	+++	+	–	–
Route of administration	SC or IV	SC or IV	IV	SC
Clearance	Renal and RES	Renal	Renal	Renal
Pregnancy category	C	B	B	B
Special notes	Activates platelets. Does not inhibit clot-bound thrombin	Higher risk of bleeding compared to UFH	Lower risk of bleeding compared to UFH. Does inhibit clot-bound thrombin	Higher risk of guide catheter thrombosis during PCI

Pregnancy category B = no evidence of risk in studies, pregnancy category C = risk cannot be ruled out
UFH unfractionated heparin, *LMWH* low-molecular-weight heparin, *SC* subcutaneous, *IV* intravenous, *RES* reticuloendothelial system, *PCI* percutaneous coronary intervention

Unfractionated Heparin (UFH)

Heparin use is a class I indication for STEMI patients who will undergo primary PCI or fibrinolytic therapy [30]. Unfractionated heparin binds to antithrombin III and inhibits the activation of thrombin and therefore lacks the ability to inhibit thrombin that is clot bound. It has a molecular weight range of 12,000–30,000 Da. The usual dose is an intravenous initial bolus of 60 U/kg (4,000 U maximum) followed by a 12 U/kg/h (1,000 U/h maximum) infusion, given promptly, with a goal-activated partial thromboplastin time (aPTT) of 1.5–2.0 times normal. A disadvantage of unfractionated heparin is its unpredictable anticoagulation effects, due to variability in protein binding and the time delay until therapeutic levels are achieved. Unfractionated heparin use in myocardial infarction has an abundance of data and usually is part of the standard treatment arm in trials comparing newer agents or combinations of antithrombotic regimens. It currently can be used in all three-treatment strategies: to support PCI, fibrinolytics [38], or medical management. In patients receiving fibrinolytic therapy and aspirin, the addition of UFH is of proven benefit in patients treated with fibrin-specific thrombolytics, which are now preferred [39]. UFH may also be of benefit for patients receiving streptokinase who are at high risk for systemic thromboembolism. Thus, all patients with STEMI should be treated with anticoagulant therapy regardless of choice of fibrinolytic agent.

Low-Molecular-Weight Heparin (LMWH)

LMWHs are glycosaminoglycans with chains of residues of D-glucosamine and uronic acid in an alternate fashion. Compared to UFH, these agents have a molecular weight that ranges from 4,000 to 6,000 Da. The usual dose is an intravenous bolus of 30 mg of enoxaparin, followed by 1 mg/kg subcutaneous injection every 12 h. Unlike unfractionated heparin, LMWHs are stronger inhibitors of factor Xa than thrombin; therefore, the anticoagulation effect cannot be measured routinely. The advantages of LMWHs are a longer half-life, better bioavailability, and dose-independent clearance, resulting in more rapid predictable anticoagulation compared to unfractionated heparin. However, LMWH is associated with increased risk of major and minor bleeding in the clinical trials [40–43]. Due to this fact and given the lack of superiority to unfractionated heparin, many experts do not use LMWH in patients undergoing primary PCI and choose unfractionated heparin or bivalirudin. In current practice guidelines, LMWH with doses adjusted to age, weight, and renal function can be used as an adjunct preferentially in those patients undergoing therapy with fibrinolysis [30].

Neither unfractionated heparin nor LMWH crosses the placenta and thus does not result in fetal anticoagulation. In general, the use of LMWH is preferred over UFH due to the efficacy and ease of administration. However, UFH appears to be a more appropriate alternative to LMWH when more control of anticoagulation is needed (e.g., near the time of delivery) or patients with severe renal insufficiency [44, 45]. Current practice guidelines do not specify use of one form of heparin over the other, mostly due to lack of data from clinical trials that target this patient population.

Direct Thrombin Inhibitors

These agents bind directly to thrombin and can be used safely in patients with previous heparin-induced thrombocytopenia. Both Hirulog and bivalirudin were compared to heparin in STEMI. In patients undergoing reperfusion by fibrinolysis, direct thrombin inhibitors significantly reduced recurrence of MI but did not reduce mortality and had significantly higher rates of major bleeding [43]. When used in patients undergoing reperfusion by PCI, bivalirudin had significantly lower major bleeding and was associated with a significant reduction of 30-day and 1-year mortality; however, it was associated with increased stent thrombosis compared to heparin and glycoprotein IIb/IIIa receptor blockers [46].

Factor Xa Inhibitors

Administration of fondaparinux, a factor Xa inhibitor, was evaluated in STEMI clinical trials compared to placebo, unfractionated heparin, or enoxaparin. The use of fondaparinux is reasonable in patients with STEMI undergoing reperfusion with PCI, although concomitant unfractionated heparin is recommended to prevent occurrence of guide catheter clots and stent thrombosis [47, 48].

Antiplatelet Agents (Also See Chap. 23)

In the acute management of STEMI, these agents inhibit platelet aggregation, the release of granule contents, and platelet-mediated vasoconstriction.

Aspirin

Aspirin, a powerful cyclooxygenase enzyme inhibitor, controls the first step in the biosynthesis of the arachidonic acid derivatives, prostaglandins, and thromboxanes, namely, thromboxane A2 that stimulates platelet aggregation. The use of aspirin in STEMI has been associated with significant reduction in mortality in multiple clinical trials [49, 50]. Dose of aspirin and route of administration in acute STEMI management were outlined above. The use of aspirin is a class I recommendation for management of STEMI patients undergoing reperfusion with either PCI or fibrinolytic therapy. Aspirin remains highly beneficial even in patients not undergoing reperfusion [30].

$P2Y_{12}$ Receptor Blockers

These agents block platelet adenosine diphosphate receptor $P2Y_{12}$ with a more potent antiplatelet effect than aspirin but less than glycoprotein IIb/IIIa inhibitors. Thienopyridines ticlopidine (rarely used nowadays), clopidogrel, prasugrel, and the cyclopentyltriazolopyrimidine ticagrelor are available only in oral formulation; cangrelor is an intravenous agent but is not approved for use in STEMI (Table 20.4). Newer $P2Y_{12}$ receptor blockers (prasugrel and ticagrelor) have more potent antiplatelet effect than clopidogrel; prasugrel should not be given to elderly patients above the age of 75 years, patients with low weight under 60 Kg, and patients with

Table 20.4 $P2Y_{12}$ receptor blockers and their use in management of acute STEMI

	Loading		Maintenance	
Drug name	Dose	Timing	Dose	Duration
Clopidogrel				
Patients undergoing PCI	600 mg	As early as possible or at time of PCI	75 mg daily	1 year
Patients undergoing fibrinolytic therapy alone	300 mg (age ≤75) No loading (age >75)	As early as possible	75 mg daily	At least 14 days and up to 1 year
Patients undergoing PCI after fibrinolytic therapy	300 mg (PCI ≤24 h) 600 mg (PCI >24 h)	At time of PCI	75 mg daily	At least 1 year with DES At least 30 days up to 1 year with BMS
Prasugrel				
Patients undergoing PCI	60 mg	As early as possible or at time of PCI	10 mg daily	1 year
Patients undergoing PCI after fibrinolytic therapy	60 mg	At time of PCI	10 mg daily	At least 1 year with DES At least 30 days up to 1 year with BMS
Ticagrelor				
Patients undergoing PCI	180 mg	As early as possible or at time of PCI	90 mg twice a day	1 year

Modified from 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

PCI percutaneous coronary intervention, *DES* drug-eluting stent, *BMS* bare metal stent

a history of prior stroke or transient ischemic attack. Ticagrelor is formulated as a twice a day medication, with medication adherence being a potential concern, and because of its potency, concomitant dose of aspirin should be limited to less than 100 mg daily. The use of $P2Y_{12}$ receptor blockers in patients with STEMI has shown most benefit when used as an additive to aspirin. Unless contraindicated, these agents should be started immediately and continued for at least 1 year.

Glycoprotein IIb/IIIa Inhibitors

These drugs are potent agents that inhibit the final common pathway for platelet aggregation and clot formation. Currently, only three agents are available in the United States: abciximab, tirofiban, and eptifibatide. In reperfusion using fibrinolysis, multiple studies demonstrated that glycoprotein IIb/IIIa inhibitors with half-dose fibrinolysis improved coronary artery blood flow in STEMI patients. No significant mortality benefit was seen, and the risk of major and minor bleeding was higher [51–53]. Therefore, according to current practice guidelines, the use of these

agents upstream prior to arrival to the catheterization laboratory or concomitant use with fibrinolytic agents is not recommended. There is evidence supporting administration of glycoprotein IIb/IIIa agents at the time of PCI as they improve coronary artery flow to the infarct area and ultimately improves mortality outcomes. Thus, the guidelines recommendations were for limited use in the catheterization laboratory at the time of primary PCI only. Abciximab has historically been the glycoprotein IIb/IIIa inhibitor widely used during PCI, because it was the most studied in clinical trials. There is growing evidence that eptifibatide and tirofiban may be acceptable alternatives to abciximab in STEMI patients [54] (Chap. 23).

20.4.2.3 Reperfusion

In most patients with STEMI, early reperfusion improves myocardial salvage and significantly reduces mortality. Timing is of paramount importance for myocardial salvage, as the benefits of reperfusion decline as time elapses. Reperfusion strategies encompass three options: fibrinolytic therapy, catheter-based reperfusion, and coronary artery bypass surgery.

Optimal Reperfusion Strategy Selection

Assessment of optimal reperfusion options for STEMI can be challenging integrating multiple complex decisions, making it difficult to formulate a simple equation or a one-size-fits-all approach. An integrated assessment of the time since onset of symptoms, risk of death after STEMI, risk of bleeding related to fibrinolysis, and time required for transportation to a PCI-capable facility needs to be taken into account. PCI is preferred when there is greater risk related to the clinical presentation of the STEMI, such as development of cardiogenic shock or risk of bleeding if fibrinolysis is given. If PCI is done in a timely fashion with short door-to-balloon time, this approach should be adopted. Fibrinolysis is the preferred reperfusion strategy where there is no skilled PCI facility accessible, limited by long transportation time, or lack of an experienced operator and team. Notably, when fibrinolysis is performed early, particularly in the prehospital setting, and followed by coronary angiography and PCI when appropriate, the 1-year survival rate is comparable to that achieved with primary PCI [55].

Catheter-Based Reperfusion Strategies

Reperfusion of the myocardium affected by the infarct artery is based on passage of a balloon catheter over a guide wire. This approach now includes coronary angiography augmented with administration of potent antiplatelet agents, deployment of coronary stents, and aspiration thrombectomy as needed [19, 56].

PCI for patients with STEMI involves one of three options.

Primary PCI

This refers to the use of PCI for reperfusion in lieu of fibrinolysis therapy, and is the preferred strategy of reperfusion in STEMI patients, when executed by a skilled interventional cardiologist in a timely manner. It requires presentation of the patient to a high-volume, well-equipped center with experienced support staff. Timely performed primary PCI results in higher rates of infarct artery patency and restoration of TIMI 3 flow with significantly lower incidence of recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage, and death. Successful primary PCI lowers the incidence of long-term complications of STEMI that result from longer ischemic times or unsuccessful fibrinolytic therapy, leading to shorter hospital stays and earlier resumption of daily activities [57].

Current clinical practice guidelines recommend primary PCI for patients with STEMI with symptoms of ischemia of less than 12-h duration and those who have contraindications to fibrinolytic therapy. For patients who develop acute severe heart failure or cardiogenic shock related to STEMI, primary PCI should be performed irrespective of time of delay from MI onset. PCI of a non-infarct artery should not be performed at the time of PCI in hemodynamically stable patients, as it is associated with worse clinical outcomes. However, a recent meta-analysis from three randomized controlled trials in patients with STEMI suggests that immediate complete revascularization improves outcomes compared to culprit vessel-only revascularization, which would indicate a paradigm shift in clinical practice [58].

Placement of coronary stents at the time of primary PCI is recommended, as implantation of stents has been associated with less restenosis and need for reintervention, but does not reduce death or reinfarction. Dual antiplatelet therapy is needed for at least 1 year after placement of drug-eluting stents; newer-generation drug-eluting stents may require dual antiplatelet therapy for lesser time, as low as 6 months, to lower the risks of bleeding associated with the use of these agents. If financial or social barriers may limit patient compliance, higher bleeding risk or anticipated need for surgical or invasive procedures in the upcoming year is identified; bare metal stent implantation should be performed, as the period required for dual antiplatelet therapy is significantly less [30].

Fibrinolytic-Facilitated PCI

This refers to treatment of patients with STEMI with fibrinolysis as a bridge to intended immediate PCI. However, this option carries higher risk of major bleeding including intracranial hemorrhage. Current clinical practice guidelines state that fibrinolytic-facilitated PCI is a reasonable approach if primary PCI cannot be performed or is not readily available immediately, with transfer to PCI-capable facility as soon as logistically feasible and ideally within 24 h but not performing PCI within 2–3 h after administration of fibrinolytic therapy.

Delayed (Rescue) PCI

This refers to performance of PCI in STEMI patients with reperfusion failure of the infarct artery or infarct artery reocclusion after initial fibrinolysis therapy. It also refers to PCI performed in patients treated with an initial noninvasive strategy who develop cardiogenic shock, acute severe HF, or unstable postinfarction angina, if invasive management is not considered futile or inappropriate.

Rescue PCI is recommended on the basis of outcomes of several clinical trials that demonstrated that PCI performed on patients who failed to achieve adequate reperfusion and/or continuing ischemia after initial fibrinolysis had less incidence of reinfarction; however, there was no improvement in survival rates among those patients. Some studies report higher rates of bleeding and stroke in patients undergoing rescue PCI [30, 59, 60].

Current clinical practice guidelines strongly recommend a delayed PCI approach for hemodynamically unstable patients or those with intermediate- or high-risk findings on predischarge noninvasive ischemia testing [30]. Delayed PCI is reasonable in stable patients ideally within 24 h but not within 2–3 h after administration of fibrinolytic therapy; it should not be performed for a totally occluded artery for more than 24 h if patients are hemodynamically and electrically stable and asymptomatic.

Fibrinolytic Therapy

The objective of fibrinolysis is recanalizing the thrombotic occlusion, resulting in restoration of coronary flow; this is designed to reduce the infarct size and improve cardiac function and overall short- and long-term survival. The major advantage of this strategy is that it is widely available, easily administered, and relatively inexpensive. However, the use of these agents can have serious and sometimes detrimental complications, causing worsening mortality and associated significant morbidity. Only approximately half of patients presenting with STEMI are eligible for fibrinolytic therapy (Table 20.5), and only half of those treated with fibrinolytic agents will achieve complete reperfusion with TIMI grade 3 flow.

Administration of fibrinolytics in STEMI reduces mortality if given early, with the most favorable outcomes if given less than 2 h after symptom onset [61] (Table 20.6). TIMI 3 flow is assessed by improvement in or relief of chest pain, resolution of ST elevation, and the presence of reperfusion arrhythmias (e.g., accelerated idioventricular rhythm). These variables have been used for assessment of effectiveness of fibrinolysis but are not accurate. Lack of resolution of ST elevation is associated with a worse prognosis and should prompt consideration of proceeding to angiography and rescue PCI.

The major complications of fibrinolysis relate to bleeding. Most bleeding is not serious, but intracranial hemorrhage is the most serious complication [62]. Streptokinase (no longer marketed in the United States) had antibody-mediated

Table 20.5 Absolute and relative contraindications to fibrinolytic therapy in patients with STEMI

Absolute contraindications	Relative contraindications
• Any prior intracranial hemorrhage • Known structural cerebral vascular lesion • Known intracranial neoplasm (primary or metastatic) • Ischemic stroke within the past 3 months (except for acute stroke within 4.5 h) • Suspected aortic dissection • Active bleeding or bleeding diathesis (excluding menses) • Significant closed head or facial trauma within 3 months • Intracranial or intraspinal surgery within 2 months • Severe uncontrolled hypertension (unresponsive to emergency therapy) • For streptokinase: prior treatment within previous 6 months	• History of chronic, severe, and poorly controlled hypertension • Systolic pressure >180 mmHg or diastolic 110 mmHg • History of prior ischemic stroke >3 months • Dementia • Known intracranial pathology not covered in absolute contraindications • Traumatic or prolonged CPR (>10 min) • Recent (within 2–4 weeks) internal bleeding • Noncompressible vascular punctures • Pregnancy • Active peptic ulcer • Current use of anticoagulants: the higher the international normalized ratio, the higher the risk of bleeding • For streptokinase: prior exposure (>5 days previously) or prior allergic reaction to these agents

Modified from 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines
CPR cardiopulmonary resuscitation

resistance due to its antigenicity; therefore, patients should not receive streptokinase for STEMI if they have been treated with streptokinase products within the year.

Coronary Artery Bypass Surgery (CABG)

Despite exponential improvement of intraoperative myocardial preservation, CABG has a limited role in the acute management of STEMI. However, CABG remains indicated for cardiogenic shock, failed PCI, high-risk anatomy, and surgical repair of a mechanical complication of STEMI such as ventricular septal rupture, free-wall rupture, or severe mitral regurgitation from papillary muscle dysfunction.

20.4.3 Hospital Management

Following the initial management of STEMI including reperfusion, patients are usually admitted to the coronary care unit (CCU) for continuous ECG monitoring for potentially fatal arrhythmias that may develop after STEMI. Additional pharmacological and non-pharmacological interventions in management of STEMI are crucial.

Table 20.6 Fibrinolytic agents used in management of STEMI

	Streptokinase	Tenecteplase (TNK-tPA)	Reteplase (rPA)	Alteplase (tPA)
Dose	1.5 million units IV given over 30–60 min	Single IV weight-based bolus 30 mg for weight <60 kg, 35 mg for 60–69 kg, 40 mg for 70–79 kg, 45 mg for 80–89 kg, and 50 mg for ≥90 kg	10 units + 10 units IV boluses given 30 min apart	Bolus 15 mg, infusion 0.75 mg/kg for 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over the next 60 min; total dose not to exceed 100 mg
Concomitant use of UFH	No[a]	Yes	Yes	Yes
Fibrin specificity	No	++++	++	++
Antigenic	Yes	No	No	No
Patency rate at 90 min (TIMI 2 or 3 flow)	60–68 %	85 %	84 %	73–84 %

Modified from 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

UFH unfractionated heparin

[a]Unless there is a high risk for thromboembolism (e.g., large anterior MI, LV thrombus, atrial fibrillation, previous thromboembolism)

20.4.3.1 Inhibition of the Renin-Angiotensin-Aldosterone System

An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 h to all patients with anterior STEMI, congestive heart failure, or an ejection fraction less than or equal to 40 %, unless contraindicated. Lisinopril, enalapril, ramipril, benazepril, and captopril are examples of most commonly used ACE inhibitors. If there is intolerance to ACE inhibitors, an angiotensin II-AT_1 receptor blocker (ARB) should be given, e.g., losartan, valsartan, and candesartan. An aldosterone antagonist should be given to all patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta-blocker and who have an ejection fraction less than or equal to 40 % and either symptomatic heart failure or diabetes mellitus [30] (Chap. 36).

20.4.3.2 Beta-Blockers

Early use of beta-blockers in STEMI has been documented to reduce early and late mortality in multiple clinical trials. Perhaps reduction of reinfarction rates and cardiac arrest is the main cause [63] (Chap. 5).

According to current guidelines, oral beta-blocker therapy (e.g., metoprolol, carvedilol, bisoprolol) should be initiated in the first 24 h for patients who do not have evidence of (1) heart failure, (2) low cardiac output state, (3) increased risk of cardiogenic shock, or (4) other relative contraindications to beta-blockade (heart block, active asthma, or reactive airway disease). Intravenous beta-blockers could be given if the patient is hypertensive and does not have any of the aforementioned conditions.

Beta-blockers should be continued during and after hospitalization for all patients with STEMI who have no contraindications to their use. If there were initial contraindications to beta-blockers in the first 24 h after STEMI, this should be reevaluated to determine their subsequent eligibility. The long-term duration of routine beta-blocker therapy after uncomplicated MI in patients without HF or hypertension has not been prospectively studied. The current practice guidelines recommend a 3-year treatment course, unless left ventricular ejection fraction is impaired or ongoing angina occurs [30].

20.4.3.3 Nitrates

Nitrates may be helpful in managing angina-type chest pain in patients with coronary disease in vascular beds other than the infarct-related artery. Patients with vasospastic angina may particularly benefit from nitrates. Other than for symptom management, nitrates do not affect long-term outcomes of coronary patients, and there is no role for the routine use of oral nitrates in the convalescent phase of STEMI [30].

20.4.3.4 Calcium Channel Blockers

There is no beneficial effect on infarct size or the rate of reinfarction with the use of calcium channel blockers during either the acute or the convalescent phase of STEMI. Calcium channel blockers can be used to relieve ischemia, lower blood pressure, or control the ventricular response rate to atrial fibrillation in patients who are intolerant of beta-blockers; the most commonly used agents are amlodipine and nifedipine. Control of ventricular response rate to atrial fibrillation can be achieved with verapamil or diltiazem (Chap. 37). Caution is advised for those who have underlying left ventricular dysfunction [30].

20.4.3.5 Statins

High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 h of presentation. Statin

therapy after STEMI appears to be beneficial even in patients with baseline low-density lipoprotein levels <70 mg/dL [30]. Atorvastatin, rosuvastatin, and simvastatin are among the most commonly used (Chap. 28).

20.4.3.6 Counseling, Education, and Cardiac Rehabilitation

Prior to discharge from the hospital, all patients treated for STEMI have to be educated about physical activity; lifestyle modifications including dietary counseling, smoking cessation, influenza vaccination, weight management, and control of blood pressure; modification of lipid profile; treatment of depression; and sexual counseling. Some evidence has shown that behavior changes in addition to early postdischarge follow-up after recovery from STEMI are linked to improved outcomes.

Referral to a cardiac rehabilitation program with supervised physical exercise and an educational component has been recommended for most STEMI patients after discharge. The objectives of these programs are to increase functional capacity, reduce and improve anginal symptoms, reduce disability, improve quality of life, modify coronary risk factors, and reduce morbidity and mortality rates. Even in the setting of contemporary reperfusion and cardioprotective drug therapies, exercise-based cardiac rehabilitation programs improve clinical patient outcomes; current practice guidelines list referral to a cardiac rehabilitation program as a class I recommendation [30, 64, 65].

20.4.4 Complications of STEMI

See Table 20.7 for summary of complications following STEMI.

Table 20.7 Common complications following STEMI

Hemodynamic complications	Electrical complications
• Cardiogenic shock	Bradyarrhythmias
• Right ventricular infarction	• Sinus bradycardia
• Free left ventricular wall rupture	• Second-degree atrioventricular block
• Acute mitral regurgitation	• Complete heart block
• Ventricular septal rupture	• Bundle branch block
	Tachyarrhythmias
	• Supraventricular arrhythmias (including atrial fibrillation)
	• Ventricular tachyarrhythmias (ventricular tachycardia and ventricular fibrillation)

20.5 Concluding Remarks

Acute myocardial infarction occurs because of disruption of a vulnerable atherosclerotic plaque. The location of the plaque, the degree of inflammation within the plaque, and the integrity of the fibrous cap on the plaque are factors that determine the risk of plaque rupture, hence development of myocardial infarction. When intracoronary thrombus forms, it may obstruct the coronary lumen entirely, leading to STEMI or sudden cardiac death; lesser severe obstruction may result in no symptoms, unstable angina, or NSTEMI.

It is essential that initial assessment and management be rapid but methodical and evidence based. Early revascularization is the mainstay of improving outcomes. PCI supported by appropriate antithrombotic therapy is the preferred approach when rapidly available. Guideline-directed medical therapy, secondary prevention, and lifestyle modification complement successful long-term management.

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Chapter 21
Pathophysiology and Lifetime Risk Factors for Atherosclerosis and Coronary Artery Disease in Women and in the Elderly

Stacy Westerman, Niels Engberding, and Nanette K. Wenger

Abstract Heart disease is the leading cause of death in the United States for both men and women, and it is the major cause of morbidity, mortality, and health-care utilization for the elderly. Women and the elderly are two populations that have been underrepresented in cardiology research, and this has been associated with underrecognition and undertreatment of coronary heart disease (CHD) in these populations. There are unique considerations in the risk factors and pathophysiology of CHD in women and the elderly. Many traditional cardiovascular risk factors confer a greater risk of the development of CHD in women, and there are unique risk factors including menopausal changes and pregnancy-associated events. Uncommon coronary and cardiovascular events including coronary dissection, stress cardiomyopathy, and coronary plaque erosion more frequently occur in women. The elderly also have unique risk factors for CHD, including arterial stiffness and frailty. Comorbidities and pharmacotherapy and interventional risks can influence disease course and treatment decisions. Increased attention to the distinctive risk factors for CHD and the unique pathophysiologic features in women and the elderly can enhance our understanding of CHD in the broader population with the goal of improving outcomes.

Keywords Atherosclerosis • Sex differences • Risk factors • Hormone replacement • Microvascular disease • Women • Elderly • ACS • CHD • Diabetes • Hypertension

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21.1 Introduction

Women and the elderly are two populations that have been traditionally underrepresented in cardiology clinical trials, and this has been associated with underrecognition and undertreatment of coronary heart disease (CHD) in these populations. There are unique factors in the risk for CHD and the pathophysiology of CHD in women and in the elderly that deserve attention. This chapter will review those features of CHD in these two populations.

21.2 Coronary Heart Disease in Women

21.2.1 Background Information

Heart disease is the leading cause of death in the United States for both men and women, accounting for more than 20 % of all deaths [1]. The prevalence of CHD in women is considerably less than that in men prior to the age of 50. As women age their incidence of CHD rises significantly, nearing equal prevalence rates to men in their seventh decade of life [2]. Though awareness of heart disease as a woman's major health issue is improving, almost 50 % of women remain unaware that heart disease is their leading cause of death [3]. Women have been traditionally underrepresented in cardiology clinical trials, longitudinal studies, and basic research, and this has been associated with underrecognition and undertreatment of CHD in women [4]. While many features of coronary disease are shared between the sexes, both risk factors for and manifestations of CHD differ in significant ways between women and men. A greater understanding of these differences can lead to more appropriate identification and management of CHD in women, with the goal of better prevention and outcomes.

21.2.2 Sex Differences in CHD Risk Factors

It has been recognized for decades that differences in the prevalence of major cardiovascular risk factors do not fully explain the observed differences in CHD manifestations between the sexes [5]. Both sex differences in the ways that established risk factors contribute to CHD risk, and risk factors unique to women are relevant.

21.2.2.1 Traditional CHD Risk Factors

Smoking: Although the annual smoking prevalence has declined more than 50 % from 1965 to 2009, the rate of decline has been greater among men than women [6]. Cigarette smoking still causes about one in every five US deaths, and approximately

30 % of smoking-related deaths are due to CHD. There are conflicting data on whether female smokers have a higher likelihood of acute myocardial infarction (AMI) [7], but epidemiologic data show that female smokers are more likely to develop CHD (relative risk ratio of 25 %) and to die from ischemic heart disease compared to their male counterparts. Benefits of smoking cessation accrue equally to women and men, with excess cardiovascular risk caused by smoking returning to level of never smokers 10–14 years following cessation [8].

Hypertension: The current prevalence of hypertension in US adults is 33 % and expected to rise to >40 % by 2030. The prevalence is greater in men than women under the age of 45; similar at ages 45-65, and rates in women are greater than men after age 65. More than 80 % of women over age 75 have hypertension. The highest prevalence is in non-Hispanic black women, 45 % of whom have hypertension with earlier onset and less favorable control [9]. Hypertension appears to confer a greater risk of CHD for women than men [10] (Chap. 30).

Physical inactivity: Physical inactivity is a causative factor for 12.2 % of the global burden of myocardial infarction. Across the age spectrum as early as grade school, girls and women are more likely to self-report and to objectively measure higher rates of physical inactivity [1]. Exercise decreases the rates of diabetes, lipid levels, and diastolic blood pressure. There is a consistent decrease in CHD incidence for women across increasing levels of physical activity [11], and the cardiovascular health benefits from physical activity are greater for women than men [12].

Diabetes mellitus: Up to 80 % of deaths in people with diabetes are due to cardiovascular causes. Diabetes increases the risk of developing and dying from cardiovascular disease more significantly for women than men. Women with diabetes have a 44 % higher risk of incident CHD than diabetic men [13]. Both diabetic women and men die younger than their nondiabetic counterparts, but this difference is greater for women [1]. While men with diabetes exhibited a 43 % relative reduction in age-adjusted mortality from 1971 to 2000, women did not show any reduction; in contrast, the difference in mortality rates between diabetic and nondiabetic women doubled in these years [14].

Lipids: Elevated LDL levels impart a similar increased risk of CHD in women and men. LDL levels show a dramatic rise in menopausal women, while HDL levels decline. The protective effects of HDL may also be lessened in the menopausal years [15, 16]. Elevated non-fasting triglyceride levels are associated with increased risk of MI, CHD, and death for both women and men, but the hazard ratios are greater for women [17] (Chaps. 25 and 28).

Obesity and metabolic syndrome: Metabolic syndrome increases risk of CHD and overall mortality. While much of the increased coronary risk of obesity is due to the influence of adiposity on blood pressure, lipid levels, and blood glucose levels, there appears to be an independent effect of obesity, with increased risk at every increased level of obesity [18, 19]. Compared with men, women with BMI >30 have a higher relative risk of CHD [20]. 34.9 % of US adults are obese, with rates of obesity higher in women in each age group [21].

21.2.2.2 CHD Risk Factors Unique to Women

Menopause and accelerated risk factors: The effects of endogenous estrogen appear protective; proposed mechanisms include indirect effects, such as beneficial effects on insulin sensitivity, lipid profile, hypertension, and obesity; and direct effects on the vascular wall include regulation of vasomotor tone and inhibition of smooth muscle cell proliferation [22, 23]. At menopause, the level of endogenous estrogen drops to about one-tenth the premenopause level. Though it is difficult to dissociate the influences of chronologic aging from those of menopause on cardiovascular health, the hormonal changes of menopause independently have a negative effect on HDL levels, body fat distribution, and central adiposity, as well as vascular abnormalities including active progression of atherosclerotic lesions [24, 25].

Menopausal hormone therapy (MHT): Despite this protective effect of endogenous estrogen, the Women's Health Initiative study showed that combination menopausal hormone therapy (estrogen plus progestin) increased CHD events, while unopposed estrogen therapy provided no benefit [26]. More recent data suggest that newly menopausal women exposed to hormone therapy may not have this increased risk; this is dubbed "the timing hypothesis" and proposes that the effects of exogenous estrogen depend on the underlying health of the vasculature [27, 28]. These results can provide reassurance for the short-term treatment with MHT of postmenopausal symptoms in women with recent menopause, but do not lend support for the use of MHT for the primary or secondary prevention of CHD. The 2013 US Preventive Services Task Force statement regarding MHT recommends against its use for the prevention of chronic conditions in postmenopausal women [29].

Additional female-specific risk factors: Autoimmune rheumatic disease is more common in women, and it is associated with higher rates of CHD and accelerated atherosclerosis [30]. Pregnancy-related events including preeclampsia, gestational diabetes, and gestational hypertension all increase the risk for future cardiovascular events [31]. Depression is a risk factor for CHD and has been shown to confer higher risk of cardiovascular events and death in women, especially younger women [32].

Future directives: Traditional methods of assessing risk of future coronary events may be inadequate in women. The Framingham risk score underestimates subclinical atherosclerosis risk in asymptomatic women [33]. When considering a woman's cardiovascular risk, clinicians should screen for nontraditional factors that increase a woman's CHD risk including pregnancy-related events, menopausal status, and autoimmune diseases [31].

21.2.3 Sex Differences in Pathophysiology of CHD

Atherosclerotic cardiovascular disease affects both sexes, but additional mechanisms of coronary pathophysiology predominate in women. While some of these mechanisms may be associated with the atherosclerotic process, others affect women disproportionately for unidentified reasons (Table 21.1).

Table 21.1 Pathophysiology of CHD in women: unique features

Acute coronary syndrome	Plaque erosion occurs more frequently in younger women than in men. Unlike in plaque rupture, the plaque in erosion has a thickened fibrous cap and minimal calcification. Women present more often than men with NSTEMI, rather than STEMI
Microvascular coronary dysfunction	Typical angina with positive ischemic stress testing in the absence of significant epicardial disease. Independently associated with acute cardiovascular events
Stress cardiomyopathy	Cardiac event mimicking AMI in the absence of obstructive CAD, typically with mid- and distal left ventricular akinesis. Predominant in postmenopausal women
Spontaneous coronary artery dissection	Up to 30 % of cases are peripartum, thought to be related to increased hemodynamic stress on coronary arterial wall
Pregnancy-related MI	Pregnancy increases risk of AMI by three- to fourfold. Most common causes are coronary artery dissection, atherosclerosis, and thrombus
Combined oral contraception and CHD	COC is contraindicated in women with known ischemic coronary disease, current smokers of >15 cigarettes/day, uncontrolled hypertension, and those with multiple risk factors for CHD

Atherosclerosis and acute coronary syndrome: Atherosclerotic heart disease is initiated by chronic minimal injury to the arterial endothelium due to patterns of blood flow. Over time there is subintimal and medial accumulation of macrophages and lipids. This leads to alterations in platelet function, growth factor release, smooth muscle cell proliferation, and the development of arterial plaques [34]. Established risk factors for CHD potentiate the initial endothelial injury and increase the rapidity of progression of atherosclerotic plaques [35]. These plaques can cause stable ischemic heart disease or the more abrupt phenomenon of acute coronary syndrome (ACS), comprised of unstable angina, AMI, and sudden coronary death (Chaps. 19 and 25).

Most cases of ACS are due to sudden luminal thrombosis, which in up to 70 % of cases is due to plaque rupture [36–38]. The primary features of a plaque vulnerable to rupture are a large lipid core, a high macrophage content, and a thin fibrous cap [35]. In 25–30 % of ACS, the thrombosis is due to superficial erosion of a plaque that is rich in smooth muscle cells and proteoglycans with a thickened fibrous cap and minimal calcification [39, 40]. Plaque erosion is more common in women than men and is the primary cause of acute coronary thrombosis in women less than 50 years of age with sudden coronary death. In women older than age 50, plaque rupture remains the dominant mechanism [39].

It is unknown why younger women are more prone to plaque erosion. It has been proposed that estrogen plays a role in stabilizing atherosclerotic plaques via changes in the fibrous cap and the composition of the plaque core, leading to less vulnerable plaques in younger women [41]. The mechanism that leads to plaque erosion is unknown; theories include coronary vasospasm as an inciting event [36] and a higher thrombogenic potential in women. Smoking is an independent risk factor for plaque erosion [40, 42].

Microvascular coronary dysfunction: There are also sex differences in the coronary microvasculature. The phenomenon of typical anginal symptoms with positive ischemic stress testing in the absence of significant epicardial disease has been described as early as the 1960s [43]. Labeled "syndrome X" in 1973 [44], this entity has become further defined as microvascular angina or microvascular coronary dysfunction (MCD) when there is evidence of vasomotor abnormalities. In MCD the coronary microcirculation, which regulates myocardial perfusion, does not adequately respond to changes in myocardial oxygen requirements [45] due to altered endothelial tone, altered response to vasodilator stimuli, and adverse structural changes [46].

Women referred for coronary angiography for evaluation of chest pain are more likely than men to have angiographically normal epicardial coronary arteries [47]. In the National Heart, Lung, and Blood Institute (NHLBI) Women's Ischemia Syndrome Evaluation (WISE) study, up to half of such women had evidence of microvascular dysfunction [48]. Once thought to be a benign diagnosis, coronary endothelial dysfunction is independently associated with acute cardiovascular events [49], with an annual adverse cardiac event rate of 2.5 % [46].

The sex difference in MCD is not well understood. Hypotheses include relative estrogen deficiency in the perimenopause and menopausal periods and higher levels of chronic inflammation in women as causes of endothelial dysfunction [50].

Stress cardiomyopathy: Also referred to as takotsubo cardiomyopathy, transient apical ballooning, or broken heart syndrome, stress cardiomyopathy is a cardiac event mimicking AMI in the absence of obstructive atherosclerotic coronary artery stenosis. The distinctive and most common contraction abnormality is mid- and distal left ventricular akinesis or dyskinesis with preserved basilar function, but alternate wall motion abnormalities including right ventricular dysfunction have been described [51]. There is commonly a stressful trigger, either emotional or physical, though infrequently no trigger is identified. The incidence is estimated to be 1–2 % of patients presenting with AMI [52]. Case series document up to a 90–96 % female predominance with a mean age of 68 years [51].

The pathophysiology is not well understood. Proposed mechanisms include catecholamine toxicity and excessive sympathetic stimulation, but elevation in circulating catecholamines has not been a consistent finding. Other potential mechanisms include an increased density of sympathetic nerve endings at the LV apex, multivessel epicardial spasm, or microvascular dysfunction, possibly related to sympathetic hyperactivity. As stress cardiomyopathy is predominant in menopausal women, it has been theorized that estrogen plays a protective role on coronary vasoreactivity, in part via vasodilatory properties, and the decrease of estrogen in menopause leaves the myocardium more susceptible to endothelial dysfunction [52].

Spontaneous coronary artery dissection (SCAD): SCAD is another cause of ACS occurring primarily in young, healthy women. First described in 1931, it is a rare clinical phenomenon, its incidence ranging from 0.1 to 1.1 % [53, 54]. The mean patient age is 35–45 years, and over 70 % of cases occur in women. SCAD can be categorized as nonatherosclerotic or atherosclerotic in origin. Nonatherosclerotic associations include the peripartum state, extreme exercise, connective tissue disease such as fibromuscular dysplasia, Marfan's syndrome and Ehlers-Danlos syndrome, various vasculidities, and idiopathic [38, 55, 56].

Up to 30 % of cases occur peripartum, most frequently in women without risk factors for CHD. It is proposed that peripartum SCAD is due to the normal physiology of pregnancy, in which cardiac output and total blood volume are elevated and estrogen levels are higher. The increased estrogen causes hypertrophy of smooth muscle cells with loosening of the intercellular matrix, which in the setting of increased cardiac output and blood volume places increased stress on the coronary arterial wall [57].

Pregnancy-related AMI: Pregnancy increases the risk of AMI by three- to four-fold in age-matched women, though it remains a rare event, occurring in 3–10 per 100,000 deliveries [58]. The anterior wall of the left ventricle is most commonly affected in pregnancy-associated AMI; serious complications such as cardiogenic shock and ventricular arrhythmias are not uncommon.

The most common etiology of AMI in pregnancy is coronary artery dissection (up to 43 %), followed by atherosclerotic disease (27 %) and thrombus without underlying atherosclerosis. Vasospasm and stress cardiomyopathy are other presenting causes [59]. Women tend to present with AMI in the third trimester or postpartum period, though atherosclerotic-related AMI can occur any time during pregnancy.

The pathophysiology of coronary dissection in pregnancy is thought to be due to hormonal changes, which lead to alterations in the endothelium, compromising the integrity of the arterial wall while under the hemodynamic stresses of pregnancy. The increased risk of coronary thrombosis in the absence of atherosclerosis is attributed to the hypercoagulable state of pregnancy. Vasospasm is theorized to be secondary to increased catecholamine release and an increase in vascular reactivity to angiotensin II [59, 60] (Chaps. 60 and 61).

Combined oral contraceptive (COC) use and CHD: COC with estrogen and progesterone causes an increased risk of AMI. A recent Danish cohort study based on data from national registries shows a relative risk for myocardial infarction of up to 4.3 for the highest doses of estrogen. This risk declines with lower doses of estrogen and rises dramatically with age and for women with other risk factors for CHD [61, 62]. The risk to young, healthy women, especially at the lower doses of estrogen currently used, is negligible. Due to this link, COC is contraindicated in women with known ischemic coronary disease, current smokers of >15 cigarettes/day, uncontrolled hypertension, and those with multiple risk factors for CHD [63].

The link between COC and AMI is not well understood. Newer data show the increased risk does not persist when the use of COC is stopped, suggesting that atherosclerosis is not the mechanism of increased risk [64], but rather that a thrombotic predisposition is at play.

21.3 Coronary Heart Disease in the Elderly

21.3.1 Background Information

Cardiovascular disease is the major cause of morbidity, mortality, and health-care utilization for the elderly [65]. The burden of CHD rises with the age of a population, both in prevalence and severity of disease. By age 80 men and women have a similar

prevalence of symptomatic CHD, up to 20–30 % [66]. While men and women over the age of 80 years comprise only 5 % of the population, 20 % of MI-related hospitalizations and 30 % of MI-related hospital deaths occur in this population. Elderly adults have more left main coronary disease, multivessel disease, and coronary calcification compared to younger patients [67]. Despite this increased burden of CHD, elderly persons are significantly underrepresented in cardiovascular research studies. Limited trial data leads to uncertainty of the benefits and risks of pharmacologic and invasive treatments for elderly CHD patients, resulting in a disproportionately low use of modern cardiovascular advances in this population.

21.3.2 Risk Factors for CHD in the Elderly

For underlying reasons that are poorly understood, it appears that coronary atherosclerosis is inevitably associated with aging. In the absence of a fatal illness such as infection or malignancy, CHD seems the main determinant of the maximal life span of a human being. This is supported by the results of postmortem examinations of centenarians, all of whom died of cardiovascular causes [68]. The aging process is frequently defined as a progressive decline in the ability of an organism to withstand environmental stressors. Thus, aging of the cardiovascular system likely involves the combination of prolonged exposure to pro-atherogenic factors and a reduction in the anti-atherosclerotic function of the vascular wall. It is recommended to initiate primary prevention of cardiovascular disease early in life for exactly this reason; nevertheless, it is never too late to institute primary or secondary CHD prevention strategies.

Established cardiovascular risk factors for the general population are similarly relevant for risk assessment in the elderly. Modification of the traditional cardiovascular risk factors of cigarette smoking, physical inactivity, diabetes, hypertension, obesity, and abnormal lipids provides benefits of secondary prevention for elderly adults as well as the younger population. Owing to their increased absolute CHD risk, beneficial interventions selectively advantage elderly patients [67]. Primary prevention efforts are likewise similar for elderly patients but with attention to the higher rates of adverse pharmacologic events at elderly ages. For example, the 2014 JNC eight guidelines for hypertension recommend a treatment goal blood pressure of <150 mmHg/90 mmHg for men and women over age 60 given the lack of evidence for a benefit with more aggressive blood pressure reduction and a potential for adverse drug effects with antihypertensive medications [69]. Similarly, the 2013 guidelines on cholesterol management include no definitive recommendations on statin therapy for primary prevention in people over age 75 due to a lack of clinical evidence [70]. These are discussed in Chaps. 2 and 30.

Some age-specific CHD risk factors should be considered when evaluating the elderly population.

Arterial stiffness: Aging is associated with structural and functional changes in the vascular wall. These include degradation of elastin, smooth muscle necrosis,

and increases in collagen and calcification, leading to thickening of the arterial wall. The end result is decreased vascular distensibility and elevated arterial stiffness [71, 72]. These changes contribute to the development of systolic hypertension, increased left ventricular afterload, left ventricular hypertrophy, increased myocardial oxygen demand, and impaired coronary perfusion.

The age-related change of arterial stiffness is an independent predictor for CHD events, as well as for other manifestations of cardiovascular disease and mortality [73–75]. Arterial stiffness can be reduced by nonpharmacologic and pharmacologic interventions including exercise, heart healthy dietary changes, and blood pressure control; research is ongoing as to whether reduction in arterial stiffness independently confers CHD event risk reduction [75]. A surrogate for arterial stiffness is aortic pulse wave velocity, which can be measured noninvasively.

Frailty: Frailty is a clinical condition frequently seen in the elderly population. Its estimated prevalence ranges from 10 to 60 % depending on the population studied [76]. While frailty has been increasingly investigated, a universal definition has not been established. It is generally accepted as a syndrome characterized by decreased physiologic reserve and increased vulnerability to stressors, such that even minor stressors can lead to disproportionate declines in health status [77].

Frailty is a risk factor for the development of CHD and for CHD-related mortality; likewise, CHD and even subclinical cardiovascular abnormalities can be associated with frailty and the development of frailty [78]. A common underlying biologic pathway has been proposed linking the disease processes of CHD and frailty. Dysregulation of the hormonal, immune, and endocrine systems with a resulting increase in inflammatory cytokines has been hypothesized as one possible common mediating pathway [76]. Adverse behaviors related to frailty such as physical inactivity can also act as barriers to the promotion of anti-atherogenic lifestyle changes.

Lipids: The effect of lipid profiles on the cardiovascular risk of the elderly appears to differ from that of a younger population. Neither high total serum cholesterol nor high LDL levels predict cardiovascular mortality in the very elderly population (>85 years), but low HDL levels remain a risk factor for CHD death [79, 80]. LDL likely remains a risk factor for CHD in the elderly, but high LDL levels lose predictive value for CHD mortality due to an association between low LDL levels and cancer [81]. This association is not well understood. Research has not implicated statins nor genetically low LDL cholesterol levels as causative of this relationship [82, 83].

The 2013 ACC/AHA guidelines for statin therapy recommend moderate-intensity statin use for those greater than 75 years of age with clinical CHD. Due to limited randomized controlled trial data on patients older than 75 without clinical CHD, no definitive recommendations for statin therapy were made for primary prevention [70].

Depression: Depression is a common illness in the elderly, with depressive symptoms occurring in 19–30 % of elderly people. Depressive symptoms have been identified as an independent risk factor for the development of CHD in elderly Americans, with an increased risk of up to 40 %, as well as an increase in all-cause mortality [84]. Proposed biologic mechanisms include increased sympathetic stimulation, platelet activation and levels of fibrinogen, and adverse changes in lipid

Table 21.2 Unique features of CHD in the elderly

Diagnostic delay of CHD	Atypical symptoms; presence of confounding factors including atypical presentation and multiple comorbidities
Extent of CHD	Elderly are more likely to have more diffuse and severe atherosclerotic disease and more calcific atherosclerosis. More likely to present with NSTEMI than STEMI
Pharmacotherapy	Drug-drug interactions and alterations in drug metabolism can limit medical treatment options
Revascularization	The lack of a large body of evidence for interventions in the elderly and very elderly can lead to a treatment gap

metabolism. Other associated behaviors that likely contribute to development of CHD and adverse outcomes include physical inactivity and medication nonadherence, both of which are higher in depressed patients [85].

21.3.3 Pathophysiology of CHD in the Elderly

The primary etiology of CHD in the elderly is coronary atherosclerotic disease. While the pathophysiology of atherosclerosis is the same at younger and elderly age, particular features contribute to more extensive disease and worse outcomes in the elderly (Table 21.2).

21.3.3.1 Diagnosis of CHD

The diagnosis of CHD at elderly age can be complicated by atypical presentations of CHD and by other cardiac or noncardiac conditions that can produce myocardial ischemia and angina. Elderly patients with ACS are more likely to present with atypical symptoms including atypical chest pain, dyspnea, diaphoresis, nausea, and syncope [86, 87]. Decreased physical activity, orthopedic ailments, sensory deficits such as hearing and vision loss, cognitive decline, and other chronic diseases such as heart failure, lung disease, cerebrovascular disease, and neuromuscular disorders can all mask or confuse symptoms. While elderly patients develop ACS due to plaque rupture, they are more likely than younger patients to develop ACS due to type II myocardial infarction, i.e. MI due to an ischemic imbalance [88]. Comorbidities that lead to a mismatch between myocardial oxygen supply and demand include aortic valve disease, hypertensive heart disease, cardiac arrhythmias, anemia, and acute illness in the setting of atherosclerotic disease, all of which are more prevalent in an elderly population [89]. Attention to the underlying etiology is crucial in management of type II MI. These factors contribute to a delay in diagnosis of both chronic CHD and acute complications of CHD, which leads to worse outcomes due to the lack of timely and appropriate interventions [88].

21.3.3.2 Treatment Concerns

Pharmacotherapy: Elderly patients have altered pharmacokinetic and pharmacotherapy responses to drugs. This is due to changes in drug distribution, metabolism, and excretion, as well as physiologic changes related to aging that affect end-organ responsiveness to medical treatment [90]. Compounding the altered pharmacology of drugs in the elderly is the frequency of polypharmacy, which can lead to significant drug-drug interactions. While most cardiovascular drugs can be used safely in the elderly, caution must be applied, especially to drugs with a higher adverse effect profile, such as anticoagulant and antithrombotic agents, antihypertensives, and diabetic therapies [90, 91]. While judicious use of cardiovascular drugs in the elderly is imperative, this should not interfere with evidence-based treatments for CHD.

Revascularization: The cumulative burden of more years lived with cardiovascular risk factors is not without consequence. As described above, the elderly are more likely to have more diffuse and severe atherosclerotic disease and more calcific atherosclerosis [92]. While earlier data from the 1980s and 1990s showed that percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) had significantly higher rates of procedural complications in the elderly with less successful outcomes compared to younger patients [93, 94], more current data show both an increase in rates of revascularization in the elderly and the very elderly and declining interventional risks [95, 96].

Elderly patients can benefit from revascularization compared to medical management in many domains, including survival, major adverse cardiac events, functional capacity, quality of life, and health status [94, 97]. Newer techniques such as the transradial approach for catheterization and hybrid coronary revascularization have been shown to be safe and effective in the elderly, with lower periprocedural complications compared to older interventional techniques [98, 99]. Discussions of treatment strategy in the elderly should utilize a patient-centered team approach with an understanding of patient goals and expectations, and an appreciation that patients with the most severe disease often derive the most benefit from revascularization strategies.

21.4 Concluding Remarks

Heart disease is the leading cause of death in the United States for both men and women. Research in cardiovascular disease has focused mainly on nonelderly men, often excluding women and the elderly and very elderly. We are beginning to appreciate the ways in which these populations differ in both risk factors for and manifestations of CHD. Traditional cardiovascular risk factors are relevant, but there are other risk factors pertaining uniquely to either women or the elderly that must also be investigated when evaluating an individual's cardiovascular risk. CHD can be manifest as atherosclerosis in women and the elderly but can also present in less

common ways, particularly in these populations. An increased awareness of these issues can lead to improvement in diagnosis and treatments and realignments in research to advance our understanding of CHD and eventually improve outcomes for all populations.

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Chapter 22
Medical Management of Chronic Stable Angina

John D. Parker

Abstract Chronic stable angina remains an important cause of morbidity in patients with coronary artery disease (CAD). Although dramatic improvements in surgical and percutaneous revascularization techniques have occurred, many patients continue to have symptoms of angina and benefit from pharmacologic therapy. Traditional pharmacologic approaches to angina are reviewed along with novel and more recently introduced therapies. The presence of prior or concurrent conditions such as a prior myocardial infarction and/or significant hypertension plays important roles in the choice of antianginal class. In some patients, symptoms persist, and a second class of agent may be helpful; however, in general, a second agent should only be added once maximally tolerated doses of monotherapy have been utilized. It is emphasized that patients with stable angina, particularly those with preserved left ventricular systolic function, have an excellent prognosis. Those patients who respond well to pharmacologic antianginal therapy often do well without invasive intervention.

Keywords Coronary artery disease • Angina • Drug therapy • Exercise capacity

22.1 Introduction

Symptoms caused by stable coronary artery disease (CAD) continue to be an important clinical problem. Angina pectoris is a classic symptom of CAD, first described in the late eighteenth century by William Heberden. He provided a remarkably accurate description of the symptom complex experienced by patients where myocardial blood flow is limited by the presence of obstructive CAD. In his words, this group of patients experiences "a painful and most disagreeable sensation in the breast which seems as if it would extinguish life if it were to increase or to continue." With respect to this symptom, he went on to say that those who suffer from it "are seized while

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they are walking (more especially if it be uphill, and soon after eating) … but the moment they stand still, all this uneasiness vanishes" [1]. The term angina derives from Latin where it means, literally, *pain*/infection of the throat, while pectus, also from Latin, translates to *chest*. Although angina pectoris was thought by Osler to be a "rare disease" at the end of the nineteenth century [2], it has been recognized as a common clinical condition for several generations of physicians.

Symptoms of angina are caused by an imbalance between myocardial oxygen demand and myocardial oxygen supply. The classic approach to the therapy of angina has been to reduce myocardial oxygen demand and/or increase oxygen supply. More recently, it has been recognized that the myocardial and symptomatic response to ischemia can also be modified by altering myocardial metabolism and energy substrate utilization or by altering myocardial cellular biochemical responses to ischemia. The latter approaches have opened new windows to our understanding of the myocardial response to "demand ischemia" and approaches to its treatment. Although lifestyle modifications, antiplatelet agents, lipid-lowering therapy, and other secondary prevention approaches are of importance in the management of patients with chronic stable angina, these will not be discussed in the current chapter and are covered in Chaps. 20, 21, 23, 28, and 29.

As the technical success and safety of coronary artery bypass surgery and percutaneous coronary intervention developed over time, the majority of physicians (and in many cases their patients) came to prefer mechanical revascularization procedures to pharmacologic approaches for the management of symptoms (Chap. 20). This therapeutic preference led to an enormous increase in the number of revascularization procedures during the last two decades of the twentieth century [3–7]. Despite the popularity and increasing technical sophistication of surgical and percutaneous interventions, a significant number of patients with CAD continue to have symptoms of angina. This fact is obvious to the busy clinician and is supported by the results of both epidemiologic studies [8–11] and clinical trials [12, 13]. Although most follow-up studies suggest that the prevalence of recurrent or residual angina is higher following PCI than after coronary artery bypass surgery [14], angina remains a clinical problem in many patients regardless of the revascularization approach.

22.2 The Management of Angina

This chapter will focus on the management of patients who have symptoms of angina (or angina equivalent dyspnea) in the setting of stable CAD. This discussion will not focus on the continued controversy of the role of pharmacologic versus interventional management approaches or on the choice of percutaneous versus surgical intervention (Chap. 23). However, there are many patients in which revascularization versus continued pharmacologic management is the correct choice. For example, patients who continue to have angina despite a concerted trial of pharmacologic therapy should be referred for coronary angiography with an eye toward

potential revascularization (Chap. 24). In contrast, there are many patients in whom mechanical revascularization is not possible, because of co-morbidities and/or the nature of their anatomy. It is this group of patients who represent a growing population that can benefit greatly from the pharmacologic, antianginal therapy.

22.3 The Goals of Medical Management of Angina

Effective pharmacologic management of symptomatic angina must start with the correct diagnosis and a complete history of the symptom complex. The differential diagnosis is broad and goes beyond the scope of the current discussion. However, it is incumbent on the prescriber to be aware of the differential diagnoses involved in the assessment of a chest pain syndrome and, importantly, to recognize situations in which true symptoms of angina are not secondary to obstructive CAD, for example, significant anemia or left ventricular outflow tract obstruction.

For decades, the only recognized therapy for angina was sublingual nitroglycerin and, during some periods, inhaled amyl nitrate. Classically, sublingual nitroglycerin has been used to treat spontaneous episodes of angina or provide relief from angina brought on by exertion. Despite the success of pro re nata sublingual nitrate therapy, the chronicity and disabling symptoms of angina demanded the development of long-acting therapy that could prevent the development of angina throughout the day. Initial attempts to develop therapies providing sustained improvement in the symptoms of angina involved the use of newly developed long-acting oral nitrates. Early reports of such therapy highlighted a host of problems related to the state of clinical trial development at that time [15]. These included difficulties in developing standardized testing and endpoints, the importance of placebo controlled approaches, and the need for adequate sample sizes. Although a number of candidate organic nitrates were tested, only isosorbide dinitrate, oral nitroglycerin, and pentaerythritol tetranitrate came to be accepted in clinical practice. Of note, concerns about their bioavailability [16] and recognition of the development of tolerance caused [17] continued controversy about their true therapeutic efficacy that was to continue for more than a quarter century.

Pharmacologic approaches to the therapy of exertional angina have classically involved the use of agents that reduce myocardial oxygen demand and/or increase myocardial oxygen supply in response to exercise. The traditional approach to the prophylaxis/prevention of angina includes the use of long-acting nitrates, beta-blockers, and calcium channel antagonists and did not see substantive change for more than 30 years. Newer agents that modify the balance between myocardial oxygen supply and demand include nicorandil, which is a nitric oxide donor and a potassium channel opener, as well as the sinus node inhibiting agent, ivabradine (Chaps. 50 and 52). Both of these agents are effective in the therapy of angina and are available in many countries (although not in North America). Another approach to the therapy of angina has been the use of agents that modify myocardial metabolism, reducing the utilization of fatty acids, thus favoring the oxidation of

glucose. Trimetazidine, a drug felt to have this mechanism of action, has been marketed as an antianginal drug in many countries since the 1970s, but evidence of its therapeutic efficacy is limited, and the drug has never been approved in North America (Chap. 17). Ranolazine is another effective antianginal agent now available in most countries. When originally introduced, ranolazine was also felt to be an inhibitor of myocardial fatty acid oxidation, although now its stated mechanism of action is inhibition of a late inward sodium channel, which favorably modifies myocyte cellular responses to ischemia.

Since the 1970s, drugs for the therapy of angina have received regulatory approval based on their ability to improve exercise duration in the setting of controlled clinical trials. In Europe, bicycle exercise testing protocols are more commonly employed, while in North America, treadmill exercise testing is used in studies leading to regulatory approval. Drugs approved for the therapy of angina produce modest increases in exercise time, usually less than a 1-min increase in exercise duration on treadmill exercise testing, as compared to placebo [18–24]. Despite the modest increase in mean exercise duration, some patients experience quite dramatic increases in exercise capacity in response to medical therapy. Importantly, all available classes of antianginal agents have similar effects on exercise duration. Therefore, there is no clear indication to choose one class versus another based on this outcome. In the past, drugs were approved based on their ability to improve exercise capacity as compared to placebo in the absence of other antianginal agents. More recent approvals have involved the testing of agents used in addition to specified background antianginal therapy. An important feature of the approval process used in the treatment of stable angina is that the drugs tested demonstrate efficacy throughout most of the day (in most cases between 8 and 12 h). This requirement reflects the desire of the pharmaceutical industry, as well as regulatory authorities, to provide drug therapy that improves the exercise tolerance throughout the day. This is a high standard, surpassing the requirements of drugs used in other disease states (such as chronic heart failure and pulmonary hypertension).

22.4 Organic Nitrates (Table 22.1)

Although nitrates have been used in the therapy of angina for more than a century, their mechanism(s) of action remains incompletely defined. As potent dilators of capacitance veins, they lower preload, reducing ventricular chamber volumes, which in turn lower myocardial oxygen consumption via reductions in systolic and diastolic wall stress. Nitrates also lower arterial blood pressure and increase the distensibility of conduit arteries, actions that also reduce oxygen consumption [25]. A common assumption is that nitrates improve coronary blood flow by dilating epicardial coronary arteries at sites of stenoses; however, there is little evidence that this plays an important role in their effects in the setting of chronic angina [26, 27]. There is also evidence in animal models, but not in humans, that the organic nitrates improve myocardial efficiency, decreasing oxygen consumption at any given level of myocardial work [28, 29].

Table 22.1 Pharmacologic characteristics of the common organic nitrates

	SL GTN	TD GTN	ISDN	IS-5-MN (phasic release)
Half-life	6–9 min	6–9 min	1–2 (4–5) h[a]	4–5 h
Elimination	Hepatic	Hepatic	Hepatic	Hepatic
Heart rate	↑	↔	↑	↔
Vascular resistance	↓↓	↔	↓	↔
Usual dosage (mg)	0.4–0.6 mg	0.2–0.6 mg/h (intermittent)	5[b]–30 mg TID (eccentric)	60–240 mg OD

SL sublingual, *TD* transdermal, *GTN* glyceryl trinitrate, *ISDN* isosorbide dinitrate, *IS-5-MN* isosorbide-5-mononitrate

[a]Half-life of active metabolite isosorbide-5-mononitrate

[b]5 mg ISDN may be administered sublingually for prevention of angina

For more than a century, sublingual nitroglycerin has been the classic therapy for acute attacks of angina. Many patients carry a sublingual preparation to be used in the event that they have the spontaneous occurrence of angina. Sublingual nitroglycerin, taken shortly before activity, is also very effective at increasing exercise tolerance. Although this prophylactic use was reported more than half a century ago, the development of new sublingual nitroglycerin preparations (sublingual sprays and aerosols) was associated with the completion of clinical trials confirming that such therapy leads to an impressive increase in exercise capacity in patients with angina [30]. Isosorbide dinitrate, in small doses (generally 5 mg tablets), can be used sublingually. It is occasionally prescribed to prevent symptoms before an activity likely to precipitate angina and can be helpful in certain patients with refractory effort angina [31].

A number of long-acting nitrates are available and approved for the therapy of chronic stable angina. These include transdermal nitroglycerin [20, 32], isosorbide dinitrate [33], and isosorbide-5-mononitrate [34, 35]. Short-acting formulations of isosorbide dinitrate are widely available; however, they are rarely used because of their short duration of action and requirement for multiple daily doses. While long-acting forms of isosorbide dinitrate continue to be marketed, there is no evidence to support their use. Transdermal nitroglycerin, when used intermittently, and isosorbide-5-mononitrate in prolonged or phasic release formulations are effective in the therapy of angina and are widely available. Oral nitroglycerin remains available in certain countries, but there is no clear evidence of therapeutic efficacy, and it is no longer recommended in the therapy of chronic angina. Pentaerythritol tetranitrate is another organic nitrate used in the therapy of chronic angina. However, lack of objective evidence of therapeutic efficacy led its withdrawal from the North American market. It continues to be available in many countries; however, the results of the largest clinical trial to date, the CLEOPATRA study, failed to demonstrate an improvement in exercise performance in 655 patients randomized to pentaerythritol tetranitrate as compared to placebo [36].

When administered using dosing regimens or formulations that lead to sustained plasma concentrations during the day, all nitrates are associated with the development

of tolerance [37]. Tolerance is referred to as the loss of both the hemodynamic and symptomatic effects of nitrates and is now widely recognized as a limitation of their continuous use. This phenomenon, until clearly recognized, led to earlier conclusions that long-acting nitrates were not effective in the chronic therapy of angina. Tolerance develops rapidly, within 24 h, but is also rapidly reversed. The latter observation led to the discovery that tolerance could be avoided with intermittent dosing regimens which allowed for a nitrate-free period each day. The mechanism(s) of nitrate tolerance has been the subject of debate for more than 30 years and has been discussed in detail elsewhere [38–40]. Many pharmacologic approaches have been explored in efforts to prevent tolerance; however, the only widely accepted approach has been the use of intermittent dosing regimens [25].

22.5 Beta-Adrenergic Blockers (Tables 22.2a and 22.2b)

Beta-adrenergic blockers were first approved for the therapy of angina in the mid-1960s, although controversy delayed their introduction in the United States. This class of therapy proved to be highly effective in the therapy of chronic angina [22, 23, 41–43]. Beta-blockers reduce myocardial oxygen demands by decreasing heart rate, blood pressure, and inotropic responses to exercise. By limiting the increase in heart rate in response to exercise, they can improve myocardial blood flow by increasing diastolic time intervals. A number of beta-blockers are available for the therapy of angina. The available agents have important differences in terms of pharmacokinetics, beta-1 receptor selectivity, routes of elimination, and lipophilicity. The choice of beta-blocker is driven primarily by pharmacokinetic properties and clinical characteristics of the patient. Once-daily preparations, in general, are preferred. Beyond that, the presence of chronic obstructive lung disease or diabetes favors the use of agents with beta-1 receptor selectivity. In those with significant renal insufficiency, beta-blockers that are eliminated primarily through the kidney should be avoided (Chaps. 5 and 8).

In the therapy of angina, it is important for the clinician to appreciate the wide variation in clinically effective doses. The pharmacokinetic properties of individual beta-blockers are quite variable, particularly in those that undergo primary hepatic

Table 22.2a Pharmacologic characteristics of common β-1-selective beta-adrenergic blockers

	Atenolol	Metoprolol	Bisoprolol	Acebutolol
Half-life (h)	6–9	3–4	10–12	3–4[a]
β-1 selectivity	+	+	+	+
Sympathomimetic activity	No	No	No	Yes
Lipophilicity	Low	Moderate	Moderate	Moderate
Elimination	Renal	Hepatic	Hepatic and renal	Hepatic and renal
Usual dosage (mg)	50–100 OD	50–100 BID	2.5–10 OD	200–600 BID

[a]Active metabolite of acebutolol (diacetolol) has a half-life of 8–12 h

Table 22.2b Pharmacologic characteristics of common nonselective beta-adrenergic blockers

	Propranolol	Timolol	Nadolol	Pindolol
Half-life (h)	2–5	3–5	14–25	3–4
β-1 selectivity	0	0	0	0
Sympathomimetic activity	No	No	No	Yes
Lipophilicity	High	Moderate	Low	Moderate
Elimination	Hepatic	Hepatic	Renal	Hepatic and renal
Usual dosage (mg)	20–80 mg QID[a]	2.5–10 OD	40–160 OD	200–600 BID

[a] alternative-dosing regimen is BID

elimination. Further, the effect of beta-blockers is dependent on the degree of underlying sympathetic activity and the sympathetic response to exercise. In the majority of patients, dosing is determined by resting heart rate and blood pressure responses. However, it should be remembered, particularly in the therapy of angina, that resting heart rate is a poor indication of the effect of a given dose on the heart rate response to exercise. Since the impact of beta-blockers on the chronotropic response to exercise is a crucial determinant of their effectiveness in the therapy of angina, patients who have a poor clinical response to initial dosing should undergo either a walk test or formal exercise testing to assess their heart rate response during stress. In the past, beta-blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) were promoted for use in the setting of angina based on the assumption that they would be associated with less drug-induced fatigue; however, they appear to be less effective and are no longer in common clinical use.

22.6 Calcium Channel-Blocking Agents (Table 22.3) (See Also Chap. 37)

A number of the calcium channel antagonists are effective in the treatment of stable angina [41–51]. All calcium channel antagonists have a common mechanism of action which is their ability to block L-type calcium channels in smooth muscle and myocardium, reducing cytosolic concentrations of calcium. There are three different types of calcium channel antagonists that have different hemodynamic, chronotropic, and inotropic effects. Dihydropyridines have pronounced effects on peripheral resistance vessels but little effect on heart rate or the cardiac conduction system. Nifedipine was the first dihydropyridine introduced into practice, initially in short-acting formulations but now widely available in slow-release formulations that allow once-daily dosing. In its long-acting formulation, nifedipine is effective in the therapy of both angina and hypertension. Immediate-release nifedipine capsules remain available for the therapy of angina but are not recommended because of their tendency to precipitate pronounced hypotension and/or worsening angina [52, 53]. Amlodipine is another dihydropyridine that has been widely approved for the therapy of angina and hypertension. It is a once per day drug with a long half-life

Table 22.3 Pharmacologic characteristics of common calcium channel antagonists

	Nifedipine (GITS)	Amlodipine	Diltiazem (SR)	Verapamil (SR)
Half-life (h)	2–5	30–50	4–6	5–12
Elimination	Hepatic	Hepatic	Hepatic	Hepatic
Heart rate	↑	↔	↓	↓
Vascular resistance	↓↓	↓↓	↓	↓
Dosage (mg)	20–90 OD	2.5–10 OD	120–360 OD	180–360 BID

↑increase, ↓decrease, ↔no change

and is generally well tolerated. A number of other dihydropyridine calcium channel antagonists are available including felodipine, nicardipine, and nisoldipine; however, these drugs are not approved for the therapy of angina in most countries and, if used in short-acting formulations, can increase the frequency of angina. Diltiazem, a benzothiazepine, and verapamil, a phenylalkylamine, are also effective in the treatment of angina. Although they reduce peripheral vascular resistance, these drugs also have prominent electrophysiologic effects, reducing heart rate and prolonging atrioventricular conduction (Chap. 48). Short-acting formulations of diltiazem and verapamil are still available but rarely used for chronic therapy. Long-acting, once-daily formulations of diltiazem are commonly used in the therapy of angina, reducing heart rate, blood pressure, and inotropic responses to exercise. Verapamil, although it is an effective antianginal, is not commonly used in the therapy of angina, presumably because of its recognized prominent negative inotropic effects.

The mechanism(s) of action of calcium channel antagonists in the therapy of angina is complex and varies by class. The dihydropyridines do not reduce heart rate at rest or in response to exercise but lower myocardial oxygen demand by reducing both blood pressure and inotropic responses during exercise. Diltiazem and verapamil also lower blood pressure and inotropic responses to exercise with additional negative chronotropic responses that can reduce myocardial oxygen consumption while increasing coronary blood flow. Some studies have suggested that calcium channel antagonists can directly increase coronary blood flow [54–56], although there is little evidence that this plays a significant role in patients with stable angina. This is not a great surprise since coronary blood flow responses to drug therapy during exercise are complex with variable interactions between coronary perfusion pressure, myocardial oxygen demand, and diastolic time intervals, all of which are superimposed on the autoregulation of coronary blood flow. It has also been suggested that calcium channel antagonists, particularly the dihydropyridines, can improve coronary endothelial function via favorable effects on nitric oxide bioavailability; however, the clinical relevance of this has never been established [57]. There has also been speculation that dihydropyridines might inhibit the progression of atherosclerosis, but it has never been clear whether this represents a primary effect of the drug on vascular atheroma or an indirect effect related to blood pressure and shear stress [58–60]. There are no discernible differences in the efficacy of the calcium channel antagonists in the therapy of angina. Therapeutic choices within this class are driven primarily by decisions as to whether or not a negative chronotropic effect is desired or situations in which the presence of left ventricular dysfunction makes the use of agents with negative inotropic effects contraindicated.

22.7 Other Antianginal Agents

Nicorandil is a nicotinamide nitrate, effective in the therapy of exertional angina, which has been available for many years, although not in North America [61, 62]. Nicorandil is a nitric oxide donor, increasing the availability of cGMP, which causes relaxation of capacitance veins and dilation of conduit arteries. Nicorandil also opens mitochondrial K^+-ATP channels, which causes relaxation of both peripheral and coronary resistance vessels [63–66]. Of note, its effect as an agonist of myocyte K^+-sensitive ATP channels is responsible for its effects as a pharmacologic preconditioning agent [67]. However, as with all other preconditioning stimuli, it is not known if this effect persists during chronic therapy. In addition to its beneficial effects on the symptoms of angina, a large-scale clinical trial in patients with chronic CAD revealed modest improvements in long-term clinical outcome and confirmed its safety on this patient population [68].

Ivabradine belongs to a unique class of compounds that are selective sinus node inhibitors (Chaps. 1 and 48). The discovery of the existence and function of the cyclic nucleotide-gated I_f channel (the so-called inward funny channel), which mediates an inward, mixed Na^+/K^+ current, was followed by the recognition that this channel plays a critical role in the rate of sinus node repolarization [69–72]. Ivabradine is a selective inhibitor of this channel causing reductions in both resting and exercise-induced increases in heart rate [73]. Importantly, the drug has no effect on myocardial function or the peripheral vasculature. The I_f channel is also present in cells of the retina, and because of this, drugs like ivabradine can cause visual disturbances with increased sensitivity to bright light or the spontaneous sensation of light when no stimulus is present (these have been referred to as luminous phenomena or phosphenes) [71]. Visual disturbances were relatively common with earlier I_f channel inhibitors (e.g., zatebradine), but they are infrequent and usually transient with ivabradine [72–74]. Multiple studies have demonstrated the efficacy of ivabradine in the therapy of stable angina both as monotherapy and when given in addition to a beta-blocker, and the drug is approved for the therapy of angina in many countries [23, 74, 75]. Ivabradine has also been evaluated in patients with CAD and left ventricular dysfunction. In the BEAUTIFUL (mor*B*idity-mortality *E*v*A*l*U*a*T*ion of the *If* inhibitor ivabradine in patients with coronary disease and left ventric*UL*ar dysfunction) study, ivabradine had neutral effects on long-term outcome in patients with CAD and left ventricular dysfunction, although the subgroup with a baseline heart rate above 70 beats per minute did have a significant reduction in cardiovascular event rates [76]. In the SHIFT (*S*ystolic *H*eart failure treatment with the *If* inhibitor ivabradine *T*rial) study, therapy with ivabradine improved outcome in patients with chronic heart failure due to left ventricular systolic dysfunction and a baseline heart rate greater than 70 beats per minute [77]. Although the results of these studies have been controversial, with questions raised concerning the adequacy of the dose of concurrent beta-blockade, they were consistent with the hypothesis that resting heart rate has an important impact on long-term cardiovascular outcome and that rate-reducing therapy could have beneficial effects in patients

with coronary disease even in the absence of left ventricular dysfunction. This was the rationale for the SIGNIFY (*S*tudy assess*I*n*G* the morbidity-mortality be*N*efits of the *If* inhibitor ivabradine in patients with coronar*Y* artery disease) trial that randomized more than 19,000 patients with CAD and preserved left ventricular systolic function (ejection fraction >40 %) to ivabradine versus placebo on top of standard therapy. In this study, ivabradine had no effect on long-term clinical outcome [78]. However, in the subgroup of patients ($n = 12049$) with symptoms of angina classified as greater than or equal to Canadian Cardiovascular Society Class II, the primary endpoint (cardiovascular death or nonfatal myocardial infarction) was more common in the ivabradine group (relative risk of 1.18 as compared to placebo; Fig. 22.1) [78]. The implications of this finding are still being evaluated; however, they serve to emphasize that beneficial effects on long-term outcome cannot be assumed on the basis of beneficial effects observed in shorter studies using surrogate endpoints.

Trimetazidine is available in many countries, although not North America, for the treatment of stable angina in patients with coronary artery disease. Trimetazidine is believed to have a metabolic mechanism of action, inhibiting myocardial free fatty acid oxidation while increasing glucose metabolism, which increases the amount of ATP generated per molecule of oxygen (Chap. 17). It is an effective antianginal with no effect on heart rate, blood pressure, or inotropic state. It has been available for many years in Europe and is quite commonly prescribed in patients

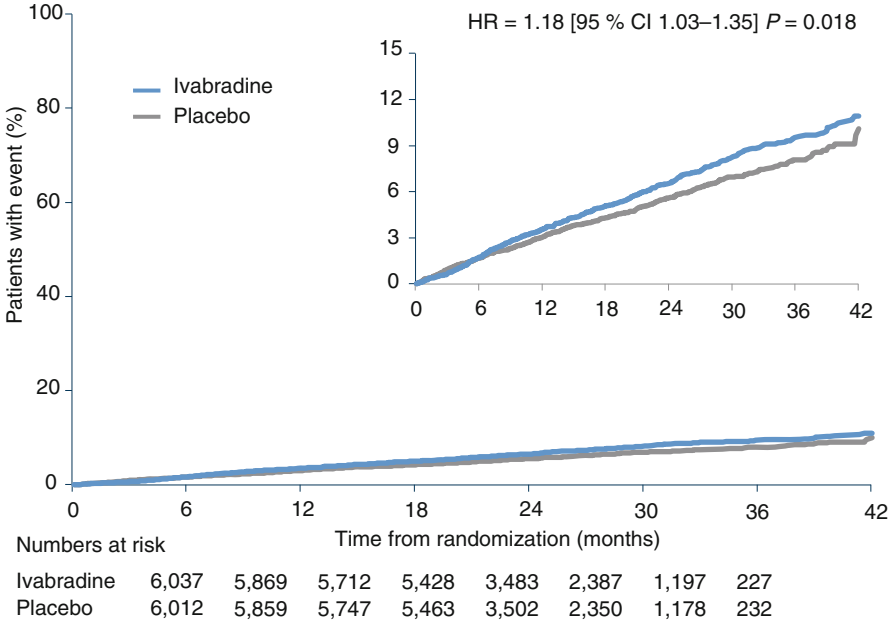

Fig. 22.1 The effect of ivabradine vs. placebo on cardiovascular death or nonfatal myocardial infarction in patients with angina CCS Class ≥II ($n = 12,049$) (Modified from reference [78])

with angina [79]. There are reports that it is effective in the therapy of angina [80, 81]; however, evidence is limited, and the European Medicines Agency recently recommended that its use be limited to those patients who do not respond to standard antianginal therapy [82].

Ranolazine is an effective antianginal with a mechanism of action that does not rely on changes in myocardial oxygen demand or supply. Initially, it was felt to have a mechanism of action similar to trimetazidine in which free fatty oxidation is inhibited, leading to preferential metabolism of glucose and more efficient utilization of oxygen [83–85]. Although still somewhat controversial, more recent observations suggest that this metabolic mechanism is not operative in clinically relevant doses. It is now felt that ranolazine inhibits a late inward sodium channel, which favorably modifies intracellular sodium and calcium responses in the setting of ischemia (Chap. 52) [86–91]. Whatever the mechanism, ranolazine is effective in the therapy of angina both when used as monotherapy and when administered in addition to other antianginal agents (Fig. 22.2) [21, 86, 92]. The safety of ranolazine therapy was supported by the results of the *M*etabolic *E*fficiency with *R*anolazine for *L*ess *I*schemia in *N*on-ST Elevation Acute Coronary Syndromes (MERLIN) study, in which 6,500 patients were followed for a median time of 348 days [93]. In this study, ranolazine had no

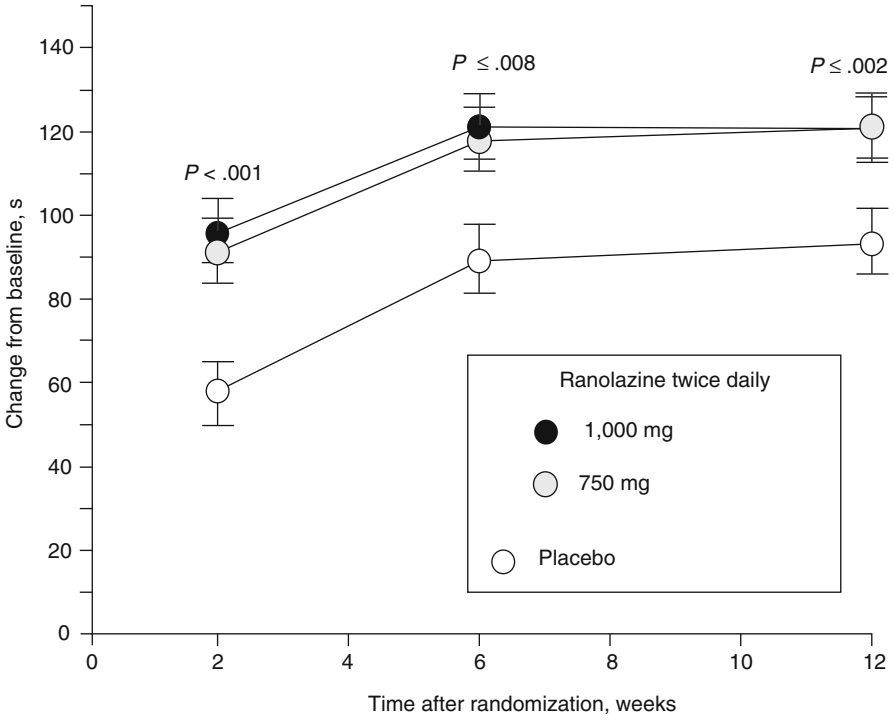

Fig. 22.2 Change in treadmill exercise duration from baseline at trough ranolazine levels over time. Values are for comparisons of each ranolazine group vs. placebo (Modified from reference [21])

beneficial effect on long-term outcome, however the study result confirmed the safety of this drug in a large population of patients with coronary artery disease. On the basis of this evidence of safety, ranolazine was approved in the United States as a first-line agent in the management of stable angina.

22.8 Combination Therapy

Any physician caring for patients with chronic angina knows that it is common to see patients who have been prescribed two and not infrequently three different drugs used for the therapy of angina. In some situations, where patients have refractory symptoms and revascularization is no longer possible, this approach is appropriate and can be beneficial. However, there are many patients who receive multiple-drug therapy in the absence of refractory symptoms [94–96]. The rationale for this may be to reduce side effects through the use of lower doses of each class and/or that the use of drugs with different mechanisms of action will be more efficacious. Studies examining combination therapy with organic nitrates, beta-blockers, and/or calcium channel antagonists have yielded inconsistent results and have been limited in their ability to define adverse effects because of small sample sizes and short-term follow-up [97–119]. This controversial area was reviewed in detail by Packer, who argued that in the absence of clear benefit, use of more than one antianginal agent puts patients at risk for side effects of combination therapy [120]. A common problem of studies using combination therapy is that they did not examine the effect of a second drug on top of maximum tolerated dose of monotherapy. Of note, consistent benefit has been demonstrated from the addition of a second agent when patients remain symptomatic on maximal monotherapy [97, 100, 109]. Recent studies of newer agents used in the therapy of angina (ivabradine and ranolazine) provide evidence that these medications are effective when these agents are added to background therapy with either a beta-blocker or calcium channel antagonists [21, 74]. However, in these cases, it is important to remember that the patients included in those studies had to remain symptomatic on background therapy in order to meet inclusion criteria.

22.9 Choice of Antianginal Therapy

There is no compelling evidence that any individual drug or class of drug is more effective at reducing symptoms of angina when compared to other agents. Despite this uncertainty, practice guidelines are uniform in their support of beta-blockers as first-line therapy, particularly in patients who have had a previous myocardial infarction (Chap. 20) [121, 122]. In patients where beta-blockers are contraindicated or not tolerated, either calcium channel antagonists or a long-acting nitrate can be used. Sometimes the choice of therapy is modified by the presence of concurrent clinical conditions such as a prior myocardial infarction (in which a

beta-blocker is preferred) or the presence of severe concomitant hypertension (where a dihydropyridine calcium channel antagonist might be chosen). Many cardiologists choose beta-blockers as first-line therapy, even in the absence of a prior infarction. These drugs are very effective in the prevention of angina, can be titrated to heart rate responses, and have long been presumed to have beneficial or neutral effects on long-term outcome. Other physicians prescribe calcium channel antagonists as first-line therapy, since they are clinically effective and are felt to have a better side effect profile. Ranolazine is a reasonable choice in patients where a beta-blocker is not tolerated or is contraindicated. Both the American and European guidelines, for example, support its use as a second-line drug when symptoms are not controlled by monotherapy with another antianginal agent [121, 122]. Ivabradine, not yet available in North America, is recommended for patients who remain symptomatic while on a beta-blocker or if a beta-blocker is contraindicated. Ivabradine seems to be particularly helpful in patients who have resting heart rates ≥70 beats per minute either in the presence or absence of another negative chronotrope.

22.10 Impact on Long-Term Clinical Outcomes

For many years, there was little or no information about the impact of most antianginals on the long-term outcome of patients with angina. In the absence of prior myocardial infarction, there has been no clear reason to make use of a particular class of antianginal in an effort to improve long-term clinical outcome. At times, concurrent conditions do drive treatment choices in patients with angina, often with reasonable assumptions that managing those conditions will be of long-term benefit. Typical examples include the presence of prior infarction, particularly with evidence of significant left ventricular dysfunction, a situation in which beta-blocker therapy would seem to be the best choice to improve long-term outcome. Another example is the presence of significant hypertension where a dihydropyridine represents a logical choice, particularly if angina and hypertension persist despite therapy with a beta-blocker.

In the case of long-acting nitrates, there have been no studies examining their effect on long-term clinical outcome in patients with stable angina. Clinical trials that led to the approval of these drugs for the therapy of angina had both small sample sizes and short-term follow-up [20, 32, 35]. In fact, there has never been a long-term study examining the impact of a long-acting nitrate on outcome in patients with chronic coronary artery disease. Although large post-myocardial infarction studies have included therapy with long-acting nitrates, the duration of therapy was short (4–6 weeks), preventing any assessment of the impact of nitrates on long-term outcome [123, 124]. There is increasing concern that long-held assumptions of safety concerning long-acting nitrate therapy may have been misplaced. Multiple studies have now documented that organic nitrate therapy leads to an increase in the bioavailability of free radicals and significant abnormalities in endothelial function [125–127]. These findings have led some to hypothesize that sustained nitrate therapy could have adverse effects in patients with CAD [40, 128], concerns that have

been supported by retrospective analysis of patients with CAD treated with long-acting nitrates [129, 130].

It has generally been assumed that beta-blockers are protective in patients with chronic coronary artery disease. In patients with a myocardial infarction, therapy with beta-blockers has been shown to improve survival particularly in patients with congestive heart failure and left ventricular systolic dysfunction (Chap. 8) [131–137]. However, studies documenting the benefit of beta-blockers in patients with a prior myocardial infarction were carried out more than 30 years ago, before multiple other secondary prevention strategies had been introduced (antiplatelet, ACE inhibition, and statin therapy). It is possible that beta-blockers do not have protective effects, particularly in the setting of smaller infarctions, in the current era where patients receive multiple secondary prevention strategies. Furthermore, no large-scale outcome study has ever been conducted to examine the clinical impact of beta-blockers in patients with stable CAD without prior infarction. Studies examining the effects of beta-blockers on symptoms of angina were not powered to address their effect on long-term outcome [22, 23, 41–43, 138, 139]. Despite these shortcomings, it has generally been assumed that beta-blockers have either neutral or potentially beneficial effects on long-term clinical outcome. Of note, recent evidence from post hoc analysis of clinical trial data and from large registries has brought both of these assumptions into question, particularly in patients who have not suffered a myocardial infarction [140, 141].

In 1995, Furberg and Psaty reported results from meta-analyses suggesting that therapy with calcium channel antagonists was associated with a significant increase in the risk of myocardial infarction. This risk was observed in patients with hypertension and in those with angina [142, 143]. At that time, the use of calcium channel antagonists was rapidly increasing in both of these patient populations. These findings received international attention and highlighted the lack of studies examining the safety of calcium channel antagonists in patients with CAD. The resulting controversy concerning calcium channel antagonist safety led to the ACTION (effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment) study, in which 7,765 patients with coronary artery disease, a history of stable angina, and preserved left ventricular systolic function were randomized to therapy with sustained-release nifedipine or placebo. In this large study, nifedipine had no impact on mortality but was associated with lower cardiovascular event rates and reduced the rate of coronary revascularization procedures (Fig. 22.3) [144]. The safety and clinical effectiveness of diltiazem has not been tested in patients with stable angina; however, it is known that it should be avoided in patients with coronary disease and significant left ventricular systolic dysfunction [145]. Finally, although verapamil is less frequently used in the therapy of angina than other calcium channel antagonists and should be avoided in patients with left ventricular systolic dysfunction, data from the INVEST (INternational VErapamil SR-Trandolapril) study found no evidence of adverse effects in a large group of patients with CAD and hypertension [146].

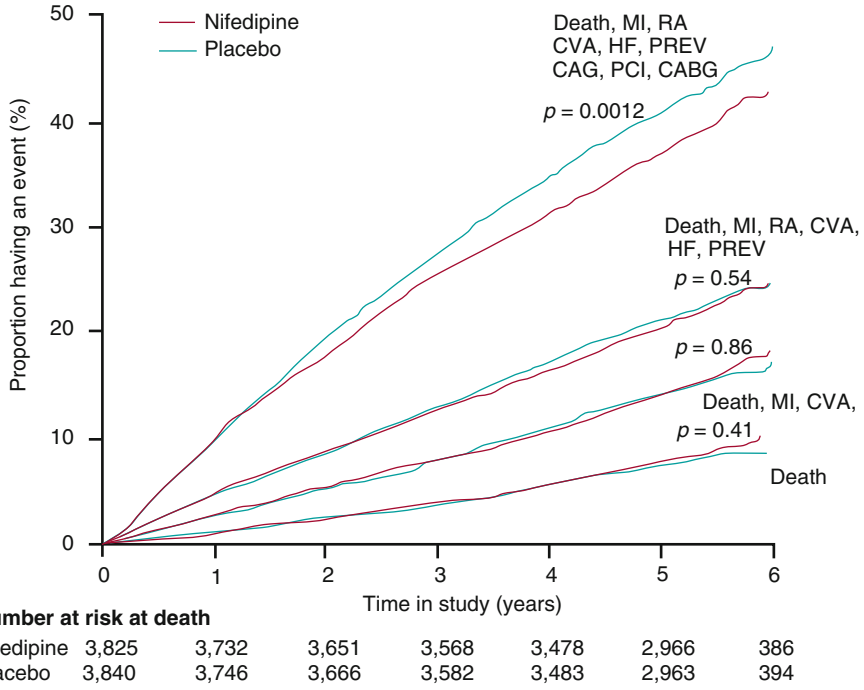

Fig. 22.3 Time to first occurrence of clinical events in the ACTION study. *MI* myocardial infarction, *RA* refractory angina, *CVA* debilitating stroke, *HF* new overt heart failure, *PREV* peripheral revascularization, *CAG* coronary angiography, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting (Used with permission. Modified from reference [144])

22.11 Safety of Other Antianginal Drugs

A number of other studies have addressed the long-term safety of drugs used in the therapy of stable angina. The IONA (*I*mpact *O*f *N*icorandil in *A*ngina) trial found that nicorandil reduced cardiovascular event rates in patients with chronic angina while confirming its safety. Although the impact of ranolazine on the clinical outcome of patients with stable angina has not been directly assessed, the MERLIN study did confirm the safety of this drug when given to patients with an acute coronary syndrome. The impact of ivabradine on clinical outcomes has been tested extensively. The BEAUTIFUL study confirmed the safety of ivabradine in a group of patients with known CAD and left ventricular systolic dysfunction. This was followed by the SIGNIFY study, which examined the effect of ivabradine on cardiovascular outcomes in patients with known CAD and preserved left ventricular systolic function [78]. When the entire 19,000 patient cohort was examined, there was no significant difference between ivabradine and placebo in the rate of cardiovascular death or nonfatal myocardial infarction. However, in the large subgroup with significant angina, a significant increase in these events was observed. Post hoc

analyses of this large study revealed that symptomatic bradycardia was relatively frequent, possibly related to the higher target dose of ivabradine used in the study (10 mg BID) than the current approved dose (7.5 mg BID). The European Medicines Agency has commented on these results, concluding that ivabradine should only be used in patients with symptomatic CAD and that the dose of 7.5 mg twice daily should not be exceeded [147].

22.12 Prognosis of Stable Angina

A clear understanding of clinical outcomes and overall mortality of patients with stable angina is important for practitioners as they choose between available treatment options. The choice of medical management versus revascularization is driven by many patient characteristics, including but not limited to age, comorbidities, the severity of coronary disease, the amount and distribution of ischemia on exercise testing, as well as symptom severity. However, it is important to emphasize that patients with stable angina (particularly in the setting of preserved left ventricular systolic function) have an excellent prognosis with very low mortality rates. Recent clinical trial data confirms this with most studies documenting mortality rates of 1–3 % per year in patients with stable angina. Studies documenting the mortality of patients with stable angina include the Swedish Angina Pectoris Aspirin Trial (2 % per year) [148], the APSIS (*A*ngina *P*rognosis *S*tudy *I*n *S*tockholm) study (1.3 % per year) [149], the ACTION study (1.2 % per year) [68, 144], the IONA study (approximately 3 % per year) [68], and, most recently, the SIGNIFY study (approximately 2–2.5 % per year) [78]. Despite some variations, the mortality rates reported confirm the fact that patients with stable angina have an excellent prognosis. From this perspective, patients with stable symptoms of chronic CAD who respond well to medical therapy and do not have high-risk features on ischemia testing can be safely and deservedly treated medically.

22.13 Concluding Remarks

The medical therapy of symptoms of angina continues to be important in the management of patients with chronic coronary artery disease. Diagnosis and management requires a careful history and a thorough knowledge of available pharmacologic options. Although regulatory authorities require that drugs used in the therapy of angina improve exercise capacity throughout the day, this may not be a goal required for all patients. The practitioner should tailor antianginal therapy to meet the needs of the patient and, as always, make an assessment of the benefits of therapy in light of any adverse effects. Finally, the responsibility of the physician in the therapy of angina goes beyond the use of drug therapy and should always include education of the patient with respect to the cause and implications of the symptoms of angina.

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Chapter 23
Therapy for Acute Coronary Syndrome and Unstable Angina

Daniel M. Shivapour and A. Michael Lincoff

Abstract Non-ST-segment elevation acute coronary syndromes (NSTE ACS) include unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI). The significant morbidity and mortality associated with NSTE ACS have motivated decades of drug development and clinical investigation, with considerable emphasis on the central role of the platelet in the pathophysiology and treatment of these disease processes. This chapter offers a broad overview of the pharmacologic treatment of NSTE ACS, with an emphasis on (1) antiplatelet agents, including low-dose aspirin, second- and third-generation P2Y12 receptor blockers, and glycoprotein IIb/IIIa receptor inhibitors; (2) anticoagulant therapy, including unfractionated heparin, enoxaparin, fondaparinux, and bivalirudin; and (3) other pharmacologic agents, including beta-blockers, nitrates, calcium channel blockers, and statins which are also used in the acute management of NSTE ACS.

Keywords Acute coronary syndrome • Antithrombotic therapy • Aspirin • P2Y12 receptor blockers • Glycoprotein IIb/IIIa receptor inhibitors • Heparin • Anti-ischemic medications

23.1 Introduction

Acute coronary syndromes (ACS) occur when atherosclerotic plaque ruptures or erodes in a coronary artery. The resulting activation of platelets and the coagulation cascade produce a platelet-fibrin clot that can lead to partial or complete obstruction of the vessel. The clinical presentation encompasses a wide spectrum, which

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includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment myocardial infarction (STEMI). Unstable angina and NSTEMI are often considered together as non-ST-segment elevation ACS (NSTE ACS) and account for a growing percentage of all ACS cases, with current estimates ranging from 50 % to 70 % [1, 2] (see also Chap. 19). The pharmacologic management of ACS is a highly evidence-based discipline that is guided by decades of rigorous investigation. The goals of pharmacologic therapy include improving survival, reducing morbidity, preventing the progression of coronary artery disease, and treating ischemic pain. This chapter reviews the science supporting the pharmacologic treatment of NSTE ACS and provides an overview of each of the categories of pharmacologic agents used in the acute management of NSTE ACS. Dosing guidelines and special considerations for each of the antithrombotic agents reviewed in this chapter are summarized in Table 23.1 (also see Chap. 20).

23.2 Antiplatelet Therapy

The central role of the platelet in the pathophysiology of NSTE ACS has been well established. When an atherosclerotic plaque erodes or ruptures within a coronary artery, the lipid-rich necrotic core and subendothelial matrix are exposed to circulating pro-thrombotic factors. Von Willebrand factor (vWF) plays a key role in the initiation of thrombosis, as it binds to the subendothelial matrix and subsequently attracts platelets through a combination of shear stress forces and binding at the glycoprotein (GP) Ib receptor. The binding of vWF to the GP Ib receptor is an important step in the platelet activation pathway via the P2Y12 ADP receptor. As the initial ruptured plaque defect in the coronary endothelium is covered by activated platelets, this promotes further platelet recruitment and activation to the site of injury in a paracrine fashion. This complex process is mediated through platelet-derived factors including adenosine diphosphate (ADP) and thromboxane A2 (TXA-2). The activation of platelets produces a conformational change in the glycoprotein IIb/IIIa receptors, which are essential to the formation of thrombus as they facilitate platelet cross-linking with fibrinogen. In order to rapidly and effectively interrupt these platelet activation pathways in the setting of NSTE ACS, a combination of multiple antiplatelet agents is employed to target different steps in the process.

23.2.1 Aspirin

Aspirin (acetylsalicylic acid or ASA) is a cornerstone of ACS therapy. Several clinical trials and subsequent meta-analyses have shown that ASA lowers ischemic morbidity and mortality rates by as much as 50 % in ACS [3–7]. The enzyme cyclooxygenase-1 (COX-1) is responsible for the conversion of arachidonic acid

Table 23.1 Dosing guidelines for antithrombotic agents in NSTE ACS

Medication	Dosing	Special considerations
Aspirin	*Initial dose*: 324 mg non-enteric coated chewed at presentation *Maintenance dose*: 81 mg daily	
Clopidogrel	*Initial*: 300–600 mg loading dose *Maintenance*: 75 mg daily	
Prasugrel	*Initial*: 60 mg loading dose *Maintenance*: 10 mg daily	Do not use if prior TIA or stroke Extra caution if age >75 years or <60 kg
Ticagrelor	*Initial*: 180 mg loading dose *Maintenance*: 90 mg twice daily	
Abciximab	*Initial*: 0.25 mg/kg IV bolus followed by 0.125 mcg/kg/min (max 10 mcg/min) infusion	Started at time of PCI and continued for up to 12 h after at the discretion of the physician
Eptifibatide	*Initial*: 180 mcg/kg IV bolus followed by 2 mcg/kg/min infusion (1 mcg/min/kg if CrCl <50)	Started at time of PCI and continued for up to 12–18 h after at the discretion of the physician Contraindicated in dialysis patients
Tirofiban	*Initial*: 25 mcg/kg IV bolus followed by 0.15 mcg/kg/min infusion (0.075 mcg/kg/min if CrCl <30)	Started at time of PCI and continued for up to 12–18 h after at the discretion of the physician
Unfractionated heparin	*Initial*: 60 U/kg IV bolus (max 4,000) followed by weight-based infusion adjusted to aPTT goal (common starting infusion dose 12 U/kg/h)	
Enoxaparin	*Initial*: 30 mg IV once may be given as loading dose; thereafter 1 mg/kg SQ every 12 h	Follow anti-Xa levels in renal impairment or severe obesity
Bivalirudin	*Initial*: 0.75 mg/kg IV bolus followed by 1.75 mg/kg/h infusion	Reduce dosing in renal failure Recommended only if PCI planned
Fondaparinux	*Initial*: 2.5 mg IV once may be given as loading dose; thereafter 2.5 mg SQ daily	Extra caution in renal impairment or patients weighing <50 kg Recommended only if PCI is *not* planned

Abbreviations: *mg* milligram, *TIA* transient ischemic attack, *kg* kilogram, *IV* intravenous, *PCI* percutaneous intervention, *mcg* microgram, *min* minute, *U* units, *aPTT* activated partial thromboplastin time, *CrCl* creatinine clearance, *SQ* subcutaneous, *hr* hour

into TXA-2 within platelets, a potent platelet aggregator and endothelial vasoconstrictor which subsequently facilitates the activation of other platelets. Aspirin exerts its antiplatelet effects by irreversibly inhibiting the COX-1 enzyme, effectively blocking the synthesis of TXA-2. Since platelets do not synthesize new

enzymes, the functional defect induced by aspirin therapy persists for the life of the platelet. Initial therapy in any suspected or confirmed NSTE ACS presentation should include a 325 mg dose of non-enteric-coated chewable ASA to allow for rapid absorption, followed by indefinite low-dose maintenance therapy (81 mg daily) for those patients with confirmed ACS. Recent evidence has shown there is no benefit to a higher 325 mg daily maintenance dose, and it is associated with higher rates of bleeding complications [8].

At the recommended doses used in ACS, aspirin has few notable drug interactions or significant adverse events. The adverse effects of aspirin are dose related and are extremely rare at low dosages (exact quantification of frequency is not possible). As with all antiplatelet and anticoagulant agents discussed in this chapter, bleeding is associated with aspirin use and may occur at virtually any site. Multiple variables affect an individual patient's bleeding risk, including dosage, concurrent use of multiple antithrombotic agents, which affect hemostasis, and underlying patient comorbidities. Patients who develop GI adverse effects should be treated with a proton pump inhibitor, and many are then able to tolerate low-dose aspirin therapy. True hypersensitivity reactions (angioedema, bronchospasm, and/or hives) are very rare; however, aspirin desensitization can be performed, if present.

23.2.2 P2Y12 Receptor Blockade

The addition of a second antiplatelet agent to aspirin ("dual antiplatelet therapy") marked a significant advance in the treatment of ACS. Several oral medications are available to inhibit platelet activity at the level of the P2Y12 ADP receptor that provides an additive antiplatelet effect to the thromboxane A2 inhibition by aspirin. There are three FDA-approved thienopyridines (clopidogrel, prasugrel, and ticlopidine) which irreversibly inhibit ADP-mediated platelet activation and aggregation by binding to the platelet P2Y12 receptor. Ticlopidine was the first approved agent; however, due to its delayed onset of action and unfavorable hematologic adverse events, it is no longer used in contemporary treatment of NSTE ACS. Clopidogrel, considered a "second-generation" agent, and the "third-generation" prasugrel and ticagrelor (a reversible P2Y12 antagonist) are the currently used agents.

23.2.3 Clopidogrel

Clopidogrel, an irreversible P2Y12 receptor antagonist, is a prodrug, which requires conversion into its active metabolite by the hepatic cytochrome P450 2C19 isoenzyme. It has a variable time to peak effect of approximately 2–4 h depending on the loading dose chosen [9, 10]. The foundation of its use in the NSTE ACS population was established by the Clopidogrel to Prevent Recurrent Events (CURE) trial, which demonstrated a 20 % relative reduction (9.3 % vs. 11.4 %, $P<0.001$) of composite endpoints

including cardiovascular death, nonfatal MI, and stroke, at the expense of more major bleeding (3.7 % vs. 2.7 %, $P=0.001$). The subsequent Clopidogrel and Metoprolol in Myocardial Infarction (COMMIT) trial also demonstrated a highly significant 9 % proportional reduction in death, reinfarction, or stroke (9.2 % vs. 10.1 %; $P=0.002$) when clopidogrel was added to standard aspirin therapy in a predominantly STEMI patient population (93 % STEMI, 7 % NSTE ACS) [11]. Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor should be initiated as soon as possible after presentation for a patient with ACS. As clopidogrel may particularly increase bleeding in patients who undergo coronary artery bypass surgery (CABG) [12], guidelines recommend stopping clopidogrel at least 5 days prior to CABG. Concerns regarding CABG-related bleeding have led some clinicians to delay clopidogrel administration until a patient's coronary anatomy is angiographically defined. Unless there is a very high suspicion that the patient will require urgent surgery, however, we advocate for the early administration of clopidogrel so as to not withhold its anti-ischemic benefits from the vast majority of patients with NSTE ACS who will not require urgent surgical revascularization [13].

The required activation of the prodrug clopidogrel by the hepatic cytochrome P450 2C19 (CYP2C19) system creates important therapeutic considerations. Genetic polymorphisms of CYP2C19 and some medications, such as omeprazole, have been associated with pharmacokinetic/pharmacodynamic (PK/PD) effects on clopidogrel activation. Observational studies have suggested an association with worse outcomes in patients with slow conversion; however, randomized studies using genetic polymorphisms and platelet function testing to guide more aggressive antiplatelet therapy have thus far failed to show a benefit of treatment modifications based upon such testing [14–16]; we do not recommend routine use of functional or genetic testing in routine clinical practice. There has only been one randomized controlled trial testing coadministration of clopidogrel and omeprazole, and it did not show an effect of omeprazole on cardiovascular outcomes [17].

The most common adverse effects of clopidogrel are bleeding and minor dermatologic reactions (rash, pruritus, or similar in less than 5 % of patients). As with all antiplatelet and anticoagulant agents discussed in this chapter, the risk of bleeding is increased by combining antithrombotic agents, and multiple variables will affect an individual patient's bleeding risk. In our practice, we do not consider any drug interactions to present an absolute contraindication to clopidogrel usage, including omeprazole based on the recent evidence presented above. Experience with clopidogrel in the setting of severe liver dysfunction is limited, and while not an absolute contraindication to its use, caution and extra monitoring for bleeding may be considered in patients with severe hepatic impairment.

23.2.4 Prasugrel

Prasugrel is a third-generation thienopyridine that irreversibly inhibits the P2Y12 receptor. While it is also a prodrug requiring hepatic metabolism to its active metabolite, this conversion requires fewer enzymatic steps and thus occurs with a more rapid and less

variable pharmacodynamic profile than with clopidogrel [18]. Its metabolism is not dependent on the CYP2C19 isoenzyme, and proton pump inhibitors are not known to have any clinically significant PK/PD interaction with prasugrel. The foundation for prasugrel's use in NSTE ACS was established by the TRITON-TIMI 38 trial, which demonstrated a lower rate of composite endpoints, including cardiovascular death, nonfatal MI, and nonfatal stroke (9.9 % vs. 12.1 %, $P<0.001$), as well as a lower risk of in-stent thrombosis in patients who underwent percutaneous intervention (1.1 % vs. 2.4 %, $P<0.001$); however, these ischemic benefits were again at the expense of a higher rate of non-CABG major bleeding including fatal bleeding (2.4 % vs. 1.8 %, $P=0.03$) [19]. A notable subgroup of patients who had a net negative outcome was those with a prior history of stroke or transient ischemia attack (TIA), and prasugrel use in such patients is not recommended. Additional populations in which special caution is advised include patients over 75 years of age and patients weighing <60 kg as increased bleeding complications were noted in these groups. In an important distinction from the CURE trial, NSTE ACS patients in TRITON-TIMI 38 only received the prasugrel loading dose after their coronary anatomy was angiographically defined and percutaneous revascularization planned, and in most cases prasugrel should be held for 7 days prior to CABG due to the high bleeding risk. The trial did not evaluate prasugrel for an early conservative management strategy for NSTE ACS. The subsequent TRILOGY-ACS trial found no difference in the rates of death, MI, or stroke at 12 months with clopidogrel versus prasugrel in medically managed patients with high-risk NSTE ACS [20].

Similar to clopidogrel, the most common adverse effects of prasugrel are bleeding and minor dermatologic reactions (e.g., rash, in less than 5 % of patients). Labeling also notes a less than 5 % incidence of other minor reactions including headache, nausea, dizziness, and fatigue. As with all antiplatelet and anticoagulant agents discussed in this chapter, the risk of bleeding is increased by combining antithrombotic agents, and multiple variables will affect an individual patient's bleeding risk. In our practice we do not consider any drug interactions to be an absolute contraindication to prasugrel; however, like clopidogrel, the use of prasugrel in the setting of severe liver dysfunction has not been well studied.

23.2.5 Ticagrelor

Ticagrelor is a third-generation reversible P2Y12 antagonist that, unlike the thienopyridines, is an active drug and does not require hepatic conversion to an active metabolite. It exhibits the most rapid onset, greatest inhibition, and least individual variability of the oral P2Y12 agents [21]. The foundation of its use in NSTE ACS was established by the PLATO trial in which ticagrelor demonstrated a lower rate of composite cardiovascular events (death, MI, and stroke 9.8 % vs. 11.7 %, $P<0.001$) with fewer cases of in-stent thrombosis and without a significantly increased risk of major bleeding compared to clopidogrel. There was, however, a higher incidence of non-CABG major bleeding including intracranial hemorrhage in the ticagrelor group (4.5 % vs. 3.8 %, $P=0.03$) [22]. Because of its reversible pharmacokinetics, its antiplatelet effects attenuate more quickly than the thienopyridines. Therefore, while it is

still recommended to hold ticagrelor for 5 days prior to CABG, experienced surgical centers can often operate earlier with acceptable bleeding outcomes.

The most common adverse effect reported for ticagrelor is dyspnea in up to 15 % of patients. Ticagrelor-related dyspnea does not require specific treatment nor does it mandate therapy interruption. While not completely understood, this is thought to be a bradykinin-mediated symptom and rarely is severe enough to require discontinuation of ticagrelor therapy. Like prasugrel, ticagrelor is also associated with low rates of minor dermatologic reactions (e.g., rash) and nonspecific symptoms such as headache, nausea, dizziness, and fatigue in less than 5 % of patients. As with all antiplatelet and anticoagulant agents discussed in this chapter, the risk of bleeding is increased by combining antithrombotic agents, and multiple variables will affect an individual patient's bleeding risk. In contrast to the thienopyridines, the use of ticagrelor is explicitly contraindicated in patients with severe hepatic dysfunction, and another agent should be considered. Similar to clopidogrel and prasugrel, the use of ticagrelor in moderate liver dysfunction has not been well studied. Ticagrelor has a notable drug interaction with other agents affecting CYP3A4 metabolism. Specifically, concomitant use of ticagrelor should be avoided with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, dexamethasone, phenobarbital, and phenytoin) or strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, nefazodone).

23.2.6 Glycoprotein IIb/IIIa Receptor Inhibitors

The glycoprotein IIb/IIIa receptor inhibitors (GPI) are intravenous medications that inhibit platelet aggregation and thrombus formation by preventing the binding of fibrinogen or circulating vWF on the platelet surface. The three agents currently approved in the USA are abciximab, eptifibatide, and tirofiban. Abciximab is a Fab fragment of a humanized murine antibody that exhibits a very strong affinity for the glycoprotein receptor. While it has a short plasma half-life (approximately 30 min), abciximab's strong binding results in platelet inhibition continuing for days after the infusion is stopped. Eptifibatide, a small-molecule cyclic heptapeptide, and tirofiban, a synthetic nonpeptide antagonist, both reversibly inhibit the IIb/IIIa receptors on the surface of platelets with a shorter duration of action (half-life approximately 2 h with platelet activity normalizing approximately 4 h after discontinuation).

At proper doses, all three GPI agents are very potent inhibitors of platelet aggregation; however, their use has been diminishing as much of their supporting evidence came prior to the contemporary era of routine oral dual antiplatelet therapy. Several, large randomized control trials have investigated GPI use in multiple contexts, including ACS and elective percutaneous intervention (PCI). When reviewing this literature, it is important to carefully understand the indications and the patient populations studied in each of these trials as they influence the noted differences in results, and the relative benefits and risks may vary significantly based on the context in which the medication is being given. Table 23.2 presents a brief summary of select, landmark GPI trials. Multiple trials examining abciximab and eptifibatide with aspirin and heparin in high-risk and NSTE ACS patients undergoing PCI found 30–50 %

Table 23.2 Select major trials of GP IIb/IIIa inhibitors

Trial name	GPI studied	Number of patients	Trial design	Results	Comments
EPIC [23]	Abciximab	2,099	Prospective, double-blind, high-risk patients (ACS or "high-risk anatomy") on ASA and heparin randomized to abciximab vs. placebo	At 30 days, there was a 30 % reduction in the primary composite endpoint	These benefits were subsequently noted out to 6 months and 3 years
EPILOG [24]	Abciximab	2,792	Prospective, double-blind trial in patients undergoing elective or urgent PCI randomized to abciximab with standard-dose, weight-adjusted heparin; low-dose, weight-adjusted heparin; or placebo with standard-dose, weight-adjusted heparin	At 30 days, the composite event rate was 11.7 % in the placebo group, 5.2 % in the abciximab/low-dose heparin group, and 5.4 % in the abciximab/standard-dose heparin group	These benefits were achieved without a significant increase in major bleeding and were subsequently demonstrated to remain favorable at 1 year follow-up [25]
EPISTENT [26]	Abciximab	2,399	Prospective, random assignment to stent plus placebo; stent plus abciximab; or balloon angioplasty plus abciximab	At both 30 days and 6 months, the primary endpoint was lowest in the stent plus abciximab group	The benefits were present regardless of whether the stent was elective or urgent
GUSTO IV ACS [27]	Abciximab	7,800	Prospective, ACS patients with no planned intervention, randomized to placebo vs. abciximab bolus/24-h infusion vs. abciximab bolus/48-h infusion	At 30 days, there was no difference between the three groups for the primary composite endpoint	There was no added benefit of abciximab in medically managed patients with positive cardiac biomarkers (NSTE ACS)

PURSUIT [28]	Eptifibatide	10,948	Prospective, double-blind, random assignment to eptifibatide vs. placebo for up to 72 h	At 30 days, the eptifibatide group had lower rates of the primary composite endpoint (14.2 % vs. 15.7 %)	The benefit was present in both patients treated with medical management and early revascularization The benefit was apparent by 96 h and persisted through 30 days
PRISM [29]	Tirofiban	3,232	Prospective, double-blind, ACS patients treated medically randomized to IV heparin vs. tirofiban for 48 h	At 48 h, the primary composite endpoint was 32 % lower in the tirofiban group (3.8 % vs. 5.6 %)	At 30 days, the frequency of the composite endpoint was not significantly different between the two groups. The benefits of tirofiban at 30 days were in high-risk patients with positive cardiac biomarkers [30]
PRISM-PLUS [26]	Tirofiban	1,915	Prospective, double-blind, ACS patients randomized to IV heparin, tirofiban, or IV heparin plus tirofiban prior to PCI	At 7 days, the composite endpoint was lowest in the patients who received IV heparin plus tirofiban	At 30 days, the benefit of the IV heparin plus tirofiban combination remained, and there was no significant increase in major bleeding

Abbreviations: *ACS* acute coronary syndrome, *ASA* aspirin, *IV* intravenous, *PCI* percutaneous intervention, *NSTE ACS* non-ST-elevation acute coronary syndrome

reductions in short-term ischemic endpoints at the expense of increased bleeding [23, 28, 31, 32]. While bleeding complications were reduced by adjustments in weight-based dosing of GPIs and concurrent lowering of heparin dosing, minor bleeding and the risk of thrombocytopenia remained increased. In NSTE ACS patients managed medically, again prior to the routine use of P2Y12 antagonists, trials with eptifibatide and tirofiban showed a reduction in ischemic endpoints; however, the magnitude of benefit was lower than with patients undergoing PCI [26, 29]. An important 2002 meta-analysis reinforced the benefits of GPI in NSTE ACS patients treated with aspirin and heparin who did not undergo early revascularization (conservative/medical management), analyzing six trials enrolling 31,402 patients. It found a 9 % reduction in the odds of a combined endpoint of death or myocardial infarction at 30 days with GPI compared with placebo or control (10.8 % vs. 11.8 %; odds ratio 0.91 [95 % CI 0.84–0.98]; $p=0.015$); however, major bleeding complications were increased by GPI (2.4 % vs. 1.4 %; $p<0.0001$), and the benefits appeared to be limited to the highest risk patients [33]. More recent trials reflecting the routine use of clopidogrel early in the course of treatment for patients with NSTE ACS or bivalirudin in PCI did not demonstrate an incremental benefit for ischemic outcomes with the routine addition of GPI [34–37]. Therefore, current guidelines call for dual, not triple, antiplatelet therapy (ASA and usually P2Y12 antagonists rather than GPI), with the addition of GPI reserved for patients who remain unstable, have a large thrombus burden on angiography, or have very high-risk clinical features. Dose reduction must be used in patients with significant renal impairment receiving either eptifibatide or tirofiban, and dialysis is an absolute contraindication to eptifibatide use.

As with all antiplatelet and anticoagulant agents discussed in this chapter, the risk of bleeding is increased by combining antithrombotic agents, and multiple variables will affect an individual patient's bleeding risk. In our practice we do not consider any drug interactions to be an absolute contraindication to use with the GPI agents. Labeling for abciximab, eptifibatide, and tirofiban reflects adverse effects to include the rare occurrence of nausea and other GI intolerances.

23.3 Anticoagulants

The effects of thrombin on the activation of platelets, conversion of fibrinogen to fibrin, and activation of factor XIII all contribute to fibrin cross-linking and clot stabilization. Thrombin activity at the site of a vulnerable coronary plaque rupture may result in delayed or incomplete reperfusion of the occluded vessel and may contribute to its reocclusion. Anticoagulants such as unfractionated heparin, low molecular weight heparins, direct thrombin inhibitors, and fondaparinux all interfere with the activity of thrombin and therefore have a fundamental role in the acute management of patients presenting with NSTE ACS.

23.3.1 Unfractionated Heparin

Unfractionated heparin (UFH) is a glycosaminoglycan of varying molecular weights that accelerates the action of antithrombin (formerly known as antithrombin III), the enzyme that inactivates thrombin and factor Xa, thereby preventing conversion of fibrinogen to fibrin. Dosing is weight based, and a traditional NSTE ACS bolus of 60 units/kg (not to exceed 4,000 units) has a dose-dependent half-life of 30–60 min. The foundation for its use in NSTE ACS was highlighted by a meta-analysis of six relatively small randomized controlled trials that demonstrated a 33 % reduction in death or MI among unstable angina patients treated with aspirin plus heparin compared to those treated with aspirin alone [38]. Select features from these six historical trials, which formed the basis for the use of UFH in NSTE ACS, are presented in Table 23.3.

A distinct advantage of UFH is that its anticoagulant effect can be followed with routine activated partial thromboplastin times (aPTT) or point-of-care activated clotting times (ACT) in the catheterization laboratory. Additional advantages include its widespread availability, low cost, rapid clearance after the infusion is discontinued, and the ability to reverse its anticoagulant effects with protamine in urgent situations. It is well suited for the use in both medically managed patients and those undergoing early PCI. Potential disadvantages include the higher incidence of heparin-induced thrombocytopenia with UFH compared to other heparin preparations, platelet activation, inability to inhibit clot-bound thrombin due to steric hindrance, circulating inhibitors, and inconsistent PK/PD due to nonspecific binding to multiple other proteins.

At the recommended doses used in ACS, UFH has few notable drug interactions or significant adverse events. Similar to aspirin, exact quantification of the frequency minor adverse events associated with UFH has not been defined. As with all antiplatelet and anticoagulant agents discussed in this chapter, bleeding is associated with UFH use and may occur at virtually any site. Multiple variables affect an individual patient's bleeding risk, including dosage, concurrent use of multiple antithrombotic agents, which affect hemostasis, and underlying patient comorbidities. In our practice we do not consider any drug interactions to be an absolute contraindication to UFH use.

In situations where urgent reversal of UFH is required, protamine sulfate can be administered. Protamine neutralizes the anticoagulant activity of UFH by combining with the strongly acidic heparin molecules to form a stable, inactive complex. Dosing of protamine sulfate is dependent upon the amount of heparin the patient has received and the time elapsed since the last heparin dose. Full neutralization of heparin effect is achieved with a dose of 1 mg protamine sulfate per 100 units UFH given, administered as a slow intravenous infusion (not greater than 20 mg/min and no more than 50 mg over any 10 min period). Of note, protamine can cause anaphylaxis in patients who have previously been exposed in any form (including diabetic patients treated with protamine-containing insulin), and thrombocytopenia following protamine administration has also been reported.

Table 23.3 The effect of UFH plus ASA vs. ASA alone from select historical trials in NSTE ACS

Study	Year	Number of patients	Eligibility after symptom onset	Treatment	Control	Duration of treatment	Primary endpoint	UFH plus ASA event rate	ASA alone event rate	Odds ratio (95 % confidence interval)
Theroux et al. [39]	1988	243	<24 h	UFH bolus plus infusion	ASA plus placebo bolus plus infusion	5–6 days	Death, MI, refractory angina, urgent revascularization	2/122 (1.6 %)	4/121 (3.3 %)	0.50 (0.09, 2.66)
Cohen et al. [40]	1990	69	<48 h	UFH bolus plus infusion	ASA	3–4 days	Death, MI, recurrent ischemia	0/37 (0 %)	1/32 (3.1 %)	Not calculable
RISC [41]	1990	399	<72 h	UFH bolus every 6 h	ASA plus placebo bolus	4 days	Death or MI	3/210 (1.4 %)	7/189 (3.7 %)	0.39 (0.10, 1.47)
ATACS [42]	1994	214	<48 h	UFH bolus plus infusion	ASA	3–4 days	Death, MI, recurrent angina	4/105 (3.8 %)	9/109 (8.3 %)	0.46 (0.15, 1.45)
Holdright [43]	1994	285	<24 h	UFH bolus plus infusion	ASA	2 days	Death, MI, recurrent ischemia	42/154 (27.3 %)	40/131 (30.5 %)	0.89 (0.62, 1.29)
Gurfinkel [44]	1995	143	<24 h	UFH bolus plus infusion	ASA plus placebo bolus plus infusion	5–7 days	Death, MI, refractory angina, urgent revascularization	4/70 (5.7 %)	7/73 (9.6 %)	0.60 (0.18, 1.95)

Abbreviations: *UFH* unfractionated heparin, *ASA* aspirin, *NSTE ACS* non-ST-elevation acute coronary syndrome, *MI* myocardial infarction

23.3.2 Enoxaparin

Low molecular weight heparins (LMWH) are a group of agents derived from UFH that act via antithrombin and preferentially inhibit factor Xa more than thrombin. Three LMWH agents have been approved for clinical use in the USA: enoxaparin, dalteparin, and tinzaparin. Of all the LMWH, enoxaparin is the most rigorously studied in the setting of ACS and is the agent typically used in the USA. Enoxaparin exhibits much less binding to plasma proteins and endothelial cells than UFH, giving it a more consistent and predictable anticoagulant effect. When it is given intravenously, it has a time to peak effect of 5–10 min, compared with 3–5 h when administered subcutaneously. Enoxaparin's 5–7 h half-life is dose independent; however, dose adjustment is required in patients with renal insufficiency.

Multiple trials have demonstrated a reduction in death and MI among conservatively managed NSTE ACS patients treated with enoxaparin compared with UFH; however, in patients undergoing early invasive management, LMWH was noninferior to UFH for ischemic endpoints but was associated with increased bleeding [45–48]. Table 23.4 highlights select features from four landmark trials comparing enoxaparin to UFH in NSTE ACS. Similar to the previous discussion of the GPI historical trials, it is important to carefully examine the indications, patient populations, and co-interventions in each of these trials as they contribute to the noted differences in results and influence the relative benefits and risks of a given treatment strategy in a particular patient. For example, only one of these trials (SYNERGY) utilized contemporary dual antiplatelet therapy (aspirin plus P2Y12 receptor blocker or GPI). More recent meta-analyses using lower doses of LMWH suggest that bleeding can be reduced, but no large-scale trials have definitively established the role of this agent in invasive management. Furthermore, two notable limitations to a frequently cited 2012 meta-analysis include that it was not performed with individual patients' data and that it incorporated studies including STEMI and stable angina patient populations, potentially limiting its applicability to the NSTE ACS patients for which this chapter is focused [52]. Therefore, in contemporary practice with routine dual antiplatelet therapy, LMWH use is primarily focused on NSTE ACS patients selected for conservative management.

Special dosing consideration is required in very obese patients or those with significant renal insufficiency, and anti-Xa levels should be followed carefully in those populations. Heparin-induced thrombocytopenia occurs at lower rates with LMWH than with UFH; however, platelet counts should be still be monitored. Unlike UFH, enoxaparin is not reversible with protamine, and its anticoagulant effect is not able to be monitored with routine labs (aPTT or ACT) in the catheterization laboratory. In patients who require CABG, enoxaparin should be stopped at least 24 h prior to surgery, and patients should be bridged with UFH.

At the recommended doses used in ACS, enoxaparin has few notable drug interactions or significant adverse events. The most commonly reported adverse effects in its labeling are mild GI side effects (e.g., nausea, diarrhea in less than 5 % of patients) and minor issues at the injection sites (e.g., irritation, bruising, and discomfort). As with all antiplatelet and anticoagulant agents discussed in this chapter,

Table 23.4 Select major trials of enoxaparin compared to UFH in NSTE ACS

Trial name	Number of patients	Trial population	Results	Comments
ESSENCE [45]	3,171	Unstable angina or acute NSTEMI patients treated with aspirin received enoxaparin vs. UFH therapy for a minimum of 48 h to a maximum of 8 days	*Composite*: at 30 days, enoxaparin had a lower rate of composite endpoint events (death, MI, or recurrent angina) (19.8 % vs. 23.3 % for UFH, $P=0.016$) *Major bleeding*: there was no difference between the groups in the 30-day incidence of major bleeding complications (6.5 % vs. 7.0 %) *Repeat revascularization*: the need for repeat revascularization procedures at 30 days was significantly less in the patients assigned to enoxaparin (27.1 % vs. 32.2 %, $P=0.001$)	Revascularization was not intended in this trial These benefits were maintained at 12 months for both the composite endpoint (32 % vs. 36 % for UFH, $P=0.022$) and the need for repeat revascularization (36 vs. 41 %, $P=0.002$) [49]
TIMI-11B [46]	3,910	Unstable angina or acute NSTEMI patients treated with aspirin received enoxaparin vs. UFH therapy for a minimum of 3 days. This trial also included an outpatient phase (to day 43)	*Composite*: at 8 days, enoxaparin had a lower rate of composite endpoint events (death, MI, or urgent revascularization) (12.4 % vs. 14.5 % for UFH, $P=0.048$) *Major bleeding*: there was no difference between the groups in the predischarge incidence of major bleeding complications (1.5 % vs. 1.0 %)	Revascularization was not intended in this trial The benefit of enoxaparin was limited to patients with elevated troponin

A to Z trial [48, 50]	3,987	Unstable angina or acute NSTEMI randomized to receive either enoxaparin or UFH in combination with aspirin and tirofiban	*Composite*: at 7 days, there was no significant difference in the incidence of composite endpoint events (death, MI, or refractory ischemia) (8.4 % vs. 9.4 % for UFH, $P=0.048$)	74 % of patients met NSTEMI criteria, and an early invasive strategy was pursued in 55 % of study patients. In a prespecified subgroup analysis, there was no difference in outcome for the patients treated with an early invasive strategy, whereas there was a significant reduction in the primary endpoint for patients treated with a conservative strategy
SYNERGY [47, 51]	10,027	Unstable angina or acute NSTEMI patients planned for an early invasive strategy randomized to receive either enoxaparin or UFH in combination with aspirin either P2Y12 or GPI	*Composite*: at 30 days, there was no significant difference in the incidence of composite endpoint events (death or nonfatal MI) (14.0 % vs 14.5 % for UFH) *Major bleeding*: the incidence of in-hospital major bleeding complications was higher with enoxaparin (9.1 % vs. 7.6 %, $P=0.008$)	There remained no difference in composite endpoint rates at 6 and 12 months In patients with high bleeding risk undergoing an early invasive strategy for NSTE ACS who are treated with contemporary dual antiplatelet therapy, UFH may be preferable to enoxaparin due to the increased bleeding risk highlighted by this trial

Abbreviations: *UFH* unfractionated heparin, *ASA* aspirin, *NSTE ACS* non-ST-elevation acute coronary syndrome, *MI* myocardial infarction, *GPI* glycoprotein IIb/IIIa receptor inhibitors

bleeding is associated with LMWH use and may occur at virtually any site. Multiple variables affect an individual patient's bleeding risk, including dosage, concurrent use of multiple antithrombotic agents which affect hemostasis, and underlying patient comorbidities. In our practice we do not consider any drug interactions to be an absolute contraindication to LMWH use.

23.3.3 Bivalirudin

Bivalirudin is a 20-amino-acid synthetic direct thrombin inhibitor that exerts antithrombotic effects by reversibly binding to both clot-bound and circulating free thrombin. It has a half-life of 25 min and a response that is proportional to its dosing, with coagulation parameters returning to baseline approximately 1 h after its discontinuation in patients with normal renal function. The foundation for its use in NSTE ACS comes from the ACUITY trial, which showed bivalirudin alone was non-inferior compared to UFH or LMWH plus GPI for a composite endpoint of death, MI, or unplanned revascularization in patients undergoing an early invasive strategy with approximately 40 % less major bleeding [36]. These findings were confirmed in subsequent investigations, and bivalirudin remains an alternative to UFH for NSTE ACS patients selected for early invasive management [35]. Special dosing of bivalirudin infusions is required in patients with renal insufficiency based on the severity of renal impairment.

At the recommended doses used in ACS, bivalirudin has few notable drug interactions or significant adverse events. The most commonly reported adverse effects in its labeling are headache, back pain, and mild GI side effects (e.g., nausea, GI upset). As with all antiplatelet and anticoagulant agents discussed in this chapter, bleeding is associated with bivalirudin use and may occur at virtually any site. Multiple variables affect an individual patient's bleeding risk, including dosage, concurrent use of multiple antithrombotic agents which affect hemostasis, and underlying patient comorbidities. In our practice we do not consider any drug interactions to be an absolute contraindication to bivalirudin use.

23.3.4 Fondaparinux

Fondaparinux is a synthetic analog of the heparin pentasaccharide that causes an antithrombin-mediated, selective inhibition of factor Xa. It can be administered subcutaneously with a time to peak effect of 2.5 h and a half-life of approximately 20 h in patients with normal renal function, which allows for predictable anticoagulant effects with once-daily dosing. The foundation for its use in NSTE ACS comes from the OASIS-5 trial, which showed patients treated with fondaparinux had non-inferior rates of the composite endpoint of death, MI, or refractory ischemia at 9 days along with over 50 % lower rates of major bleeding when compared with

enoxaparin (2.4 % vs. 5.1 %, $P<0.00001$); at 6 months fondaparinux produced a significant reduction in all major endpoints [53]. In this and other trials, however, fondaparinux was associated with increased catheter-related thrombus formation during PCI [54]. Therefore, the use of fondaparinux is typically reserved for patients with a high risk of bleeding selected for a conservative management strategy. Extra caution and monitoring are required when using fondaparinux in patients weighing <50 kg or with any degree of renal impairment.

Similar to many of the other agents described above, the most common adverse effects of fondaparinux are bleeding and nonspecific minor symptoms such as nausea, dizziness, and fatigue in less than 5 % of patients. As with all antiplatelet and anticoagulant agents discussed in this chapter, the risk of bleeding is increased by combining antithrombotic agents, and multiple variables will affect an individual patient's bleeding risk. In our practice we do not consider any drug interactions to be an absolute contraindication to fondaparinux. Its use has not been well studied in the setting of severe renal or hepatic dysfunction.

23.4 Anti-ischemic Medications in ACS

In addition to antithrombotic agents acting on unstable coronary plaque, concurrent goals of pharmacologic therapy in NSTE ACS are to improve survival, reduce morbidity, prevent the progression of coronary artery disease, and relieve ischemic pain. To achieve these goals, several additional classes of medications play an important role in the management of NSTE ACS patients. Beta-blockers and nitrates have well-established antianginal effects and are often utilized in early stabilization and treatment. While not considered first-line agents in the contemporary medical management of NSTE ACS, calcium channel blockers may also be employed in select circumstances. In most cases, the anti-ischemic pharmacotherapy regimen established during the acute inpatient hospitalization should be continued after discharge (with the exception of intravenous heparin or nitroglycerin). Appropriate combination therapy with antiplatelet agents, beta-blockers, high-intensity statin therapy, and angiotensin-converting enzyme (ACE) inhibitors (in select patients) was shown in one study to be associated with a reduction in 6-month mortality by as much as 90 % compared with ACS patients who received no appropriate therapy (odds ratio for death for all indicated medications used versus none of the indicated medications used 0.10 [95 % CI 0.03–0.42; $P<0.0001$]) [55].

23.4.1 Beta-Blockers

Beta-adrenergic blockade can inhibit the effects of catecholamines on the beta-1 adrenergic receptors in the myocardium, producing decreased myocardial oxygen demand through reduction in myocardial contractility, heart rate, and systemic

blood pressure. Heart rate reduction also prolongs the diastolic filling time, which may allow for additional coronary blood flow to the ischemic territory (Chap. 5).

The evidence supporting the benefit of beta-blockers in ACS has come primarily from randomized trials of ST-elevation MI (STEMI) patient populations. For patients with acute myocardial infarction, there is some evidence that early initiation of beta-blocker therapy may reduce both infarct size and early mortality and when continued long term may subsequently reduce the risk of death. A meta-analysis examining nonrandomized beta-blocker use in several large clinical trials suggested that there may be mortality benefit of beta-blockade among patients who undergo PCI for ACS [56]. The 2001 CAPRICORN trial also demonstrated a mortality benefit when patients with acute MI and LV dysfunction received a gradual up-titration of low-dose carvedilol [57]. There have been no randomized trials specifically addressing the efficacy of these drugs in non-ST-elevation MI (NSTEMI); however, there is no significant evidence suggesting different outcomes in NSTE ACS patient populations, and we routinely initiate beta-blockade therapy in these patients in the absence of clinical contraindications.

Certain patient populations may not be candidates for early initiation of beta-blocker therapy in NSTE ACS – specifically, patients with hemodynamic compromise or decompensated heart failure, patients with severe bradycardia or high-degree heart block (i.e., greater than first degree) who do not already have a permanent pacemaker, or patients whose cardiac event was precipitated by cocaine abuse. A relative contraindication to early beta-blocker therapy is patients who are at high risk for developing heart failure or shock (e.g., age >70 years old, systolic blood pressure <120 mmHg, heart rate >120 or <60 beats per minute, and patients with a significant delay in presentation from onset of symptoms). Such patients, however, should be frequently re-evaluated as these comorbidities are optimized and it is often possible to initiate beta-blocker therapy prior to discharge from the hospital. Pulmonary conditions such as chronic obstructive pulmonary disease (COPD) and asthma are sometimes cited as absolute contraindications to beta-blocker use; however, in our practice we have found beta-blockers to be safe, effective, and well tolerated in NSTE ACS with mild, moderate, and sometimes even severe pulmonary disease. This is consistent with the findings of a 2001 study of 54,962 ACS patients over the age of 65 years who had no other contraindications to beta-blocker therapy that found beta-blockers were associated with a lower 1-year mortality in patients with mild or moderate COPD or asthma (adjusted relative risk 0.85 compared to no beta-blockers) [58]. Therefore, in the absence of the above contraindications, we recommend the cautious use of short-acting beta-1 selective beta-blockers (e.g., metoprolol tartrate) titrated to desired heart rate and blood pressure goals in a step-down or intensive care unit setting for all patients with NSTE ACS.

Drug interactions and adverse events will differ among each of the agents in the beta-blocker class. In general, class-wide adverse events from beta-blocker use include bradycardia, hypotension, PR interval prolongation, dizziness, fatigue, depression, and minor dermatologic reactions (e.g., rash, pruritus, etc.). Special caution should be used when combining a beta-blocker with a calcium channel blocker as together these agents will have additive risks of bradyarrhythmic

adverse effects. In our practice we do not consider any drug interactions to be an absolute contraindication to utilizing our preferred beta-blockers, specifically metoprolol or carvedilol.

23.4.2 Nitrates

Nitroglycerin produces nitric oxide-mediated vasodilation in both the venous and arterial circulations. The venous effects of nitrates allow increased venous capacitance, which in turn reduces cardiac preload, reduces ventricular wall stress, and decreases myocardial oxygen demand. The arterial effects of nitrates occur both in the coronary and peripheral arterial circulations. The modest systemic effects on peripheral afterload further reduce myocardial oxygen demand, and the direct vasodilator effect of nitrates on the coronary arteries can improve blood flow and oxygen supply to the ischemic territory.

While there are only minimal rigorous clinical trial data examining the use in NSTE ACS populations, early treatment with nitrates remains a cornerstone of therapy for the control of blood pressure and ischemic chest pain in this setting. The initial administration of nitroglycerin for the treatment of angina in NSTE ACS is often sublingual at a dose of 0.4 mg every 5 min as needed. An IV infusion of nitroglycerin can also be used, commonly starting at a dose of 10 μg/min and titrated as needed to control symptoms. Blood pressure should be carefully monitored in NSTE ACS patients treated with nitrates, as they are at risk for hypotension. Beyond the acute setting, the long-term role for nitrate therapy in patients following NSTE ACS is less well established. Nitrates should not preclude adequate therapy with agents proven to reduce mortality, such as beta-blockers or ACE inhibitors; however, they may have a role in the treatment of recurrent ischemic symptoms, such as angina, or in select patients with concurrent heart failure.

An important drug interaction of which to be aware is that nitrates should be avoided in patients who actively use oral phosphodiesterase inhibitors and other potent pulmonary hypertension vasodilators (e.g., riociguat) due to the risk of profound systemic hypotension. Nitrates are also contraindicated in patients with suspected right ventricular (RV) ischemia, hypertrophic obstructive cardiomyopathy (HOCM), and/or severe intravascular volume depletion, as preload reduction in these settings can result in severe hypotension even with very low doses. The most commonly reported adverse effect for all nitrate preparations is headache (by labeling, can occur in up to 35 % of patients). Nitrate-induced headache often subsides with dose reduction and does not require specific treatment nor does it mandate therapy interruption. Other adverse effects may include fatigue, dizziness, flushing, and minor dermatologic reactions (e.g., rash, pruritus, etc.) in less than 5 % of patients. When oral nitrates are used for long-term therapy, it is important to schedule doses such that patients have an adequate nitrate-free period each day so that tachyphylaxis does not develop to the hemodynamic and antianginal effects of nitrates. While the biochemical basis for nitrate tolerance remains incompletely understood, it is thought to be due

to attenuation of the vascular effect of nitrates and not an alteration in pharmacodynamics or pharmacokinetics. When using a short-acting oral nitrate, it is reasonable to prescribe evenly spaced doses during the daytime (e.g., 8 am, 1 pm, and 6 pm with meals) which then allows a substantial nitrate-free period overnight to minimize the development of tachyphylaxis, as opposed to scheduled doses at evenly spaced intervals throughout a 24-h period (e.g., every 8 h) (Chap. 40).

23.4.3 Calcium Channel Blockers

Calcium channel blockers (CCBs) produce relaxation of myocardial and vascular smooth muscle cells by inhibiting inward calcium influx across the cell membrane (Chap. 37). The two categories of CCBs include the dihydropyridines (amlodipine, nifedipine, and felodipine) and the non-dihydropyridines (verapamil and diltiazem), both of which may exhibit mild effects on coronary vasodilation. The predominant effect of the dihydropyridines is a decrease in afterload via relaxation of peripheral vascular smooth muscle; however, these agents can sometimes cause reflex tachycardia, which can worsen ischemia. In the absence of concomitant beta-blockade, there is evidence that dihydropyridines may actually cause harm [59]. Non-dihydropyridines primarily affect AV nodal conduction, but they also reduce myocardial contractility that can significantly worsen congestive heart failure in patients with LV dysfunction or shock. Retrospective studies of diltiazem and verapamil demonstrated increased mortality in patients with LV dysfunction, and meta-analyses of trials involving CCBs for NSTE ACS suggest no overall benefit with regard to preventing death or nonfatal MI [60–62]. For these reasons, CCBs are not considered first-line agents in the contemporary medical management of NSTE ACS. In certain patient populations (e.g., beta-blocker intolerant, refractory supraventricular arrhythmias, etc.), there may be a limited role for CCBs as second-line therapy for adjunctive relief of angina or for heart rate and/or blood pressure control.

Drug interactions and adverse events will differ among each of the agents in the calcium channel blocker class. In general, class-wide adverse events from the non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are similar to beta-blockers and include bradycardia, hypotension, PR interval prolongation, dizziness, fatigue, depression, and minor dermatologic reactions (e.g., rash, pruritus, etc.). Special caution should be used when combining a beta-blocker with a calcium channel blocker as together these agents will have additive risks of bradyarrhythmic adverse effects. The non-dihydropyridine CCBs should not be utilized in patients with decompensated congestive heart failure or significant LV dysfunction. Class-wide adverse events for the dihydropyridine CCBs (amlodipine, nifedipine, and felodipine) may include edema (which is often dose related and mild), flushing, palpitations, fatigue, dizziness, and minor dermatologic reactions (e.g., rash, pruritus, etc.) in less than 5 % of patients. In our practice we do not consider any drug interactions to be an absolute contraindication to utilizing our preferred dihydropyridine CCB (amlodipine), and it can be used safely for afterload reduction in patients with LV dysfunction.

23.5 Ancillary Therapies in ACS

In addition to antithrombotic and antianginal agents, the final categories of pharmacotherapy in the optimal medical management of NSTE ACS include ACE inhibitors and high-intensity statin therapy. These agents have important roles with regard to secondary prevention of future events and efforts to induce favorable ventricular remodeling following a myocardial infarction. As with the antianginal agents discussed above, the pharmacotherapy regimen for ACE inhibition and statin established during the acute inpatient hospitalization should be continued after discharge and further titrated as needed on an outpatient basis.

23.5.1 ACE Inhibitors and Angiotensin II Receptor Blockers

Inhibitors of the renin-angiotensin-aldosterone system have well-described beneficial effects on afterload reduction and positive ventricular remodeling following MI. While there are extensive data for a mortality benefit in patients with chronic CAD, heart failure with reduced LV ejection fraction, and diabetes, there are less robust clinical trial data to guide their use in the acute management of NSTE ACS [63–66]. In the absence of contraindications, such as renal failure or hyperkalemia, we recommend early initiation of short-acting formulations to allow rapid dose titration (e.g., captopril 12.5 mg every 8 h) in hemodynamically stable patients. Our practice is to titrate a short-acting agent to achieve target blood pressure and then covert to an equipotent dose of a long-acting ACE inhibitor (e.g., lisinopril, usually in 20–40 mg daily dosing) at discharge. Angiotensin II receptor blockers (ARBs) can be substituted in patients who are intolerant of ACE inhibitors.

Drug interactions and adverse events will differ slightly among each of the agents in the ACE inhibitor and ARB classes. In general, class-wide adverse events from ACE inhibitors include hyperkalemia, hypotension, a bradykinin-mediated dry cough, dysgeusia, angioedema, and minor dermatologic reactions (e.g., rash, pruritus, etc.). The dry cough some patients experience with ACE inhibitors does not require specific treatment nor does it mandate therapy interruption; however, if patients are unable to tolerate it, they can be switched to an ARB as that class of medications does not produce this adverse effect. Class-wide effects from ARBs are otherwise similar and may include hyperkalemia, hypotension, dyspepsia, angioedema, and minor dermatologic reactions (e.g., rash, pruritus, etc.). Special caution and close monitoring must be used when combining an ACE inhibitor or ARB with other medications which can raise potassium levels (e.g., spironolactone) (Chap. 36). We do not recommend combining ACE inhibitors and ARBs in the same patient; beyond that, in our practice we do not consider any drug interactions to be an absolute contraindication to utilizing our preferred agents (short-acting captopril or long-acting lisinopril) in the setting of NSTE ACS.

23.5.2 HMG Coenzyme A Reductase Inhibitors (Statins)

HMG coenzyme A reductase inhibitors, more commonly known as "statins," improve cardiovascular outcomes by lowering LDL, and their use is considered standard of care in the therapy of NSTE ACS. There may be additional mechanisms of benefit in ischemia independent of LDL reduction, and the "pleiotropic" effects of statins have been postulated to include improvement in endothelial dysfunction, stabilization of atherosclerotic plaque, and increased nitric oxide bioavailability, in addition to antioxidant, anti-inflammatory, and antithrombotic properties [67] (Chap. 28). A meta-analysis of clinical trials found a significant benefit to early initiation of high-intensity statin therapy in the setting of ACS compared to conventional lower-dose therapy [68]. In the absence of contraindications such as severe transaminitis, prior intolerance, or concomitant use of cytochrome P450 inhibitors, we recommend administration of high-dose statin therapy (typically atorvastatin 80 mg) early in NSTE ACS presentations. In our practice, our goal of high-intensity statin therapy is to reduce the LDL as low as possible in patients with NSTE ACS, ideally to less than 70 mg/dL (1.82 mmol/L).

Drug interactions and adverse events will differ slightly among each of the agents in the statin class. In general, class-wide adverse events from statins include myalgias, muscle spasms, myositis, arthralgias, nausea, diarrhea, and dyspepsia; however, these rarely will rise to a severity prompting treatment discontinuation. It is important to note that intolerance to one statin agent does not mean a patient is intolerant or "allergic" to all statin agents, and it is common these patients can tolerate a different agent at equipotent dosing without adverse effects. An important drug interaction to be aware of exists for patients with human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) – atorvastatin should not be combined with commonly used antiretroviral agents such as tipranavir, ritonavir, or telaprevir. In patients with HIV/AIDS, preferred statins include rosuvastatin or pitavastatin as they are not expected to have substantial interactions with antiretroviral agents. Although pravastatin is an acceptable alternative in this setting due to its lack of metabolism through the CYP3A4 system, it is not as efficacious as rosuvastatin or pitavastatin in reducing LDL cholesterol.

23.6 Concluding Remarks

The pharmacologic management of ACS is a highly evidence-based discipline that is guided by decades of rigorous investigation. While much attention has been given to the technological advances in PCI, the majority of benefit with regard to improving survival, reducing morbidity, and preventing the progression of coronary artery disease can be attributed to the significant advances in adjunctive pharmacotherapies for ACS. This chapter has provided a broad overview of each of the categories of pharmacologic agents used in the acute management of NSTE ACS. A fundamental goal of

therapy is to achieve a robust antithrombotic effect with a combination of antiplatelet and antithrombotic medications while balancing the associated risks of bleeding. Aspirin remains the cornerstone of ACS therapy and should be given early in combination with a second antiplatelet agent (most commonly P2Y12 antagonists rather than GPI), with the addition of GPI reserved for patients who remain unstable, have a large thrombus burden on angiography, or have very high-risk clinical features. While there are multiple anticoagulants with significant supporting evidence, unfractionated heparin has remained a durable choice and has many properties which make its use favorable in the acute management of NSTE ACS (e.g., widespread availability, low cost, rapid clearance, easy point-of-care monitoring, and reversal with protamine). Several new antithrombotic agents are currently under investigation, and the "holy grail" for new antithrombotic therapies remains to achieve a predictable, uniform response that offers improved efficacy without significantly increasing bleeding complications. During the index hospitalization for ACS, all patients should also be started on high-intensity statin therapy, beta-blockers, and ACE inhibitors unless there are specific clinical contraindications. Together with optimization of modifiable cardiovascular risk factors such as hypertension, hyperlipidemia, smoking status, and diabetes mellitus, the importance of a comprehensive evidence-based pharmacologic approach for the management of NSTE ACS cannot be overemphasized.

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Chapter 24
Drug-Eluting Stents and Coronary Artery Disease

Eliano Pio Navarese, Mariusz Kowalewski, and Michalina Kołodziejczak

Abstract Over the past 10 years, drug-eluting stents (DESs) have become the most widely used devices worldwide for management of coronary artery disease by consistently reducing rates of target vessel revascularizations in comparison to the previous bare-metal stents (BMS). DES technology is a dynamic field, which rapidly evolved with different generations of DESs available; after DES implantation, dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 inhibitor is mandatory to reduce the risk of thrombotic complications. In this chapter, we outline the differences between DESs and BMSs, the efficacy and safety of first- and second-generation DESs, the recently introduced fully absorbable DESs, and the clinical evidence on the duration of the DAPT.

Keywords Drug-eluting stents • Coronary artery disease • Coronary angioplasty • Bare-metal stents • Dual antiplatelet therapy • P2Y12 inhibitor

24.1 Introduction

After the first percutaneous transluminal coronary balloon angioplasty performed in 1977 [1], coronary interventional techniques have evolved very fast. Important components introduced in the field are the metallic scaffolds known as stents to prevent arterial recoil and restenosis after balloon dilatation. Advances in stent technology have contributed to the widespread adoption of percutaneous coronary intervention (PCI) for the treatment of coronary artery disease in several clinical

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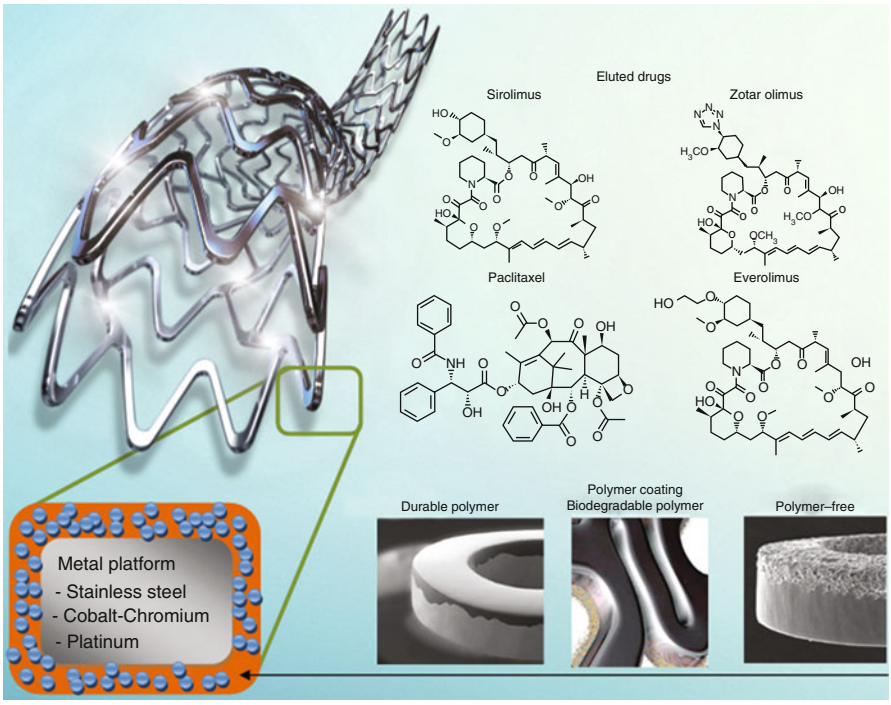

Fig. 24.1 Drug-eluting stent structure composed of a metallic stent, a polymer-based drug delivery platform, and a pharmacologic agent. Various available platforms, polymers, and drug agents are described

scenarios. Since the beginning, stent design has undergone constant refinement, including the development of drug-eluting stents (DESs) (Fig. 24.1) [2]. In this chapter, we outline the evolution of stent technology represented by DESs.

24.2 DES Structure

DESs are composed of a metallic stent, a polymer-based drug delivery platform, and a pharmacologic agent (typically an immunosuppressant and/or antiproliferative compound) (Fig. 24.1). The goal of DES technology is to minimize PCI-related vascular inflammation and cellular proliferation. Available platforms are made of stainless steel, cobalt-chrome, or platinum-chrome. Cobalt-chrome alloys provide increased radial strength and radiopacity, as compared with stainless steel, allowing for development of thinner struts with improved deliverability of the device. Another characteristic is that platforms made with thinner struts may result in less arterial injury and reduce the risk of in-stent restenosis (ISR), in turn associated with lower thrombotic risk. Platinum-chrome alloys can further improve radial strength. Polymer coatings that are applied to the stent surface serve as drug carriers and allow a controlled drug release. We discuss the progress in polymer technology aimed at decreasing local inflammatory reactions and thrombosis by improving the

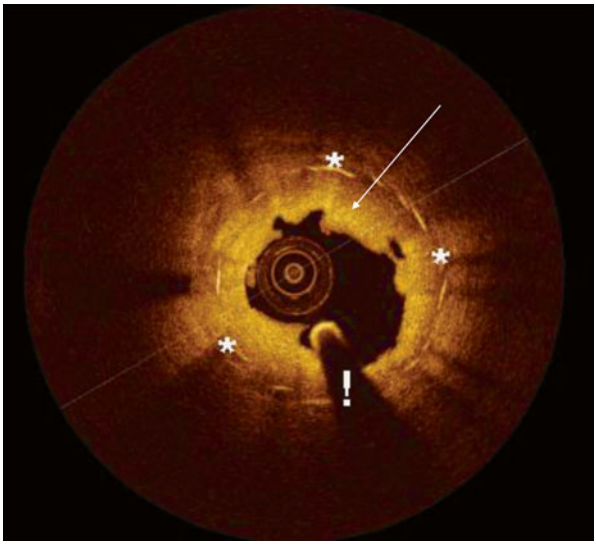

Fig. 24.2 Optical coherence tomography (OCT) image of in-stent restenosis. Restenosis is demonstrated as neointimal proliferation (*arrow*) beyond the stent metallic struts (*) inside the vessel lumen. OCT catheter (!)

biocompatibility of polymers. DESs that have been approved by the Food and Drug Administration (FDA) have durable polymer coatings. However, new platforms for DES feature polymers that biodegrade after drug elution, resulting in a stent surface similar to that of a bare-metal stent. First-generation stents released sirolimus or paclitaxel and had stainless steel platforms, whereas new-generation stents release everolimus or zotarolimus and feature cobalt-chrome or platinum-chrome platforms with thinner strut thickness and more biocompatible, durable polymer coatings.

24.3 Challenges with First DESs

24.3.1 Neointimal Formation and In-stent Restenosis

The lack of endothelial coverage and the consequent inflammatory response in the vessel wall are able to stimulate a remodeling process with internal migration and proliferation of medial smooth muscle cells (SMCs) and deposit excess extracellular matrix (ECM) proteins that ultimately obstruct the vessel lumen [3–6]. This cascade of molecular processes can ultimately lead to development of the angiographic ISR, an intra-stent narrowing owing to new formed plaque that can require further intervention (Fig. 24.2).

24.3.2 Stent Thrombosis

Stent thrombosis (ST) is a catastrophic event that is associated with increased myocardial infarction (MI) rates culminating in increased mortality (Fig. 24.3). Intense controversy regarding the safety of DES has been sparkled in the last few years as

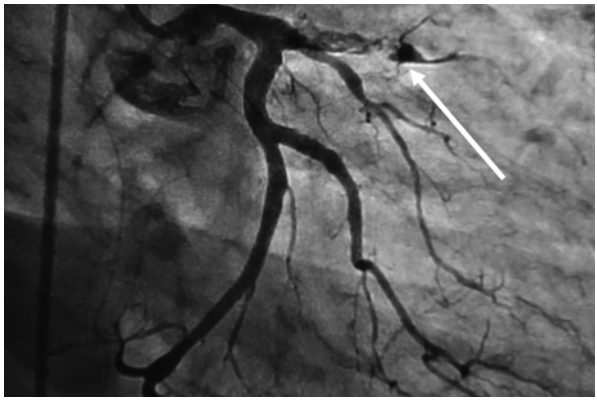

Fig. 24.3 Angiographic image of stent thrombosis. *Arrow* points to the distal stent portion in the proximal left anterior descending coronary artery

long-follow-up data reports were gradually becoming available and showed an increased risk of late ST and MI in patients treated with a first-generation DES after discontinuation of dual antiplatelet therapy (DAPT). The incidence of ST up to 1 year follow-up seems similar for DES and old bare-metal stents (BMS) and ranges from 0.6 to 3.2 % for BMS and 0.6 to 3.4 % for DES, depending on patient and lesion characteristics [7–10]. Before the introduction of DES, ST was perceived as a complication occurring early after stent implantation. The typical clinical presentation of ST consists of chest pain and ischemic electrocardiographic changes in the target vessel territory, presenting in some cases as acute MI. However, ST can also manifest itself as sudden death, or it can be asymptomatic in the setting of collateral vessels. A multitude of mechanisms are potentially involved into the occurrence of ST as well as various patient-related, lesion-related, procedural, and post-procedural factors [11–19]. The suggested pathophysiological mechanisms after DES implantation that predispose to ST are the following: (1) the exposure of blood before re-endothelialization to prothrombotic subendothelial constituents, stent struts, and/or polymer material can lead to activation of the extrinsic pathway of the coagulation cascade; (2) a persistent slow coronary blood flow and low shear stress can activate the intrinsic pathway; (3) inadequate pharmacological suppression of platelet activation (e.g., after premature discontinuation of DAPT); and (4) the presence of a systemic prothrombotic state (e.g., due to acute coronary syndrome or malignancy). A meta-analysis found that most consistently reported predictors are early DAPT discontinuation, the extent of coronary artery disease, and total stent length [18].

24.4 DES Characteristics

24.4.1 First-Generation DES

Over the past 10 years, first-generation DESs, especially sirolimus-eluting stent (SES) and paclitaxel-eluting stents (PES), have become the most widely used devices worldwide for management of coronary artery disease. However, despite their clear superiority in preventing ISR and that the need for repeat

revascularization due to eluted antiproliferative drugs is certainly proven, concerns have emerged in regard to their long-term safety, strictly late and very late thrombotic events. In a network meta-analysis [20] (an analysis of studies of multiple interventions that makes use of direct and indirect comparison) involving 38 trials and more than 18,000 patients, there was a marked reduction in the rate of repeat revascularization with both SES and PES, as compared with BMS. Based on this analysis, seven patients (95 % confidence interval [CI], 6–8) would need to be treated with SES and eight patients (95 % CI, 7–10) with PES in order to prevent one repeat revascularization, as compared with BMS. However, stents that release sirolimus or paclitaxel have been associated with an increased risk of very late ST, as compared with BMS [10, 21]. In contrast, the risks of death and MI with SES and PES were similar to the risks with BMS [20] which may be explained by the low incidence of very late ST (annual rate, 0.2–0.6 %) and the compensatory effects of a reduced risk of ISR, which is manifested as MI in 10–20 % of patients [22, 23]. The lack of a significant difference in mortality or MI between first-generation DES and BMS despite the increased risk of very late ST with DES may be because ISR is not always a benign phenomenon, presenting as acute MI in 3.5–19.4 % of patients. Thus, a small increase in a low-frequency event (late or very late ST) with frequent, serious, life-threatening consequences may be blunted by a large reduction of a more common event (ISR), which is more rarely associated with serious clinical consequences.

24.4.2 DESs Versus BMSs

BMSs were the first devices used for coronary stenting. Interestingly, although these devices reduced rates of restenosis compared with balloon angioplasty, ISR, classified as a narrowing within the stented segment of at least 50 %, continued to develop in up to 20–30 % of lesions [24, 25]. Although stent insertion prevents arterial recoil and stabilizes vascular dissections, ISR might still occur because of exuberant neointimal accumulation much akin to “scar formation” the mechanisms of which are discussed in detail later. In addition to acting as a vascular scaffold, stents soon evolved to become drug delivery systems in the form of modern DESs. One collaborative network meta-analysis indicated that DESs and BMSs are associated with similar rates of overall and cardiac mortality and that use of SES is associated with a reduction in the risk of MI compared with the use of BMS and PES [20]. Although there was little evidence of an overall increase in definite ST associated with DESs, the authors found PES to be associated with an increased incidence of late ST compared with BMS and SES. Wide credibility intervals precluded definite conclusions on a potential increase of late ST with SES compared with BMS. A secondary analysis showed a marked reduction in target lesion revascularization (TLR) with both DES, which was more pronounced for SES than for PES. Lastly, little evidence was found of an increased risk of mortality associated with either DES in diabetic patients, but wide confidence intervals again precluded definite conclusions.

A recent series of pooled analyses of randomized trials comparing DES with BMS found preliminary evidence for an increased risk of late ST (later than 30 day

occurrence) associated with DESs as compared to BMS [8, 10, 26, 27]. These analyses included between 4 [10, 26] and 14 [27] trials and between 1,748 [10, 26] and 4,958 [27] patients. A pooled analysis of four trials including 428 diabetic patients by Spaulding and colleagues [26] found a significant increase in mortality with SES compared with BMS. These results are difficult to interpret: the number of patients was small and the mortality rate of diabetic patients was surprisingly low among those with BMS. Despite the statistical significance, chance could have contributed to Spaulding and colleagues' results. The increase in the risk of Academic Research Consortium (ARC)-defined definite late ST that was found for PES compared with BMS was lower—but more precise—than the increase reported in a pooled analysis by Stone and colleagues [10]. The use of per-protocol definitions for ST could have resulted in an overestimation of the risk increase associated with PES. Late ST occurs less frequently with SES than with PES, which is concordant with a recent observational study by Daemen and colleagues [28]. With regard to target lesion revascularization, the results are mainly driven and compatible with those from the two largest trials—REALITY [29] and SORT OUT II [30]—which failed to show a significant difference in TLR between the two drug-eluting stents. Confidence intervals were large for both. SORT OUT II did not include scheduled, protocol-driven clinical follow-ups. Instead, data were ascertained from death and hospital registries, which could have resulted in diagnostic misclassification and biased estimates of differences between the two DESs [31].

24.4.3 Second-Generation DES

Second-generation DESs offer numerous improvements over their first-generation counterparts. Namely, second-generation devices have decreased strut thickness, improve flexibility/deliverability, enhanced polymer biocompatibility/drug elution profiles, and superior re-endothelialization kinetics. In contemporary practice, second-generation devices are now the predominant coronary stents implanted worldwide [32].

24.4.3.1 Endeavor® Zotarolimus-Eluting Stent

The Endeavor zotarolimus-eluting stent (ZES; Endeavor) is a second-generation stent based on a stronger cobalt-chromium stent platform, with improved flexibility and decreased stent strut size. In addition, the ZES uses a novel phosphorylcholine polymer coating with stable, lipid membrane analogue designed to maximize biocompatibility and minimize inflammation associated with previous polymers. As well, the polymer is engineered to shorten the drug elution time such that most of the drug is eluted during the initial injury phase. Zotarolimus is a sirolimus analogue with similar immunosuppressant properties but enhanced lipophilic properties. This key difference was featured to enhance vessel wall localization and minimize the dispersion into the circulation [33]. Indeed, preliminary animal models supported the potential benefits

of this novel stenting system, resulting in less local inflammation and improved re-endothelialization compared with SESs and PESs [34]. The ENDEAVOR I trial was the first to demonstrate safety and efficacy of ZESs in humans [35]. The ENDEAVOR II trial compared the ZES with the Driver BMS, showing improved major adverse composite events (MACE) at 2 years [36]. The subsequent ENDEAVOR III trial then compared ZES with SES, with the ZES paradoxically showing greater in-stent late lumen loss (ISLL) and IRS (11.7 % vs. 4.3 %) but less MACE (0.6 % vs. 3.5 %) [37]. Long-term follow-up to 5 years displayed a "catch-up" phenomenon whereby rates of in-stent restenosis increased in SES patients to levels comparable with ZESs [38]. Similar in design, the ENDEAVOR IV trial compared ZES with PES and again found higher rates of ISR in the ZES group [39]. These findings persisted for 3 years, but clinical outcomes, mainly because of fewer MIs, were less common with the ZES, thereby suggesting a potential benefit in regard to vascular healing [40]. However, these trials were underpowered to adequately assess differences in ST. The PROTECT trial specifically addressed the incidence of ST in a randomized study of ZESs versus SESs in more than 8,700 patients followed up to 3 years and failed to demonstrate a difference in definite or probable ST rates between Endeavor and Cypher stents [41].

24.4.3.2 Resolute® Zotarolimus-Eluting Stent

The Resolute represents a refinement of the Endeavor stent, using the same cobalt-chromium (Driver) stent platform and zotarolimus agent but with a novel trilayered polymer. Similarly, the newer Resolute Integrity (sometimes classified as a third-generation DES) uses the same drug and novel trilayered polymer but is based on the new Integrity stent platform providing improved deliverability. This novel trilayered polymer is composed of three main components: a hydrophilic polymer for biocompatibility, a hydrophobic polymer for drug elution control, and a polyvinyl polymer which rapidly releases the drug immediately after implantation. The net effect is the suppression of the initial inflammatory response, followed by most of the drug being eluted over the next 60 days in an attempt to improve the late healing characteristics. The RESOLUTE trial was the first clinical study to evaluate the Endeavor Resolute and enrolled patients with simple de novo lesions in a prospective, single-arm, nonrandomized trial demonstrating clinical outcomes similar to its predecessors with no cases of ST [42]. The RESOLUTE All-Comers trial then compared the Resolute with the Xience V (everolimus-eluting stent [EES]). This study population contained greater lesion complexity and demonstrated non-inferiority of the Resolute system in terms of target lesion failure (cardiac death, target vessel MI, ischemia-driven target lesion revascularization) [9]. In the recent DUTCH PEERS randomized trial, the zotarolimus-eluting stent was non-inferior to the everolimus-eluting stent with respect to the primary endpoints of target vessel failure defined as a composite of safety (cardiac death or target vessel-related MI) and efficacy (target vessel revascularization) at 12 months (absolute risk difference 0.88 %, 95 % CI −1.24–3.01 %; upper limit of one-sided 95 %, CI 2.69 %; non-inferiority $p=0.006$). Both stents were similarly efficacious and safe and provided excellent clinical outcomes [43].

24.4.3.3 Everolimus-Eluting Stent

Everolimus, a derivative of sirolimus, is a cell cycle inhibitor designed to overcome the physicochemical properties that rendered the oral administration of sirolimus difficult [44]. Similar to its predecessor, everolimus inhibits SMC proliferation in vitro and vascular intimal thickening in animal transplant models [45]. Its cytostatic properties rendered it a potentially valuable addition to the evolving arsenal against ISR, prompting the development of the Xience V/Promus CoCr-EES in parallel to the ZES as another second-generation DES. In 2004, Grube et al. published the prospective, randomized, single center, the FUTURE I feasibility trial, demonstrating safety and improved in-stent late loss (ISLL) (i.e., narrowing of the stented segment) over BMSs at 12 months [46]. This was followed by the SPIRIT FIRST trial demonstrating similar results with EES versus BMS in de novo coronary lesions [47]. Later, the SPIRIT II trial demonstrated improvements in ISLL and neointimal volumes over the Taxus PES [48]. Similarly, the SPIRIT III trial compared the Xience V and Taxus Express demonstrating improvements in late lumen loss and lower MACE rates largely because of a few MIs [49]. The subsequent second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE) trial demonstrated improved stent and clinical outcomes in a "real-world" experience, providing further support for the superiority of second-generation EES over their PES counterparts [7]. Finally, the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial demonstrated non-inferiority of EES to SES in inhibiting late loss at 9 months and clinical events at 12 months [50]. The newer Promus Element has the identical drug/polymer profile of the Xience V/Promus but offers improved deliverability with a novel platinum-chromium scaffold, demonstrating non-inferiority to the Xience V/Promus in de novo lesions [51].

In summary, regarding DESs, first-generation SESs and PESs provided major advances in the treatment of obstructive CAD with marked reductions in ISR. Second-generation stents appear to be safe and efficacious and provide a modest improvement in outcomes compared with their first-generation counterparts. This difference in outcomes was recently emphasized in a large ($n = 94{,}384$ patients) observational study. Compared with the first-generation DESs and BMSs, second-generation devices are associated with a lower risk of ISR, ST, and mortality [52] Thus, these new stent platforms represent the state of the art in DES design and form the cornerstone of modern PCI.

24.4.3.4 First-Generation Versus Second-Generation DES

A large-scale meta-analysis by Navarese et al. so far comparing first-generation versus second-generation DES [53] with 31,379 patients included showed the following findings:

1. Second-generation EES and ZES significantly reduced the incidence of MI compared with first-generation PES.
2. Only second-generation EES significantly reduced the odds of definite and definite/probable ST compared with first-generation DES (Fig. 24.4).

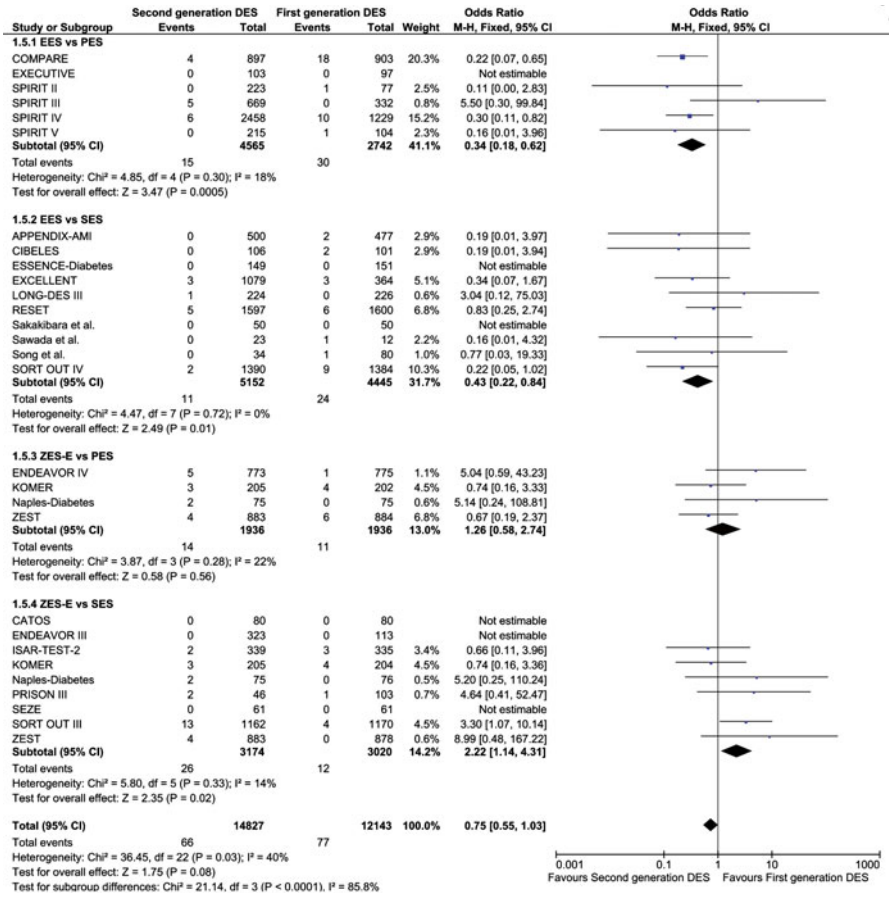

Fig. 24.4 Individual and summary odds of short-term (<1 year) definite stent thrombosis in studies comparing first- and second-generation drug-eluting stents. ORs and 95 % CIs are reported as summary statistics. The size of a square is proportional to the weight of each study (Adapted from [53])

3. Second-generation EES and ZES-R and the first-generation SES are similar to each other with regard to their efficacy and significantly better than ZES-E and PES with regard to repeat coronary revascularizations.

Single and composite safety endpoints did not differ in direction or magnitude of the effect favoring durable polymer EES. The inflammation induced by the durable polymers of first-generation DES may result in delayed healing and incomplete covering of stent struts by new and functional endothelium with uncovered stent struts serving as a source for future episodes of ST. Secondly, other factors such as stent malapposition, mechanical tissue injury caused by stent struts during implantation, and, finally, polymer hypersensitivity or even toxicity, as is the case for PES [54] and in turn associated with persistent fibrin deposition, might also play a potential role. Second-generation DES was introduced to address the concerns raised by

first-generation DES by both optimizing their metallic stent platform or polymer and eluted drug. That is, second-generation EES uses thin struts coated with durable, fluorinated polymer, which has been shown to have thromboresistant properties in experimental studies. Similarly, ZES-R combined more rapid elution kinetics than SES in the same time offering thinner, more biocompatible phosphorylcholine polymer placed on a cobalt alloy stent platform. In the meta-analysis, which compared first-generation versus second-generation DES data for most robust evidence of safety endpoints, second-generation EES was found superior to first-generation PES but not to SES. This might have been attributed to the proven overdose and/or accumulation of paclitaxel in the arterial wall due to a coronary uptake, in turn leading to toxicity, inflammation, and late in-stent stenosis, which is not the case with SES [55]. The superiority of thin strut EES and ZES in reducing the incidence of MI in the short clinical follow-up might also come from mechanistic reasons. Indeed, the positive clinical effect might be related to the more frequent side-branch jailing with thick strut devices (SES Cypher 140 μm and PES Taxus Express 134 μm vs. ZES Endeavor/Resolute 91 μm and Abbott Xience V 81 μm), resulting in turn in higher rates of periprocedural MI [56–58]. Although ST should be considered a surrogate safety endpoint, which must be interpreted in the perspectives of MI and mortality, it remains a devastating complication and is often associated with high rates of mortality and morbidity. Second-generation EES was associated with significantly lower rates of definite and definite or probable ST in short-term analysis compared with first-generation DES; this finding is in line with other meta-analyses [53, 59] showing the superiority of EES over BMS and first-generation and second-generation DES in reducing early (0–30 days) and late (31 days–12 months) ST. This analysis integrated the most updated data and enriches the previous findings of longer follow-up clinical data for particular devices, demonstrating for the first time that EES reduces definite and definite or probable ST also beyond these time frames (very late ST) compared with first-generation DES. Notably, data on EES do not reflect the performance of second-generation ZES-E in terms of stent thrombosis; indeed, Endeavor was found to even increase the incidence of definite ST as compared with SES at ≤1 year, mainly driven by the results of the SORT OUT III [60–62] and ZEST [63] trials. As zotarolimus is a synthetic analogue of sirolimus, the disparities between stents are attributed to different kinetics of drug release from the polymers used for drug elution (1 week with ZES and 3 months with SES). It is postulated that quick zotarolimus release and high initial concentrations not only affect the healing of the plaque and arterial wall but may also allow for exposure of the atheromatous debris to the bloodstream. Thus, increasing the risk of early ST, which is of particular importance in high-risk patients with acute coronary syndrome or multivessel disease. Design-related factors such as strut thickness, type of antiproliferative agent, drug elution kinetics, elution time, and type of polymer are all factors that may as well impact efficacy outcomes [64]. Although not a new finding, all limus-eluting DESs, with the exception of ZES-E, were associated with significantly lower rates of target lesion revascularization (TLR)/target vessel revascularization (TVR) than the first-generation PES. Taken together, inflammation-causing properties of paclitaxel along with the short-release

curve of ZES-E preclude optimal suppression of procedure-related injury responses, in turn resulting in subsequent intimal hyperplasia and increased need for repeat revascularization [34]. Unlike ZES-E, the more recently introduced ZES-R, which has a much longer (up to 180 days) release curve than of the same antiproliferative agent, zotarolimus, is associated with a significant reduction in TVR/TLR compared with ZES-E [65]. Not surprisingly, MACE analysis confirmed the single-outcome findings with second-generation EES outperforming first-generation PES at ≤1 year and beyond. Remarkably, the initial short-term benefit of SES over ZES-E, attributable mainly to higher rates of repeat revascularization with the latter, becomes less pronounced at long-term follow-up when drug elution is over.

24.4.4 Biodegradable Polymer DES

To improve the safety of first-generation DES, new devices have been developed that use either type of biodegradable polymers combined with stainless steel platforms. Both of them have been tested in randomized controlled trials. A large meta-analysis, with 63,242 patients, examined the safety and efficacy profile of second-generation durable polymer DESs and biodegradable polymer DES (BP-DES) compared with first-generation DES and with each other [32]. Second-generation durable polymer EES and ZES-R, the first-generation SES, and the BP-DES were similar to each other concerning their efficacy and significantly better than ZES-E and PES with respect to coronary revascularizations. There was a safety gradient, with EES and ZES-R resulting in lowest rates of death and MI. Conversely, BP-DES, ZES-E, and PES were being associated with significantly increased odds of MI or stent thrombosis compared with EES. One of the most important findings was the significant increase in the odds of MI with BP-DES compared with durable polymer EES (Fig. 24.5). To date, BP-DES has been perceived as safer than first-generation SES and non-inferior to second-generation EES, mainly on the basis of results from individual trials powered only for composite endpoints of safety and efficacy [66–70]. When single (instead of composite) endpoints of safety were analyzed, the analysis provided new insights suggesting that BP-DES is associated with a similar (not higher) safety to the first-generation SES and a significantly higher rate of MI than EES. Indeed, the second-generation durable polymer EES and ZES-R were associated with the most favorable safety profile compared with not only the first-generation durable polymer PES but also the second-generation ZES-E and BP-DES.

In a broader perspective, the study by Navarese et al. [32] showed that among all devices compared, the durable polymer second-generation EES and ZES-R were the safest DES to date. These findings agree with those of two previous network meta-analyses [59, 71] that compared first- and second-generation DES with BMS. However, the study substantially differed from the others by incorporating the most recent evidence from head-to-head DES comparison trials and forming the largest DES database ever analyzed, with a total of 63,242 patients. Addition of

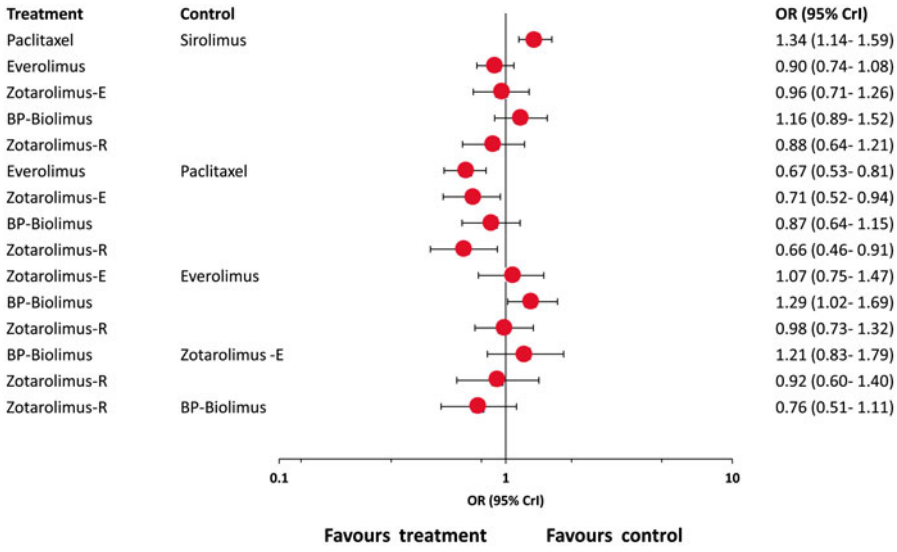

Fig. 24.5 Network meta-analysis findings on comparative efficacy of first- and second-generation drug-eluting stents (DES) as compared to biodegradable polymer DES and to each other for the outcome of myocardial infarction (MI). Analysis demonstrated significant reduction of the odds of MI with first-generation sirolimus (SES) and second-generation everolimus (EES) and Endeavor and Resolute zotarolimus (ZES-E and ZES-R) as compared to first-generation paclitaxel (PES). Additionally EES was found superior to BP-DES concerning reducing the odds of MI (Adapted from [32])

BP-DESs, which are used mainly in Europe and Asia, provided a comprehensive overview of the most widely used DES in current clinical practice worldwide, not compared so far within their class in such a scale for safety and efficacy endpoints. To date, the direct comparison between BP-DES and BMS is limited to single trials, making indirect comparisons through this "weak" common link imprecise and meaningful conclusion difficult. The safety of first-generation DES has been extensively debated. The relatively high rates of stent thrombosis associated with these devices, a phenomenon that translates into increased rates of death or MI, raised concerns regarding their widespread use, despite their clear efficacy benefits over BMS [28, 72]. Further studies showed that the mechanisms of stent thrombosis after DES implantation are complex, with factors related to device design being of paramount importance. Indeed, the inflammation induced by the durable polymers of first-generation DES could cause delayed healing and incomplete covering of stent struts by new and functional endothelium, with uncovered stent struts representing a source for future episodes of ST [73]. Other factors such as stent malapposition and mechanical tissue injury caused by stent struts during implantation, however, also play a role in stent thrombosis [7].

New-generation DESs have dealt with the limitations observed with first-generation devices in different ways; BP-DESs use abluminal biodegradable polymers that dissolve within 6–9 months, with the residual metal platform presumably regaining a safety profile similar to a BMS beyond this time frame [74].

Conversely, second-generation durable polymer DESs have replaced first-generation polymers with more biocompatible and thinner polymers [75–77]. Interestingly, the design improvements of the new-generation durable polymer DES have run in parallel with a reduction of definite stent thrombosis rates, compared with the first-generation PES and SES in early, late, and very late phases of follow-up [78]. Furthermore, late stent thrombosis with EES being the first and most studied prototype is reduced not only when compared with first-generation DES but also with BMS. This suggests that the durable fluoropolymer used in these devices might be "thromboresistant" and more biocompatible than BMS [59, 71, 79]. This in turn generates a shift from the contention of an increased risk of stent thrombosis with DES compared with BMS toward the converse relation. In contrast, BP-DES has failed to provide a significant reduction in 1 year ST rates compared with SES, with both available trials showing a numerical advantage of SES [66, 68]. Although the 5-year follow-up of LEADERS [80]—the only available trial with a long follow-up—shows a significant reduction of the 1–5-year rates of ST compared with SES, the overall rate at 5 years was not significantly lower than is for SES, pointing once more to the impact of first-year outcomes. Stent thrombosis, however, remains a surrogate safety endpoint and needs to be interpreted in the context of objective safety endpoints such as death and MI. Durable polymer DES yielded lower odds of death and MI compared with BP-DES, with EES reaching a significant reduction in MI. Of note, this finding is in line with the results of the NEXT and COMPARE II trials [69, 70] both of which showed a numerical reduction of MI associated with EES compared with BP-DES, which became significant for Q-wave MI in the latter. The advantage with regard to MI observed with thin strut devices such as EES might be related not only to ST but also to lower rates of periprocedural MI resulting from side-branch jailing, which in turn for mechanistic reasons might be more frequent with thick strut devices [56]. Higher degrees of re-endothelialization achievable with these stents compared with the thick strut devices have been shown in preclinical [57] and optical coherence tomography studies [58], which also might play a role.

These findings on safety among different DES should also be viewed in the context of patients treated with DES who need to undergo noncardiac surgery. Surgery represents one of the most common reasons for premature discontinuation of antiplatelet therapy, which is associated with a significant increase in mortality and major adverse cardiac events [81]. Indeed, the favorable profile observed with second-generation DES might become clinically relevant in this context, in light of recent studies suggesting the safety of shorter overall duration of dual antiplatelet therapy (DAPT) in patients treated with these devices [82, 83]. In this perspective, newer thin strut biodegradable polymer DES recently introduced in the market might have the potential to enhance safety and efficacy outcomes after percutaneous coronary intervention (BIO-RESORT, TWENTE III, and EVOLVE II QCA). Analyses beyond 1 year confirmed maintenance of the direction of the estimates observed at 1 year follow-up. Efficacy factors related to design, such as strut thickness, type of antiproliferative agent, drug elution kinetics, and elution time, as well as type of polymer, could all affect efficacy outcomes [64, 84].

New-generation EES, BP-DES, ZES-R, and first-generation SES were associated with reduced rates of TLR and target vessel revascularization (TVR) compared with ZES-E and/or first-generation PES. These findings therefore confirm on a larger-scale comparable efficacy of BP-DES and second-generation DES shown in the recent NEXT trial, powered for TLR as a primary endpoint [70]. Although not a new finding, in this analysis, all "limus"-eluting stents, with the exception of ZES-E, were associated with significantly lower rates of TLR and TVR than was the first-generation PES. This finding could derive from the differences in the healing process after implantation between paclitaxel and "limus"-eluting stents. Indeed, the toxicity caused by the long-lasting presence of paclitaxel in the vessel wall could give rise to vascular healing process, with prolonged fibrin deposition and inflammation, as shown in preclinical and postmortem studies [34, 73]. On the other hand, with ZES-E, short-release kinetics could result in insufficient inhibition of neointimal hyperplasia. Indeed, the more recently introduced Resolute ZES, which has a much longer (up to 180 days) release curve of the same antiproliferative agent, zotarolimus, is associated with a significant reduction in TLR and TVR compared with ZES-E.

There are in vitro data that raise issues with regard to biodegradable polymer technology. (1) It has been demonstrated that the polymer-based coating of the biodegradable stent (Biomatrix, Biosensors, Singapore) provides lower elasticity than durable polymers. This may lead to defects and fragility (cracks) of the coating following stent expansion during more than mild overstretches of the stent [77]. Therefore, after post-dilatation, embolization of material and microvascular obstruction could occur, or there might be reduced antiproliferative power because of detachment of polymer fragments. (2) The chronic swelling of the stent as it absorbs water to dissolve has been shown to influence the degree of neointimal hyperplasia [85]. Because the biodegradable polymer is expected to be totally degraded within 12 months following device implantation, the stent irregularities are unlikely to result in unfavorable clinical events. Thus, these data are only hypothesis generating and need to be confirmed in large-scale clinical trials with a long follow-up.

Several recently published or presented randomized clinical trials (RCTs) have performed head-to-head comparisons of the first-generation DES with the new BDS. The LEADERS [66] study with an all-comer design was the first head-to-head comparison of a stent platform eluting biolimus from a biodegradable polymer with a first-generation SES. At 9 months follow-up, the primary endpoint, a composite of death, MI, and TVR, occurred in 9.2 % of patients treated with BP-DES and 10.5 % of patients treated with DES, demonstrating the non-inferiority of BP-DES compared to the DES (p for non-inferiority = 0.003). Similarly, the ISAR-TEST-4 [86] with 2,600 enrolled patients compared a novel biodegradable polymer-based, rapamycin-eluting stent with two leading limus-based DES, the Cypher (using sirolimus) (Cordis, Johnson & Johnson, Warren, NJ, USA) and the Xience (using everolimus) (Abbott Laboratories, Abbott Park, IL, USA). At both 30 days and 12 months, BP-DES was significantly non-inferior ($p = 0.005$) to the "limus" DES for a composite endpoint that included both safety (cardiac death/MI) and clinical restenosis. Conversely, the COSTAR DES trial [87] found that the novel

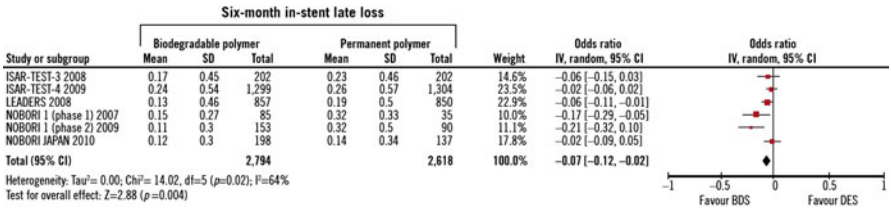

Fig. 24.6 A significant 6-month reduction in in-stent late loss (ISLL) observed among the patients treated with biodegradable polymer DES as compared to controls (Adapted from [84])

platform was not non-inferior to a Taxus DES (Boston Scientific, Natick, MA, USA). At 8 months, the incidence of MACE (11.0 % vs. 6.9 %, $p<0.005$) and late loss (0.49 mm vs. 0.18 mm, $p<0.0001$) was significantly higher with the COSTAR stent. In a recent meta-analysis [84], no clear advantage for BP-DES was shown as compared to DES in the rates of TLR and TVR, despite a significant 6-month reduction in ISLL observed among the BP-DES-treated patients (Fig. 24.6). ISLL is a frequently used parameter to quantify the degree of neointimal hyperplasia after coronary stenting [88]. A strong, direct, and significant association between ISLL and clinical impact, measured as number needed to treat to prevent one TLR, has also been demonstrated [89]. In the current meta-analysis, the lack of association between ISLL and TLR may be explained by the fact that the majority of the included RCTs were underpowered for low rates of binary events (e.g., TLR). On the other hand, the use of a continuous variable like ISLL allowed the efficacy of BP-DES versus DES to be compared without the need for extremely large patient populations. The finding of a decreased ISLL with BP-DES as compared to DES in that meta-analysis suggests a potential anti-restenotic efficacy of BP-DES; however, caution must be exercised in interpreting this result, which needs to be confirmed in future large RCTs with longer follow-up.

24.4.5 Polymer-Free DES

As a reflection of the dynamic progress in DES design, the new technology of biodegradable polymer DES and polymer-free DES has been developed and recently introduced to the market. Biodegradable polymer DES employs polymers that dissolve after time in which antiproliferative drug elution is needed. As shown in previous trials and a recent meta-analysis, first biodegradable polymer stents have been found not inferior to first-generation DES with long-term benefits seen mainly in regard to reduction of ST rates [66, 84]. On the other hand, once the degradation process of the polymer is completed in these devices, what remains is a bare-metal scaffold with thick-struts design. This platform may provide lower elasticity than durable polymers, with an increased risk of fragility and micro-damage to the coating, and potential "jailing" of side branches. As demonstrated in a landmark network meta-analysis, these factors explain the lower safety profile with biolimus

biodegradable polymer stents as compared to the second-generation DES [32]. The improved design of polymer-free stents has addressed these limitations [90].

Clinical evidence from RCTs testing these new devices has however provided inconclusive results mainly due to the low number of enrolled patients. In the randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings—the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST) trial [91]—the polymer-free rapamycin-eluting stent was compared to durable polymer paclitaxel-eluting stents for the prevention of restenosis. No significant differences were observed in regard to 9-month angiographic and clinical outcomes. The combined incidence of death or MI was similar between the two groups (4.4 % in the rapamycin stent group vs. 4.0 % in the paclitaxel stent group) and restenosis-driven TLR rate was 9.3 % in both groups. The conclusions of the recently published 5-year follow-up of the ISAR-TEST trial [92] supported the hypothesis that the delayed ISLL reduction with polymer-free DES may indeed reduce the propensity for late inflammatory interactions, which in turn reduce rates of late thrombotic events. The incidence of ST, however, did not differ significantly between polymer-free DES and durable polymer DES arms in the trial (0.5 % vs. 1.6 %). The results of the present meta-analysis are in line with a recently published pooled analysis of individual patient data of 686 patients from two RCTs, ISAR-TEST, and LIPSIA Yukon trials [93]. However, the short follow-up analyzed the limited number of studies and patients included along with non-applicable publication bias analysis, hindered from drawing definitive conclusions with regard to the clinical performance of such devices. The recent meta-analysis [94] incorporated data of 6,178 patients with both short- and long-term follow-up, and its results were consistent in showing comparable but not superior outcomes with the polymer-free DES in comparison to their durable polymer counterpart in both the main and sensitivity analyses performed. Polymer-free technology has the potential advantage that might reduce the inflammatory and prothrombotic risk related to the polymer. On the other hand, these devices are basically BMS with some surface modification: either a roughened surface or microporous surfaces serving as reservoirs for drug; owing to the particular design of these devices, the modified process of coating through microporous surfaces or nanofilms might, however, impair the loading dose of the drug to be eluted [95].

Importantly, it has been shown that besides the efficacy and dose of a drug, drug release kinetics also has direct relevance with the treatment effect [96]. Drug release kinetics of polymer-free DES are likely to be different from those of permanent polymer DES due to the different strut surface; potential nonuniform drug deposition combined with the specially modified stent surface structures may lead to initially fast and later slow drug release [95]. Indeed, despite the advancement with nanoporous technology, the nanoporous polymer-free DES has brittle coating that may crack or delaminate during stent deployment, in turn resulting in a too rapid kinetic of drug release. A further attempt to improve the design of polymer-free DES has been made with polymer-free dual DES in the ISAR-5 trial [97], in which the antioxidant, probucol, has been added to rapamycin (sirolimus). Probucol, a lipophilic and antioxidant, may facilitate absorption of the drug into the vessel wall and drug retention in the vessel itself. However, it remains unclear whether the pro-

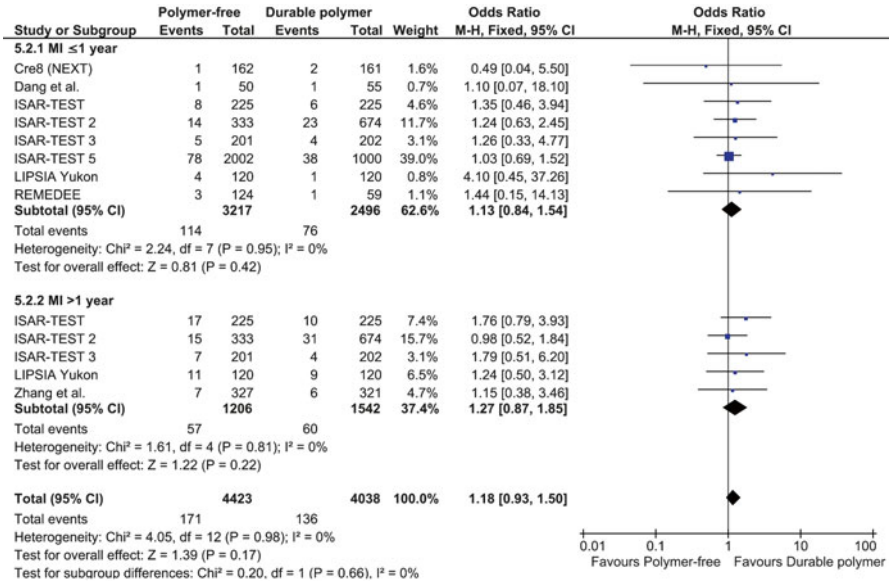

Fig. 24.7 Individual and summary odds ratios with 95 % confidence intervals (CI) for MI in patients treated with polymer-free DES versus durable polymer DES stratified by follow-up duration at short (1 year) and long term (>1 year) (Adapted from [94])

bucol's known antioxidant action or its presumable role in facilitating a controlled sirolimus release was responsible for the improvements in stent performance seen in the trial. The recent reports support the thesis of polymer-free devices being comparable to durable polymer DES, without however providing additional benefits (Fig. 24.7). It should be noted that both short- and long-term adverse events were very low in the durable polymer group, even if the devices used were almost always first-generation stents. This finding probably reflects the period at which the included trials were performed, a time when the lessons of correct stent deployment and minimization of the risk of stent malapposition and under-expansion were well learned. Moreover, it should be well kept in mind that the mechanisms of ST are multifactorial and that the potential pro-inflammatory effect of polymers is only one of the leading factors. Thus, the efforts made by manufacturers in finding new solutions like the absence of a durable polymer should be praised but considered one of the many aspects of this late-occurring complication of PCI.

24.4.6 Fully Bioabsorbable DES

DESs incorporating an antiproliferative drug reduced the rates of ISR, but they can be associated with an irregular and delayed endothelialization, requiring prolonged DAPT to reduce the risk of late and very late ST (≥1 year). The intrinsic limitations

of DESs prompted the idea of creating new devices that are able to provide mechanical support when it is needed and then disappear from the vessel, allowing its natural healing and avoiding the risks associated with having a permanent metallic cage. Bioresorbable materials have therefore been adopted to refine the actual stents, with the intent of providing mechanical support initially when elastic recoil and constrictive remodeling are of concern but with absorption of the devices thereafter. There are several theoretical advantages to use a bioabsorbable stent technology. Once the device disappears, the patient would not need prolonged DAPT, thereby decreasing the risk of bleeding, especially in older patients. Indeed potential advantages of having the stent disappear from the treated site also include reduced or even abolished late ST, improved lesion imaging with computed tomography or magnetic resonance, facilitation of repeat treatments (surgical or percutaneous) to the same site, restoration of vasomotion, and freedom from side-branch obstruction by struts and from strut fracture-induced restenosis. The progression of stenosis seen 7–10 years after stenting has been attributed, at least in part, to inflammation around metallic struts, which might be another reason for using a fully absorbable DES. There are also reasons related to patient preferences; some patients indeed say they prefer an effective temporary implant rather than a permanent prosthesis. Complete polymer resorption occurs approximately 2 years after implantation.

A number of devices are being evaluated, but to date and only in Europe, there are just two types of bioabsorbable vascular scaffold (BVS) available for clinical use in "real-world" patient: the Absorb BVS (Abbott Vascular, Santa Clara, CA, USA) and the DESolve BVS (Elixir Medical, Sunnyvale, CA, USA). Absorb BVS consists of a semicrystalline poly-L-lactide (PLLA) backbone and conformal coating of amorphous poly-D,L-lactide (PDLLA), which contains everolimus as an antiproliferative agent. PLLA and PDLLA are degraded to lactate mainly by hydrolysis. Crystalline residues are phagocytosed by macrophages and are metabolized via the Krebs' cycle and other metabolic pathways [98]. Complete polymer reabsorption occurs approximately 2–3 years after implantation. The available clinical results of the performance of the absorbable stents come from the ABSORB trial [99]. ABSORB Cohort A was a single-arm, prospective, open-label, first-in-human study with safety and imaging endpoints [100]. Between March 2006 and July 2006, Cohort A enrolled 30 patients with stable angina, unstable angina, or silent ischemia and a single de novo lesion in a native coronary artery of 3.0 mm. Patients were treated with the bioabsorbable vascular scaffold (BVS) 1.0 version, and there were two available stent lengths (12 and 18 mm). Clinical endpoints were cardiac death, MI, ischemia-driven target lesion revascularization, ischemia-driven MACE (composite of cardiac death, MI, or ischemia-driven revascularization), and ST. During up to 4 years of follow-up, there was only one non-Q-wave MI related to the treatment of a nontarget stenosis in a patient with a BVS implanted 46 days earlier. There were no cases of cardiac death or scaffold thrombosis up to 4 years. This MACE rate has remained unchanged from the 6-month follow-up. By using multimodality imaging such as multi-slice computed tomography, angiography, intravascular ultrasound (IVUS), and optical coherence tomography (OCT), this study demonstrated at 2-year follow-up the restoration of vasoreactivity in a coro-

nary segment scaffolded after administration of acetylcholine (Ach), methylergonovine, and nitrates. However, after 6 months of follow-up, there was an angiographic in-scaffold late lumen loss (LLL) of 0.44 mm, as a result of loss of radial force from a reduction (−11.8 %) of the scaffold area as measured by IVUS.

The ABSORB Cohort B trial [101, 102] is a multicenter, single-arm trial assessing the safety and performance of the BVS (Rev. 1.1, Abbott Vascular) in the treatment of patients with stable angina, unstable angina, or silent ischemia and a maximum of two de novo native coronary artery lesions with a maximum diameter of 3.0 mm and a length of #14 mm. The clinical endpoints were similar to Cohort A. The trial enrolled 101 patients, 45 of whom (group B1) were randomized to angiographic and invasive imaging at 6-month and 24-month follow-up, and 56 of whom (group B2) were randomized to invasive follow-up at 12 months and 36 months. At 6-month follow-up there were no cases of cardiac death or scaffold ST, and the ischemia-driven MACE rate was 5 out of 101 (4.9 %), three non-Q-wave MIs, and two ischemia-driven PCIs. Interestingly, there were no differences in MACE between vessels <2.5 mm or ≥2.5 mm (3 of 41 [7.3 %] cases in small vessels vs. 2 of 60 [3.3 %] in large vessel cases; $P=0.3933$). In group B2 at 12-month follow-up [102], there were two non-Q-wave MIs (one periprocedural and one iatrogenic) and two ischemia-driven TLRs, resulting in a MACE of 7.1 % (4 of 56). The 2-year follow-up of Cohort B1 (45 patients) has recently been presented, showing a MACE rate of 6.8% (one non-Q-wave MI and two ischemia-driven target lesion revascularization), which is unchanged from the 6-month and 1-year follow-ups, with no cases of scaffold ST or cardiac death. After 2 years, there were no differences in ILL (0.29 ± 0.16 mm vs. 0.25 ± 0.22 mm, $p=0.4391$) and in-segment binary restenosis (5.3 % vs. 5.3 % $p=1.0000$) between "small vessel" [reference vessel diameter (RVD) <2.5 mm] and "large vessel" [RVD >2.5 mm] group. Moreover, there were no differences in MACEs and in plaque composition between groups, but IVUS showed a significant late lumen increase and positive vessel reshaping in the small vessel group.

Limits of BVS are technical and clinical. BVS is a semicrystalline biodegradable polymer and, compared to nonbiodegradable stent technology, has restricted expansion characteristics, very important strut thickness (157 um) with a larger crossing profile (≤0.060″ for the 2.5 and 3.0 mm diameter and ≤0.065″ for the 3.5 mm diameter) and higher rigidity. This has led to concerns regarding its trackability, deliverability, and performance, particularly in complex lesions. Although some preliminary registry data are already available, further randomized trials are ongoing to further elucidate the role of absorbable DESs in different clinical settings and will definitively clarify the role of this novel and promising technology in clinical practice.

24.5 DES in STEMI

Studies performed so far comparing second-generation DES with first-generation DES or BMS in patients with STEMI have not been powered to detect significant differences in the occurrence of death, MI, or ST [79, 103] (Chaps. 19 and 20).

Moreover, previous meta-analyses have compared pooled PES and SES versus BMS, thus leaving undetermined whether there are stent-related differences between these two devices or whether second-generation DES have improved outcomes compared to first-generation DES (or BMS) [104, 105]. One network meta-analysis comparing DES with BMS specifically in STEMI [106] found the following: (1) cobalt-chromium (CoCr)-EES was associated with significantly lower rates of 1-year cardiac death/MI, MI, definite ST, and definite/probable ST than BMS, whereas SES was associated with significantly lower rates of cardiac death/MI than BMS; (2) the reduction in cardiac death/MI and in ST with CoCr-EES compared to BMS was already apparent at 30 days and was maintained up to 2-year follow-up; (3) CoCr-EES was also associated with significantly lower rates of 1-year definite ST and definite/probable ST and significantly lower rates of cardiac death/MI up to 2-year follow-up than PES; and (4) while SES was associated with the greatest reduction in TVR at 1-year follow-up, CoCr-EES was the most effective stent when follow-up was extended beyond 1 year. There was a significantly lower risk of 1-year cardiac death/MI, MI, and ST with CoCr-EES compared to BMS. First-generation DES has in fact been shown to reduce TVR compared with BMS in patients with STEMI, with no significant effect on overall cardiac death and MI [107–109].

However, first-generation DESs have been associated with increased rates of very late ST, raising concerns over the safety of these devices in patients with STEMI [110]. Delayed healing with a large number of uncovered struts, persistent fibrin deposition, late acquired malapposition upon thrombus resolution, stent strut penetration into the necrotic core, and more frequent and rapidly developing neoatherosclerosis may be some of the possible mechanisms associated with the increased risk of late events with first-generation DES in patients with STEMI [111, 112]. Although second-generation DES has been developed to improve the safety and efficacy of first-generation DES, no study performed to date has been sufficiently powered to detect significant differences among these devices and first-generation DES or BMS in low-frequency endpoints such as ST, MI, and cardiac death [7, 113]. The observed reduction in ST, MI, and composite cardiac death/MI rates with CoCr-EES compared to BMS is consistent with experimental data suggesting that stents covered by fluorinated polymers are less thrombogenic than even BMS [75]. Reocclusion of the infarct-related artery has been associated with increased rates of mortality after STEMI [114], and the significant reduction in cardiac death/MI with CoCr-EES may be attributed to the significant reduction both in ST and TVR compared to BMS. CoCr-EES, in fact, significantly reduced early, 1-year, and 2-year definite ST, definite/probable ST, and 1-year and 2-year TVR compared to BMS. As ST rates in patients with STEMI are significantly higher than in stable patients, the absolute impact of ST on cardiac mortality may be greater in an STEMI cohort [115]. This hypothesis is consistent with the findings of the TRITONTIMI [116] trial in which a 50 % reduction in the 30-day rate of ST with prasugrel compared to clopidogrel was associated with a significant reduction in the risk of 30-day cardiac death/MI (Chap. 23). Moreover, restenosis is not always a benign phenomenon, presenting as acute MI in 3.5–19.4 % of cases [117], and reinfarction is an independent predictor of mortality in patients with acute coronary syndromes [118].

Another important finding is the relative difference in clinical outcomes among first-generation DESs. The data demonstrate that it is inappropriate to consider SES and PES as one category of DES, because significant differences in clinical outcomes are apparent between these two devices. SES, but not PES or ZES-E, was in fact associated with significantly lower rates of 1-year cardiac death/MI than BMS. Specifically, SES was associated with the greatest reduction in the risk of 1-year TVR among the other stents and with a strong trend toward a reduction in 1-year definite ST compared to BMS, both results likely contributing to the lower rates of cardiac death/MI with SES than with BMS. Although this finding was not apparent in previous meta-analyses comparing first-generation DES with BMS in patients with STEMI [104, 105, 110], this may be due to pooling SES and PES together in these studies, thus masking possible stent-related differences. Of note, no significant difference in 1-year TVR was apparent between the fast release ZES-E and BMS. Two prior network meta-analyses suggested lower rates of ST with CoCr-EES than with BMS [59, 71]. Those studies, however, did not differentiate patients with STEMI and did not report data for cardiac mortality.

24.6 Optimal Duration of DAPT After PCI with DES

DAPT consisting of aspirin plus a P2Y12 receptor antagonist (clopidogrel in stable setting or the more potent ticagrelor and prasugrel in acute coronary syndrome) is recommended after DES implantation for at least 12 months by the American College of Cardiology/American Heart Association and for 6–12 months by European guidelines [119, 120], followed by aspirin monotherapy (Chap. 23). Current recommendations however are based largely on observational data with a few randomized controlled trials. The most recent trials and meta-analyses have suggested comparable efficacy of short-term versus 12-month DAPT, especially when newer-generation DESs are implanted [118, 121, 122], but they are underpowered to draw definitive conclusions. On the other hand, very late ST still occurs with DES, especially after first-generation devices, raising the question of whether DAPT prolongation might offer clinical benefit. On the other hand, the potential benefit on ST must be weighed against the risk of increased bleeding complications, especially if novel P2Y12 inhibitors are given in combination of modern anticoagulant therapies [123].

While previous studies had suggested that short-term DAPT is effective and safe, especially with the availability of modern interventional techniques, and new-generation DES, the benefit-to-harm ratio of prolonged DAPT beyond 1 year had remained largely unknown. The recent DAPT trial showed higher reduction of ischemic complications at the price of increased major bleeding when DAPT was prolonged to 30 months versus conventional 12-month DAPT [122]. The pathophysiology of very late ST has been attributed to the incomplete re-endothelialization caused by drug- or scaffold-induced inhibition of endothelial cell proliferation, by belated stent malapposition, and by neoatherosclerosis, all occurring over time after DES implantation. The optimal duration of DAPT after DES implantation is still unknown; lumping

together all available elements, data seem to converge in suggesting a shortening of DAPT <1 year in patients at high bleeding risk and prolonging DAPT >1 year in patients with low bleeding profile and increased ischemic risk.

24.7 Concluding Remarks

Coronary stents are widely used to treat patients with coronary artery disease, with drug-eluting stents being more effective and, with regard to new-generation DES (everolimus and Resolute zotarolimus), even safer than bare-metal stents, in turn generating a paradigm shift on the performance theories of these devices. The newer durable polymer everolimus and Resolute zotarolimus-eluting stents, as well as the biodegradable polymer biolimus-eluting stents, indeed provide similar efficacy to first-generation sirolimus-eluting stents, but everolimus and Resolute zotarolimus-eluting stents are the safest devices to date. Absorbable DESs that fully degrade over time are a novel and promising technology with the potential to reduce stent thrombosis complications observed with permanent stents and bleeding complications, by allowing a shortened duration of dual antiplatelet therapy, but their use is limited in complex coronary lesions. Further randomized studies are ongoing to definitively clarify their role in clinical practice.

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Part IV
Atherosclerosis and Hyperlipidemia

Chapter 25
Atherosclerosis, Introduction and Pathophysiology

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Abstract Patients with acute coronary syndrome classically present with unstable angina, acute myocardial infarction, or sudden coronary death. In approximately 50–60 % of sudden coronary death cases, the culprit lesion exhibits an acute coronary thrombus, whereas the remainder of these cases have stable coronary plaques with greater than 75 % cross-sectional area luminal narrowing with or without chronic total occlusion or healed myocardial infarction. There are three main causes of coronary thrombosis: plaque rupture, erosion, and calcified nodule originally described from observations made at autopsy but now confirmed by optical coherence tomography. The most common cause of coronary thrombus is plaque rupture, which is characterized by a large necrotic core and a disrupted thin fibrous cap rich in macrophages that allows blood to come in contact with the highly thrombogenic necrotic core inducing luminal thrombosis. A few decades ago, it was proposed that matrix metalloproteinases liberated from macrophages were the main mechanism of fibrous cap disruption in coronary plaque rupture. On the other hand, in plaque erosion the platelet-rich thrombus is in direct contact with the intima, and the latter is rich in smooth muscle cells and proteoglycan-collagen matrix with an absence of endothelial lining. The underlying plaque in erosions consists of either pathological intimal thickening or thick fibrous cap fibroatheroma, and the frequency of these underlying lesions is similar. Calcified nodule is the least frequent cause of coronary thrombosis, which occurs in highly calcified arteries. The highly calcified arteries are composed of calcified sheets which likely break into multiple small calcified nodules that are surrounded by fibrin with a luminal thrombus. The eruptive calcified nodules are usually eccentric, protruding into the lumen, and there is an absence of endothelium and collagen above the nodules, and there is an associated platelet-rich luminal thrombus which is typically nonocclusive. This chapter focuses on plaque progression and includes the three responsible entities of thrombosis as we have learnt from studies carried out in sudden coronary death victims.

Keywords Atherosclerosis • TCFA • Plaque rupture • Plaque erosion • Calcified nodule • Plaque hemorrhage

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25.1 Introduction

Coronary artery disease (CAD) remains the major cause of morbidity and mortality, although many and continued advances in medical therapies, diagnostic imaging modalities, and greater understanding of the molecular mechanisms of atherosclerosis have contributed to its decline in the last century. Atherosclerosis is a complex disease due to its multifactorial etiology which is related to traditional risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, smoking, and family history along with the newer biomarkers such as high-sensitivity C-reactive protein, homocystine, high fibrinogen, Lp(a), LpPLa2, and others which are likely genetic in origin. In order to have an in-depth understanding of atherosclerosis, we believe it is essential to understand the morphologic features of the disease as it progresses along with the background in which it occurs. Most of the acute coronary syndromes (ACS) are believed to result from luminal thrombosis; however, not all are associated with occlusive disease (Chap. 19). Three responsible entities such as plaque rupture, erosion, and calcified nodule have been described from autopsy studies (Fig. 25.1) [1]. The underlying main mechanism of luminal thrombosis is plaque rupture (55–65 %), followed by erosion (30–35 %) and, least frequent, calcified nodule (2–7 %) [1]. A recent systematic review on the pathology of ACS showed that the worldwide incidence of thrombosis from plaque rupture might be as high as 73 %; however, this includes all patients with or without known coronary artery disease, whereas our data is generated from individuals that have their first manifestation of CAD as sudden coronary death. Indeed in the combined systematic review, the prevalence is based on the inclusion of acute myocardial infarction (AMI) cases that are hospital based and also includes coroner-based sudden death autopsies. The difference in age distribution, with much older individuals in hospital-based autopsies, is well appreciated [2]. In AMI patients, the incidence of acute plaque rupture is significantly higher (79 %) than in individuals dying suddenly who have never reached the hospital (65 %). The frequency of plaque erosion in AMI patients is lower (25 %) than that seen in sudden coronary death (35 %), and the proportion is higher in women than in men [1, 3] (Chaps. 20 and 21). This chapter will focus on the structural characteristic of each plaque type as it relates to plaque progression, with emphasis on the mechanisms involved in the formation of unstable lesions causing symptomatic or asymptomatic disease.

25.2 The Classification of Atherosclerosis

The initial concepts of the progression of atherosclerotic changes were established in the early 1980s where Velican focused on the morphological descriptions of fatty streaks to fibroatheroma and advanced plaques complicated by hemorrhage, calcification, ulceration, and thrombosis [4, 5]. Michael J. Davies, a renowned cardiac pathologist from the United Kingdom who devoted himself to the study of plaque

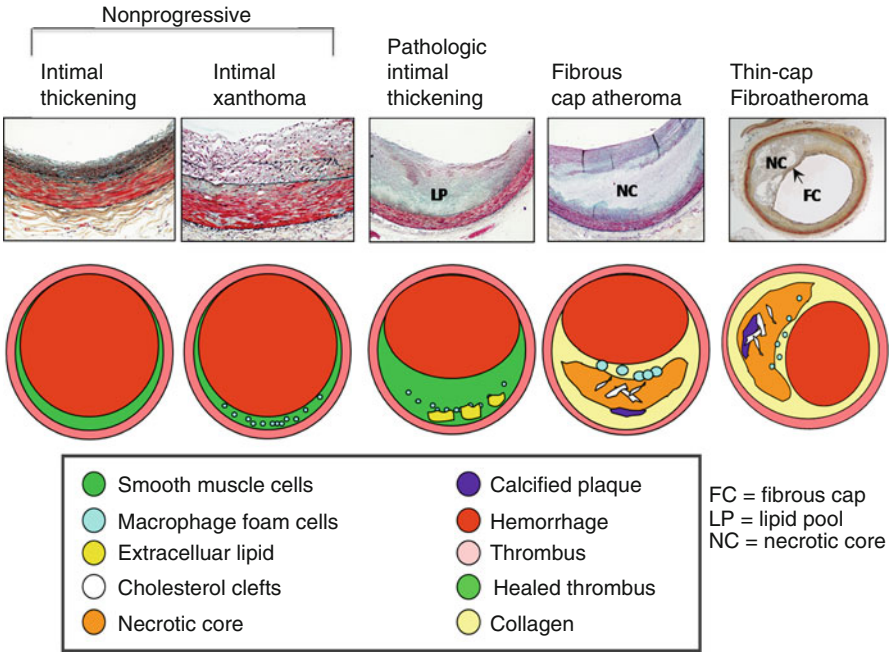

Fig. 25.1 Development of human coronary atherosclerosis. The two nonprogressive lesions are intimal thickening or intimal xanthoma (foam cell collections known as fatty streaks, AHA type II). Pathological intimal thickening (AHA type III, transitional lesions) is the first of progressive plaques marked by an acellular lipid pool rich in proteoglycan; inflammation when present is typically confined to the most luminal aspect of this plaque. Fibroatheromas are lesions with areas of necrosis characterized by cellular debris and cholesterol monohydrate with varying degrees of calcification or hemorrhage. Finally, thin-cap fibroatheroma or vulnerable plaques are recognized by their relatively large necrotic cores and thin fibrous caps (Reproduced with permission from reference [1]). *LP* lipid pool, *NC* necrotic core, *FC* fibrous cap

rupture and its associated features, described the characteristics of plaque disruption and the role of inflammation in the development of plaque instability in detail [6, 7]. Similarly Wissler, Strong, McGill, Stary, and many others have contributed to the understanding of atherosclerosis and its relation to risk factors and plaque progression [8–11].

The work of various pioneers, however, failed to note that lesions proceeding rupture share important similarities and yet have not ruptured, i.e., vulnerable plaques or thin-cap fibroatheromas, and we need to direct our focus on detection of this critical phase of atherosclerotic plaque to advance clinical care and facilitate prevention of sudden coronary death. Similarly we need to understand how plaques progress and therefore determine at which phase prevention of further progression will yield the most benefit for reducing CAD. This gap was fulfilled by Stary et al. [12, 13] in the mid-1990s under the auspices of the American Heart Association. These scientists published the first consensus report on the various types of plaques and progression of atherosclerosis. In this consensus classification, lesions were

classified into six different numerical categories: early lesions of initial type I, intimal thickening; type II, fatty streak; type III, transitional or intermediate lesion; type IV, advanced atheroma with well-defined region of necrotic core in the intima; type V, fibroatheroma or atheroma with a layer of fibrous connective tissue; and type VI, complicated plaques with surface defects and/or hematoma-hemorrhage and/or thrombosis. At this time it was not appreciated that plaque rupture was not the only mechanism of coronary thrombosis and that plaque erosion occurred in at least 25–30 % of cases and that rarely calcified nodule also caused thrombosis.

Atherogenesis refers to the development of atheromatous plaques within the inner lining (intima) of the arterial wall. Atherogenic dyslipidemia is characterized mainly by three lipoprotein abnormalities: elevated very-low-density lipoproteins (VLDL) and small LDL particles and low high-density lipoprotein (HDL) cholesterol [14, 15]. Many patients with atherogenic dyslipidemia also have an elevated serum apolipoprotein B (ApoB) [16]. Atherogenic ApoB-containing lipoproteins are synthesized from intestinal cholesterol absorption and hepatic cholesterol synthesis (Fig. 25.2). Cholesterol is absorbed from the intestine through ApoB48-containing chylomicrons, while ApoB100-containing very-low-density lipoproteins (VLDL) are produced by the liver. Subsequently, atherogenic ApoB-containing chylomicron remnants, VLDL remnants, and LDL infiltrate into the arterial wall and are taken up by macrophages and smooth muscle cells (SMCs) leading to the generation of atherosclerotic lesions.

Our laboratory, having the largest registry of human autopsy cases of patients dying from sudden coronary death in the world, reported that the numeric nomenclature was incomplete. Also, at this point it was not appreciated that the precursor lesion of plaque rupture [1] is a thin-cap fibroatheroma (vulnerable plaque) and that other causes of thrombosis existed besides rupture. Furthermore, the atherosclerosis process is considered too complicated to be categorized into numerical groups. These limitations prompted us to develop a modified version of the AHA classification. In our modified classification [1] (Figs. 25.1 and 25.3, Table 25.1), numeric AHA lesion types I to IV were abandoned and replaced by descriptive terminology to include adaptive intimal thickening, intimal xanthoma (fatty streak), pathological intimal thickening, and fibroatheroma, the latter we have further divided recently into early and late fibroatheromas. Lesions referred to as AHA types V and VI were discarded since they failed to account for the three different morphologies of thrombosis (rupture, erosion, and calcified nodule) or their relationship to stabilized plaque that is representative of lesions that have healed and that with time calcify.

25.3 Intimal Thickening and Fatty Streaks

Intimal thickening (AHA type I) is the earliest change in the arterial wall, which consists of smooth muscle cells in an extracellular matrix. Smooth muscle cell (SMC) proliferation has been observed in the media before birth but is rare after birth, whereas the intimal replication index was only 2–5 % [17]. Although intimal thickening is more frequently recognized in the atherosclerosis-prone arteries

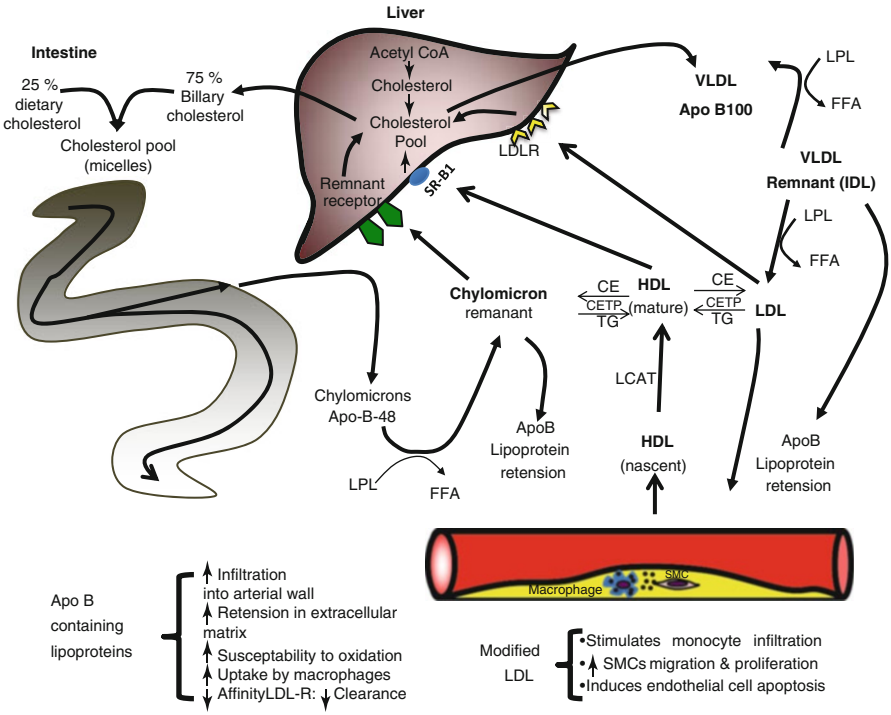

Fig. 25.2 Pathophysiology of atherogenic lipoproteins. Atherogenic ApoB-containing lipoproteins are synthesized from intestinal cholesterol absorption and hepatic cholesterol synthesis. Cholesterol is absorbed from the intestine through ApoB48-containing chylomicrons, which form chylomicron remnants following the hydrolysis of triglycerides (*TG*) by lipoprotein lipase (*LPL*) to form free fatty acids (*FFA*). ApoB100-containing very-low-density lipoproteins (*VLDL*) are produced by the liver and acted on by LPL to generate VLDL remnants (intermediate-density lipoproteins *IDL*) and low-density lipoproteins (*LDL*). Atherogenic ApoB-containing chylomicron remnants, VLDL remnants, and LDL infiltrate into the arterial wall are retained by binding to the extracellular matrix, where the lipoproteins are modified and taken up by macrophages and smooth muscle cells (*SMCs*) leading to the generation of atherosclerotic lesions. High-density lipoproteins (*HDL*) can efflux free cholesterol from the atherosclerotic lesions, where cholesterol is esterified by lecithin cholesterol acyltransferase (*LCAT*) to cholesterol esters (*CE*), and CE exchanged to ApoB-containing lipoproteins by cholesterol ester transfer protein (*CETP*). The liver can take up cholesterol from HDL through scavenger receptor B1 (SR-B1), from LDL by LDL receptors (*LDL-R*), and from chylomicron remnants by remnant receptors. Hepatic cholesterol is excreted into the intestine in bile where it can be reabsorbed into chylomicrons or is returned to circulation in VLDL particles to generate additional atherogenic ApoB-containing lipoproteins

(coronary, carotid, abdominal and descending aorta, and iliac artery) [18], it is currently regarded as an adaptive change because the number of proliferating cells is 10- to 20-fold higher in fibroatheromas (AHA type IV) as compared to lesions that show diffuse intimal thickening [19, 20].

The term "fatty streak" or "intimal xanthoma" (AHA type II, fatty streak) is primarily composed of infiltrating lipid-laden cells of either macrophage or SMC origin. Although this lesion is described as the earliest lesion of atherosclerosis in

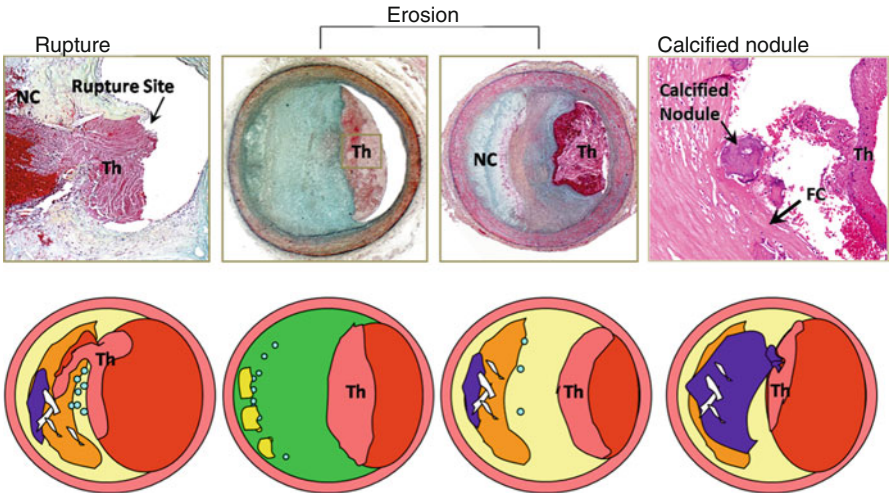

Fig. 25.3 Atherosclerotic lesions with luminal thrombi. Coronary plaque features responsible for acute thrombosis comprise three different morphologies: rupture, erosion, and calcified nodules. Ruptured plaques are thin fibrous cap atheromas with luminal thrombi (*Th*). These lesions usually have an extensive necrotic core (*NC*) containing large numbers of cholesterol crystals and a thin fibrous cap (<65 μm) infiltrated by foamy macrophages and T-lymphocytes. The fibrous cap is thinnest at the site of rupture and consists of a few collagen bundles and rare smooth muscle cells. The luminal thrombus is in communication with the lipid-rich necrotic core. Erosions occur over lesions rich in smooth muscle cells and proteoglycans. Luminal thrombi overlie areas lacking surface endothelium. The deep intima of the eroded plaque often shows extracellular lipid pools, but necrotic cores are uncommon; when present, the necrotic core does not communicate with the luminal thrombus. Inflammatory infiltrate is usually absent but, if present, is sparse and consists of macrophages and lymphocytes. Calcified nodules are plaques with luminal thrombi showing calcific nodules protruding into the lumen through a disrupted thin fibrous cap. There is absence of an endothelium at the site of the thrombus, and inflammatory cells (macrophages and T-lymphocytes) are absent (Reproduced with permission from reference [1])

accordance to the AHA classification [21, 22], it does not always progress to the advanced lesion of fibroatheroma and in fact has been shown to regress especially in the thoracic aorta of young individuals [9]. Adaptive intimal thickening lesions can also be found in adults, particularly in those with little atherosclerosis, or in locations of arteries that are resistant to the development of atherosclerosis and, in fact, do not always progress.

25.4 Pathological Intimal Thickening

Pathological intimal thickening (PIT, AHA type III lesion) is defined by us and others as the earliest lesion of progressive atherosclerosis. PIT lesions consist of SMCs within a proteoglycan and collagen-rich (type III) extracellular matrix along with

Table 25.1 Modified AHA consensus classification based on morphological description

	Description	Thrombosis
Non-atherosclerotic intimal lesions		
Intimal thickening	Normal accumulation of smooth muscle cells (SMCs) in the intima in the absence of lipid or macrophage foam cells	Absent
Intimal xanthoma	Superficial accumulation of foam cells without a necrotic core or fibrous cap. Based on animal and human data, such lesions usually regress	Absent
Progressive atherosclerotic lesions		
Pathological intimal thickening	SMC-rich plaque with proteoglycan matrix and focal accumulation of extracellular lipid	Absent
Fibrous cap atheroma	Early necrosis: focal macrophage infiltration into areas of lipid pools with an overlying fibrous cap Late necrosis: loss of matrix and extensive cellular debris with an overlying fibrous cap	Absent
Thin-cap fibroatheroma	A thin fibrous cap (<65 μm) infiltrated by macrophages and lymphocytes with rare or absence of SMCs and relatively large underlying necrotic core. Intraplaque hemorrhage/fibrin may be present	Absent
Lesions with acute thrombi		
Plaque rupture	Fibroatheroma with cap disruption; the luminal thrombus communicates with the underlying necrotic core	Occlusive or nonocclusive
Plaque erosion	Plaque composition, as above; no communication of the thrombus with necrotic core. Can occur on a plaque substrate of pathological intimal thickening or fibroatheroma	Usually nonocclusive
Calcified nodule	Eruptive (shedding) of calcified nodule with an underlying fibrocalcific plaque with minimal or absence of necrosis	Usually nonocclusive
Lesions with healed thrombi		
Fibrotic (without calcification) Fibrocalcific (±necrotic core)	Collagen-rich plaque with significant luminal stenosis. Lesions may contain large areas of calcification with few inflammatory cells and absence of necrosis. These lesions may represent healed erosions or ruptures	Absent

Reproduced with permission from reference [1]

the presence of lipid pools in the vicinity of the media [1]. Within the area of the lipid pool, there is an absence of SMCs, and the matrix is composed of hyaluronan and proteoglycans such as versican along with lipid deposition. In the precursor lesion of PIT, i.e., adaptive intimal thickening, there is presence of proteoglycan biglycan and decorin surrounding the SMCs. As the intima thickens, the SMCs undergo apoptosis close to the media with increasing deposition of basement membrane (BM) surrounding the individual cells. The BM can be visualized by periodic acid Schiff (PAS) staining. Also, apoptotic smooth muscle cell nuclei have been identified by in situ nick end labeling of human coronary and carotid plaques [23]. It has been shown that structural changes in the glycosaminoglycan chain of proteoglycans, i.e., versican and biglycan, are the initial proatherogenic proteoglycans that lead to the binding of atherogenic lipoproteins [24, 25]. In contrast, the internal

thoracic artery that is resistant to the development of atherosclerosis has a thin neointima that is rich in decorin [26].

Over time, these PIT lesions show the accumulation of macrophages toward the lumen remote from the lipid pool, although lesions of PIT do not all show the presence of luminal macrophages; PIT lesions with macrophages are considered by us as a more advanced stage of atherosclerosis. Nakashima et al. also showed early coronary lesion progression near branch points [24] consisting of extracellular lipid accumulation underneath a layer of foam cell macrophages. The reasons why macrophages accumulate in PIT lesions, although not fully understood, may be linked to specific proteins being expressed within the lipid pools, which as of today remains unknown; however, apoptotic signals may be involved. We have observed the presence of free cholesterol seen as empty fine crystalline structures in paraffin-embedded sections within the area of the lipid pool to varying degrees, but are never excessive nor long. The precise origin of free cholesterol in PIT lesions remains unknown, but they are likely derived from membranes of dying SMC [27]. It is also conceivable that extracellular lipid accumulation within lipid pools may have originated from the circulating plasma lipoprotein, which have been demonstrated in studies addressing the association of proteoglycans and plasma lipoprotein [28, 29]. Also, experimental studies have demonstrated that intrinsic phenotypic changes in smooth muscle cell at the initial stage of plaque formation in the setting of hypercholesterolemia exert a greater control over SMC apoptosis than cell-cell interactions or the microenvironment of the plaque [30, 31]. In the absence of hyperlipidemia, SMCs are efficient phagocytes of apoptotic SMCs in vitro and in vivo; however, in the presence of hyperlipidemia, there is reduced phagocytosis resulting in necrosis of apoptotic SMCs and leakage of intracellular IL-1. IL-1 acts on the surrounding viable SMCs and induces them to secret IL-6 and monocyte chemotactic protein (MCP)-1, thus initiating the progression of atherosclerosis [32]. This concept is further supported by many studies where aggressive treatment of hypercholesterolemia by statin therapy has resulted in marked reduction in the incidence of major cardiovascular event [33] (see Chap. 28).

Another feature of these early lesions of pathological intimal thickening is microcalcification, which has been demonstrated with anionic stains such as von Kossa's or alizarin red stains. The apoptotic SMC remnants as well as calcium apatite crystals have also been demonstrated by transmission electron microscopy [34, 35]. The clinical significance of these early microcalcification lesions in lipid pools remains unknown; however, with time they likely coalesce along with calcifying macrophages and likely form calcified fragments.

25.5 Fibroatheroma

Fibroatheroma represents a further progressive stage of atherosclerotic disease and is identified by the presence of an acellular necrotic core, which can be distinguished from lipid pool lesions of PIT because they lack the presence of

hyaluronan, proteoglycan such as versican and biglycan, and collagen (AHA type IV lesion) [1]. Fibroatheroma has been further classified by us into "early" and "late" necrotic cores, because we believe that this distinction may provide mechanistic insight into how necrotic cores form, grow, and evolve with time. The presence of "early necrotic core" is identified by the accumulation of macrophages within the lipid pool areas, and Bennett et al. have shown that apoptotic SMCs release IL-6 and MCP-1 which attract the macrophages and are involved in the breakdown of extracellular matrix, leading to the development of the necrotic core. Lesions with early necrotic core continue to show the presence of hyaluronan, versican, and biglycan and other matrix proteins focally, which are typically absent in more advanced "late necrotic core" fibroatheroma that exhibits necrosis, presumably due to release of matrix metalloproteinases by macrophages, resulting in complete breakdown of proteoglycans and collagen. Also, large numbers of macrophages within the areas of necrotic core display features consistent with apoptotic cell death, and free apoptotic bodies are abundant within the necrotic core, which has been aptly described by Ira Tabas as a "graveyard" of macrophages.

Increased accumulation of free cholesterol is another feature of late necrotic core. Acyl-coenzyme A:cholesterol acyltransferase 1, or ACAT1, esterifies free cholesterol and stores esterified cholesterol in macrophages [36]. Macrophage ACAT1 deficiency has been shown in mice to lead to an increase in atherosclerotic lesion area including free cholesterol accumulation in hyperlipidemic mice via disrupted cholesterol efflux, increased lipoprotein uptake, accumulation of intracellular vesicles, and accelerated apoptosis [37]. This together with the death of macrophages in the setting of defective phagocytic clearance of apoptotic bodies is thought to contribute to the development of late plaque necrosis [36, 38]. We have also shown that another source of free cholesterol in human necrotic cores is associated with the membrane of red blood cells, which are rich in free cholesterol (see below). The late necrotic core is devoid of any matrix and no longer stains for hyaluronan, proteoglycans, and collagen matrix as identified by specific stains for proteoglycans, hyaluronan, and Sirius red stain.

During the evolution toward an advanced fibroatheromatous lesion, there is an overlying layer of fibrous tissue (thick fibrous cap) composed mostly of type I and III collagen, proteoglycans, and interspersed SMCs, which play a critical role in harboring the contents of the necrotic core. The fibrous cap could undergo thinning and is now called a thin-cap fibroatheroma (TCFA) that may eventually rupture through mechanisms discussed below. The TCFA generally has a relatively large necrotic core with an overlying thin intact fibrous cap which is composed mainly of type I collagen with varying degrees of macrophages and lymphocytes. There is generally a paucity or absence of smooth muscle cells within the fibrous cap because of apoptosis. The fibrous cap thickness is a measure of plaque vulnerability, and its definition requires that it be ≤ 65 μm, which was based on the mean thickness of the thinnest part of the remnant cap of ruptured plaques that measured 23 ± 19 μm. Therefore, 95 % of the ruptured caps measured ≤ 65 μm [39].

25.6 Plaque Rupture

In regard to the characterization of thrombus composition, most acute thrombi at sites of rupture are platelet rich ("white" thrombi) (Fig. 25.3). Many factors including calcium, platelet surface receptors including GPIIb/IIIa or protease-activated receptors, and von Willebrand factor facilitate platelet aggregation and compaction of coagulum formation (Chap. 23). However, the proximal propagated thrombus exhibits mostly a fibrin-rich thrombus with interspersed red cells and is a red thrombus that occurs at sites of blood stasis because of absence of flow to the nearest side branch. The nature of the thrombus, i.e., red versus white thrombus, is of clinical importance, because it may be related to the effectiveness of thrombolytic therapy in patients presenting with acute myocardial infarction. Furthermore, the duration of the thrombus determines its characterization; a short duration forms a predominantly platelet-rich thrombus, while long-duration thrombi are likely to be longer in length and contain layered fibrin; further these thrombi begin to organize and are therefore more difficult to respond to thrombolytic therapy.

While the precise mechanism of plaque rupture is not fully understood, most researches agree that disruption of fibrous cap occurs due to the weakness of the cap from the presence of macrophages and T-lymphocytes. The macrophage infiltration is responsible for the collagen degradation and the lack of new collagen formation from interferon gamma, secreted by T-lymphocytes. Cap disruption results in exposure of necrotic core to the flowing blood, which activates coagulation and thrombus formation [1, 40]. It has only recently been appreciated that plaque ruptures are likely episodic and may occur in asymptomatic individuals [41] (Fig. 25.4). Moreover, at least 30 % of plaque ruptures occur at lesion sites with less than 75 % cross-sectional luminal narrowing [42]. We reported that the prevalence of coronary thrombosis at sites of insignificant narrowing (<70 % cross-sectional area narrowing) was 37 % in autopsy patients with plaque erosion and 26 % in plaque ruptures [42]. Mann and Davies reported that in plaques causing <50 % diameter stenosis, healed plaque rupture (HPR) was observed in <20 % of lesions, while in those with ≥51 % luminal stenosis, HPRs were observed in 73 % of plaques [43]. Also, we have similarly reported that 61 % of sudden coronary death victims have HPRs and were associated with healed myocardial infarction, increased heart weight, dyslipidemia, and diabetes mellitus [41]. Moreover, as the number of HPR in a specific lesion site increases, the degree of luminal narrowing is also progressing. Plaque ruptures without a previous healed rupture are unusual, i.e., virgin ruptures, and the latter are observed in only 11 % of patients dying suddenly [41].

Recently, much interest has focused on the role of matrix metalloproteinases (MMP) as the main mechanism of fibrous cap disruption in coronary and carotid plaque ruptures. Type I collagen provides most of the tensile strength to the fibrous cap, and some pro-inflammatory cytokines, such as INF-γ, prevent collagen synthesis by smooth muscle cells [44]. The initial proteolytic breaks in collagen fibers I and III are caused by the presence of collagenases, such as MMP-1, MMP-8, and MMP-13, while the gelatinases MMP-2 and MMP-9 support the continued degradation of

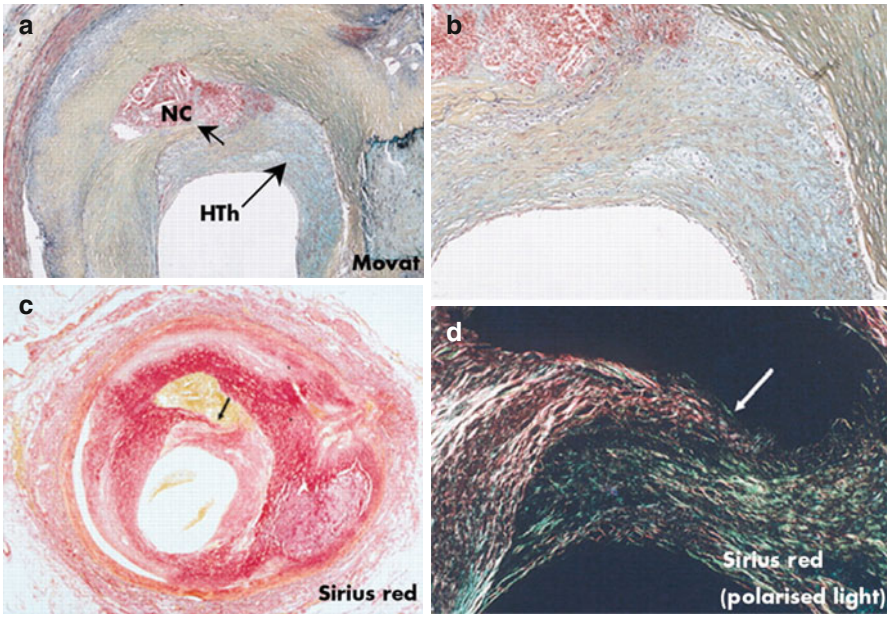

Fig. 25.4 Healed plaque rupture lesion with severe luminal narrowing. (**a**) Areas of intra-intimal lipid-rich core with hemorrhage and cholesterol clefts; an old area of necrosis (*NC*) is seen underlying a healed thrombus (*HTh*). (**b**) Higher magnification showing extensive smooth muscle cells within a collagenous proteoglycan-rich neointima (healed thrombus) with clear demarcation from the fibrous region of old plaque to right. (**c**, **d**) Layers of collagen by Sirius red staining. (**c**) Note area of dense, dark red collagen surrounding lipid hemorrhagic cores seen in corresponding view in (**a**). (**d**) Image taken with polarized light. Dense collagen (type I) that forms fibrous cap is lighter *reddish yellow* and is disrupted (*arrow*), with newer *greenish* type III collagen on right and above rupture site. (**a**, **b**) Movat pentachrome (Reproduced with permission from reference [42])

the interstitial collagens [40, 45–48]. However, the artery also has endogenous antagonists to MMPs, the tissue inhibitors of metalloproteinases (TIMPS) [49]. It has been demonstrated that "atheromatous" rather than "fibrous" carotid plaques preferentially express MMP-1 and MMP-13 [48]. Same authors also showed that collagenase-cleaved type I collagen occurs at sites that showed higher expression of MMP-1- and MMP-13-positive macrophages. There are other proteinases capable of degrading extracellular matrix including the cathepsin family (cathepsins S and K) and the inhibitor cystatin C [50]. However, these have strong elastolytic activity and have been implicated more with matrix remodeling and migration and proliferation of cells [46]. Although elastolysis may be more important in aneurysm formation, however, collagenolysis is the major determinant of plaque rupture [51]. While both collagenolysis and elastolysis are important components mediating plaque rupture, there are additional local factors contributing to this final event of arterial thrombosis, such as flow dynamics and vasospasm.

Apoptosis may also be important in the final development of plaque rupture [52]. Apoptosis of macrophages and SMCs has been observed in both progression and

regression of atherosclerotic plaques [53]. Typically, the fibrous cap of plaque rupture sites shows very few SMCs, which are essential for synthesis of extracellular matrix proteins and maintenance of the fibrous cap [54]. Geng et al. in the mid-1990s demonstrated that mediators secreted by macrophages and T-lymphocytes including IFN-γ, FasL, TNF-α, IL-1, and reactive oxygen species accelerate smooth muscle cell apoptosis in vitro [55]. These upstream effectors can activate caspases causing mitochondrial dysfunction and death via the release of cytochrome c [52]. Apoptosis is considered to be the main mechanism of decrease in smooth muscle cells seen in thin-cap fibroatheroma and in ruptured plaques [31].

Today the "danger hypothesis" indicated that the endogenous self-adjuvants are released during cell death and are the inducers of inflammation that occur in the absence of infection and are referred to as damage-associated molecular patterns (DAMPs) [56]. In atherosclerosis there are three main mechanisms that trigger inflammation: cholesterol crystals, oxidation-specific epitopes, and IL-1α. Apoptotic SMCs are phagocytosed by adjacent SMCs; however, in the presence of hyperlipidemia, there is reduced capacity for phagocytosis by SMCs that results in necrosis of apoptotic SMCs [32]. Necrotic VSMCs release IL-1α, which activates adjacent viable VSMCs to produce the pro-inflammatory cytokines IL-6 and monocyte chemotactic protein 1 [32].

Macrophage apoptosis is also commonly observed in both advanced and progressive atherosclerotic plaques. We used 40 sudden death autopsy cases: 25 had plaque rupture and 15 had stable plaques [57] and demonstrated excessive macrophage cell death at sites of plaque rupture as compared to stable plaques [57]. While our work showed a relationship between macrophage apoptosis and plaque rupture, it remains unknown whether apoptosis is a trigger of plaque rupture or a bystander. In vitro studies have suggested that oxidized LDL could induce macrophage apoptosis [52]. INF-γ regulates the mRNA expression of proapoptotic molecules like TNF-α and caspase-8 [55], and treatment with TNF-α antibodies completely neutralizes both the inhibition of DNA synthesis and apoptosis of macrophages induced by IFN-γ [58]. We have shown caspase-1 upregulation and the presence of its active p20 subunit in plaque ruptures but not in stable plaques. Immunohistochemical studies also showed caspase-1 localized to rupture sites where there was severe infiltration by macrophages, while reactivity for caspase-3 in these areas was weak.

The precise relationship of macrophage apoptosis to plaque rupture remains hypothetical; experimental evidence suggests that macrophages are involved in the degradation of extracellular matrix and also threaten cell survival [59]. A process, termed "anoikis," is defined as a form of programmed cell death which is induced by anchorage-dependent cells detaching from the surrounding extracellular matrix [59]. Collagenase (MMP-1), gelatinase (MMP-2), stromelysin (MMP-3), and gelatinase (MMP-9) have been colocalized with lesional macrophages [60]. Also, active proteases either secreted directly by inflammatory cells, such as elastase and cathepsin G by polymorphonuclear leukocytes, chymases and tryptase by mast cells, and granzymes by lymphocytes, or generated from circulating zymogens may accelerate matrix degradation and cell death [40].

On the other hand, thin-cap fibroatheromas may either occur de novo or from the protease activation that accompanies all stages of atherosclerosis including plaque rupture. The possibility that fibroatheromas form de novo comes from the finding that ruptured lesions in some cases form at very superficial sites (i.e., close to the lumen). It is likely that multilayering of macrophages in the superficial regions leads to endothelial separation from the underlying basement membrane through the release of MMPs. Also, plaque fissures or leaky vasa vasorum are responsible for intraplaque hemorrhage, and sudden enlargement of the necrotic core could result in rupture of the thin cap. Hemorrhage by itself may induce excessive macrophage infiltration, and macrophages secrete matrix metalloproteinases that lead to breaks in collagen and thinning of the fibrous cap. Furthermore, atherosclerotic plaques commonly form near the side branches, and repeated rupture and thrombus propagation and healing are likely responsible for the diffuseness of narrowing observed in coronary artery disease.

25.7 Plaque Hemorrhage

Atherosclerotic plaques display an elaborate vascular network, called intraplaque vasa vasorum (Vv), consisting of arterioles and capillaries. Vv are recruited from the adventitia into the intima and media as the atherosclerotic plaque begins to grow and actively regulate blood flow [61]. Vv have been shown to increase significantly when the extent of stenosis exceeds 25 % [62]. Also, 70 % Vv arise from the adventitia and another 30 % are luminal in origin [62]. Intraplaque hemorrhage was first described by Boyd in 1928, while Davies noted the co-occurrence of plaque rupture with plaque hemorrhage [63]. We reported in the 1980s the presence of intraplaque hemorrhage in 10 % of epicardial artery segments of patients dying with coronary heart disease, and iron was noted in 4 % [64]. We later reported that hemorrhage was associated with acceleration of plaque progression, provoked macrophage infiltration, and was a source of free cholesterol [65]. Intraplaque hemorrhage has further been shown by imaging studies to be a marker of plaque destabilization [66]. Recently, Li et al. have shown that patients treated with oral anticoagulants had greater intraplaque hemorrhage (61 %) in coronary arteries as compared to patients on antiplatelet inhibitors (53 %,) or those without any such therapy (46 %, $p=0.001$ anticoagulants vs. no therapy) and large intraplaque hemorrhages were also more frequent with anticoagulants [67].

25.8 Plaque Erosion

Plaque erosion is defined as the presence of an acute thrombus that is in direct contact with the underlying intima rich in SMCs and proteoglycan-collagen matrix with an absence of endothelial lining at the site of the thrombus. The underlying plaque in

cases of erosions consists of either pathological intimal thickening or fibroatheroma, and the frequency of each of the underlying lesions is similar. We believe that coronary vasospasm may play an important role in its pathophysiology. At the site of plaque erosion, the media is intact, i.e., no broken internal elastic lamina (IEL), whereas in ruptures the IEL and media are often destroyed. Also, because the vessel is negatively remodeled along with an intact media and IEL, these changes are suggestive of vasospastic disease. The intimal plaque in erosion lesions is rich in versican, hyaluronan, and type III collagen unlike rupture or stable plaque which is rich in type I collagen and biglycan and decorin [42, 68]. It is speculated that a selective accumulation of hyaluronan in eroded plaques may accelerate de-endothelialization and platelet aggregation. It has been shown that hyaluronan can directly promote polymerization of fibrin, which may promote SMCs migration and plaque progression. The plaque erosion lesions are frequently eccentric with minimal spotty or absent calcification. There is an ongoing debate as to the role of inflammation in the development of plaque erosion. We have demonstrated that the eroded sites show minimal inflammation, i.e., few or absent macrophages and lymphocytes [1, 42], whereas van der Wal et al. reported inflammation at the site of erosion [69]. We have observed rare cases of erosion that do show excessive inflammation, but these are few.

Although plaque erosion accounts for 25–35 % of coronary thrombi in patients dying from acute myocardial infarction or sudden coronary death, with less frequency in the former [1, 39], the risk factors that predispose to occurrence of erosion are different from those of rupture [39]. Our previous report showed that men dying from sudden coronary death with ruptured plaque had higher plasma total cholesterol (TC), lower high-density lipoprotein cholesterol (HDL-C), and higher TC/HDL-C ratio as compared to plaque erosion [39]. On the other hand, only TC correlated with plaque rupture in women [70]. Consistently smoking is associated with acute thrombosis, and smoking is an important risk factor for plaque erosion in women with coronary disease who died suddenly [70]. In our sudden coronary death registry, eroded plaques have greater proportion of females of younger age, less % stenosis, less calcification, and less plaque burden and thrombus as compared to ruptured plaques [42]. Plaque erosion accounts for over 80 % of thrombi occurring in young women, whereas in women older than 50 years, plaque rupture is the main cause of thrombosis.

In sudden coronary death victims, we have reported that distal embolization rate is higher in erosions (71 %) than in plaque rupture (42 %) [71]. Moreover, in another study we showed that 88 % of coronary thrombi in erosions exhibited late stages of healing, i.e., >24 h duration, whereas only 54 % ruptures showed the same degree of healing [72]. In the same study, we showed that 46 % of plaque erosions showed healing of >7 days duration, whereas in rupture only 9 % were of that duration. In another study, coronary thrombi in eroded plaques had a higher density of myeloperoxidase-positive cells than those of ruptured plaques [73]. Furthermore, in living patients the circulating myeloperoxidase levels are higher in patients with acute coronary syndromes with erosion as compared to those with rupture, suggesting that it may be possible to differentiate rupture from erosion by inflammatory biomarkers. However, large prospective clinical studies involving many patients are needed to confirm mechanistic differences between erosion and rupture. Also, when and if it becomes possible

to distinguish plaque erosion from plaque rupture in living patients with the use of optical coherent tomography, it may then be possible to tailor treatment strategies for erosion and rupture [74], as the former are associated with less plaque burden.

25.9 Calcified Nodule

Calcified nodule is the least frequent cause of coronary thrombi and occurs in the setting of a highly calcified disease state. Calcified nodule consists of areas of fragmented pieces of calcium that are surrounded by fibrin and results in disruption of the overlying fibrous cap and endothelium resulting in a luminal thrombus. The eruptive calcified nodule is usually eccentric, protruding into the lumen, and there is an absence of endothelium over the nodules of calcium with a platelet-rich "white" thrombus which is typically nonocclusive. While the mechanisms of nodular calcification remain unknown, fibrin is often present between the calcified spicules, along with few osteoclasts and inflammatory cells. We believe that the calcified sheets crack and break from the tortuosity of the artery with sudden rise in blood pressure [1]. Like calcified nodules, nodular calcification is also more common in highly calcified tortuous arteries, in older individuals, and in males and is preferentially found in the middle right coronary or the left anterior descending coronary arteries. The nodular calcification likely also is the result of breaks in the calcified sheet; however, the pieces of calcium remain within the intima and do not lead to luminal disruption. Nevertheless, medial disruption may be seen with protrusion into the adventitia.

A recent report from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study showed that patients with "intravascular ultrasound (IVUS)-detected calcified nodule" had fewer cardiac events as compared to those without calcified nodule [75]. However, the IVUS study cannot distinguish "calcified nodule" from "nodular calcification" because of its limited resolution. The pathologically defined calcified nodules require the presence of luminal thrombus [1]. "Non-thrombotic calcified nodules" should not be described as "calcified nodules" but as "nodular calcification." The findings of the above PROSPECT study suggest that lesions with nodular calcification are frequent and are not at high risk of future clinical events. On the other hand, recent optical coherence tomography (OCT) study seems to detect calcified nodule more accurately than IVUS. Jian et al. reported that OCT-defined calcified nodules were observed in 7.9 % of ACS patients and were more common in older patients, observations similar to ours [76].

25.10 Concluding Remarks

Disruption of fibrous cap rich in macrophages and T-lymphocytes and the contact of necrotic core with circulating blood are events that lead to the development of luminal thrombosis in plaque rupture. Plaque erosion on the other hand is also an acute

event where the thrombus is in direct contact with the intima, which is rich in SMCs and proteoglycan-collagen matrix with an absence of endothelial lining. Calcified nodule is the least frequent cause of coronary thrombi and consists of areas of fragmented calcification that produce small calcified nodules that are surrounded by fibrin with a luminal thrombus. All three processes are observed in patients presenting with acute coronary syndrome along with sudden hemorrhage into the atherosclerotic plaque which results in sudden enlargement of the necrotic core and plaque area with the latter associated with unstable angina. Understanding the mechanism of the three different entities that lead to luminal thrombus is of utmost importance if we are to find better treatment modalities for patients suffering from acute coronary syndrome.

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Chapter 26
Vascular Endothelial Dysfunction and Atherosclerosis: Role of Nitric Oxide System

Estelle R. Simo Cheyou and Ashok K. Srivastava

Abstract Nitric oxide (NO) is a vasoprotective molecule that plays a critical role in modulating endothelial functions. A compromised NO bioavailability due to defective NO generation by endothelial nitric oxide synthase (eNOS) has been suggested as one of the mechanisms leading to the pathogenesis of vascular abnormalities such as atherosclerosis. NO synthesis requires L-arginine as a substrate for eNOS as well as several cofactors for its catalytic activity. Vascular endothelial dysfunction and atherosclerosis are associated with deficiencies in the levels of arginine and eNOS cofactor tetrahydrobiopterin (BH4). Reactive oxygen species (ROS), aberrant lipid metabolism and elevated protein kinase C have also been reported to alter NO biosynthesis by modulating eNOS activity. In vitro studies as well as use of animal models of vascular diseases have provided some evidence regarding the molecular mechanisms of the reduced NO bioavailability associated with atherosclerosis. This chapter briefly summarises key studies highlighting the role of interplay between pro-atherogenic factors such as ROS, growth factors and vasoactive peptides and NO system in vascular endothelial dysfunction and atherosclerosis.

Keywords Nitric oxide • Endothelial dysfunction • Atherosclerosis • L-arginine • eNOS

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26.1 Introduction

Atherosclerosis occurs as a result of an orchestrated process encompassing vascular endothelial dysfunction, lipid accumulation, aberrant inflammatory responses and vascular cell proliferation and migration. These events underlie the progressive narrowing and thickening of the arteries with a possibility of thrombus formation and vessel occlusion leading to stroke or heart attack. Atherosclerosis is associated with impairments in the structural and functional properties of the layers within the vessel wall (see Chap. 25). In fact, vascular integrity requires a functional endothelium capable, amongst other actions, to produce vasoactive factors such as nitric oxide (NO) and endothelin-1 and a responsive media able to modulate the vessel tone through appropriate contracting, relaxing and growth responses of the vascular smooth muscle cells (VSMC) and endothelial cells. However, several metabolic events can disrupt the vessel homeostasis and result in vascular disorders. These events include the excessive generation of reactive oxygen species (ROS), overexpression of vasoactive peptides and growth factors that play a fundamental role in hypertension and the accumulation of pro-inflammatory molecules in dyslipidaemia-prone states such as obesity and type 2 diabetes mellitus (T2DM). Aberrant signalling cascades triggered individually or in concert with ROS, vasoactive peptides and growth factors are believed to contribute to physiological or structural changes in the vessel walls leading to atherosclerosis (see Chap. 28). Recent studies have suggested that derangements in the NO generation or action may be one of the factors contributing to aberrant signalling and responses associated with atherosclerosis. In this chapter, we highlight the importance of interplay between pro-atherogenic factors such as ROS, growth factors and vasoactive peptides and NO system in vascular endothelial dysfunction and atherosclerosis.

26.2 Nitric Oxide Synthesis and Signal Transduction

NO is an inert and short-lived gas. Synthesis of NO involves a reaction catalysed by a group of enzymes called NO synthases (NOS). NOS are classified as three different forms encoded by a unique gene: neuronal NOS (nNOS or NOS-1), inducible NOS (iNOS or NOS-2) and endothelial NOS (eNOS or NOS-3) [1]. Even though these enzymes are mostly constitutively expressed in neuronal, endothelial and other tissues [2, 3], their expression can be induced by agonists such as cytokines, endotoxins or growth factors [4–8]. NO formation is a two-step reaction where the amino acid L-arginine is transformed into L-citrulline. This reaction requires nicotinamide adenine dinucleotide phosphate (NADPH) and tetrahydrobiopterin (BH4) as cofactors [9, 10]. Once released, NO diffuses and acts in a paracrine fashion on neighbouring cells where it modulates target enzyme activity (Fig. 26.1).

NO exerts its biological effects through the activation of a soluble guanylyl cyclase (sGC) by binding to its NO-specific pentacoordinate ferrous heme, causing an allosteric modification that results in increased catalytic activity [11, 12]. GC in

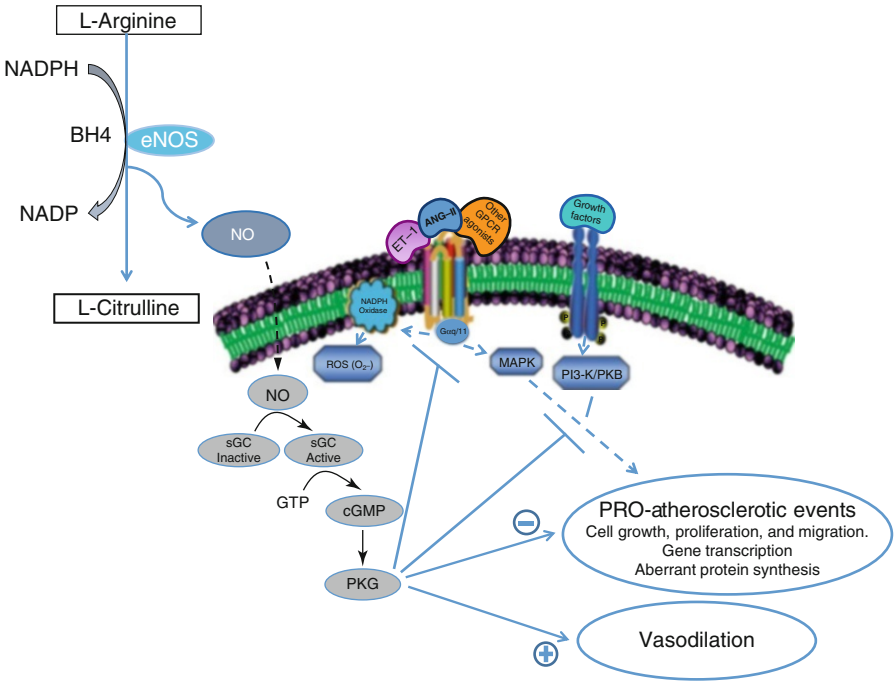

Fig. 26.1 Nitric oxide biosynthesis and signal transduction in the vasculature. Nitric oxide (*NO*) synthesis occurs in endothelial cells following a reaction catalysed by the endothelial NO synthase (*eNOS*) converting L-arginine to L-citrulline. Tetrahydrobiopterin (BH4) serves as a cofactor in this reaction. Upon its release from the endothelial cells, NO diffuses to neighbouring cells and activates a soluble guanylyl cyclase (*sGC*) that transforms the guanosine triphosphate (*GTP*) into cyclic guanosine monophosphate (*cGMP*). Binding of cGMP to its downstream effector protein kinase G (*PKG*) triggers the phosphorylation of several target proteins that mediate the physiological responses of NO. These responses include the inhibition of growth factor- and vasoactive peptide-induced mitogen-activated protein kinase (*MAPK*) signalling and phosphatidylinositol-3-phosphate (*PI3-K*) signalling as well as the inhibition of the Gq-protein-mediated activation of the nicotinamide adenine dinucleotide phosphate oxidase (*NADPH oxidase*) activity. As a result, PKG-mediated NO activity leads to an attenuation of the proatherosclerotic events such as oxidative stress, cell proliferation and migration, aberrant protein synthesis and gene transcription. In addition, PKG also mediates the vasodilatory responses to NO

turn catalyses the conversion of intracellular guanosine triphosphate (GTP) to cyclic guanosine 3′5′-monophosphate (cGMP) [13]. cGMP acts as a second messenger and transduces NO signal into intracellular events via the activation of the cGMP-dependent protein kinase (PKGs) [13]. Mammalian tissues express two different types of PKGs, type 1 (PKG-1) and type 2 (PKG-2) [14, 15]. PKG-1 is the predominant type found in cardiovascular tissues where it has been shown to mediate the anti-proliferative responses of cGMP [15–18]. PKG-1 modulates the activity of its downstream targets through serine/threonine phosphorylation. These targets include inositol-1,4,5-triphosphate (IP_3) receptor, phospholamban, troponin, myosin light chain phosphatase and c-Raf kinase [13, 19–23]. PKG-mediated actions of NO

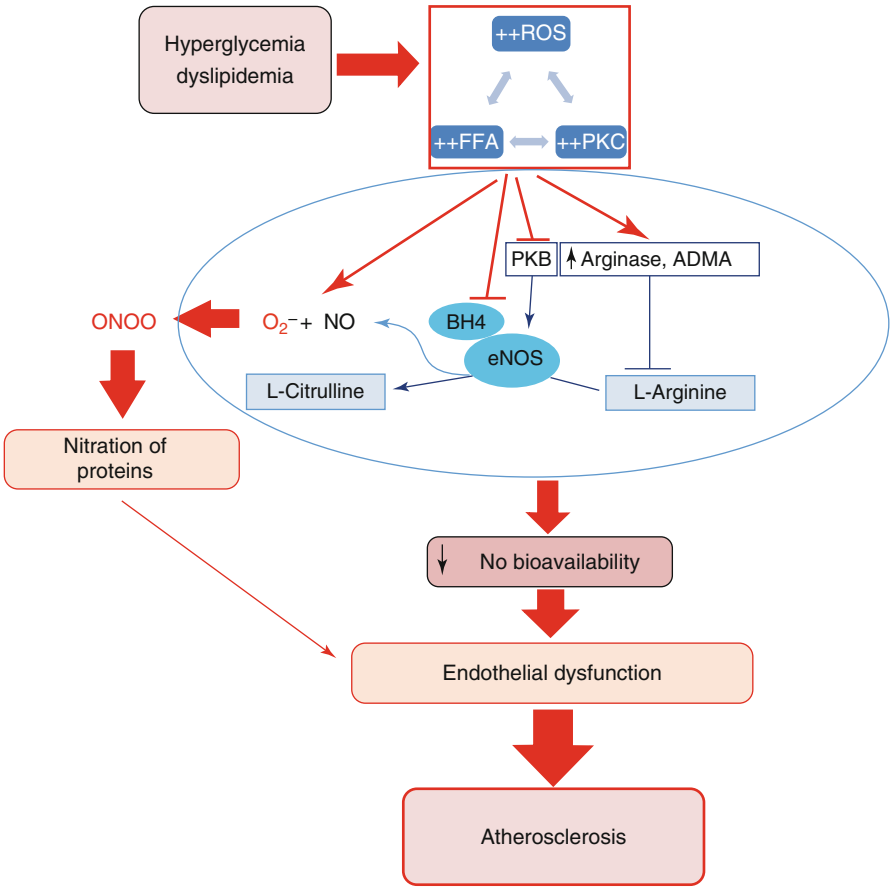

Fig. 26.2 Schematic model depicting the mechanisms leading to a decrease in NO bioavailability and subsequent vascular endothelial dysfunction. Under hyperglycaemic and dyslipidaemic conditions, both increased levels of free fatty acids (*FFA*) resulting from the metabolism of triglycerides and increased levels of glucose lead to an aberrant activation of the protein kinase C (*PKC*) that acts as a mediator of NADPH oxidase activation, the latter leading to reactive oxygen species (*ROS*) generation. ROS in turn can exacerbate protein kinase C (*PKC*) activation or FFA accumulation. The consequences of this crosstalk include quenching of bioavailable nitric oxide (*NO*) by superoxide anion to produce deleterious peroxynitrite (ONOO), oxidation and catabolism of the endothelial NO synthase (*eNOS*) cofactor BH4, inhibition of the protein kinase B (*PKB*)-mediated activation of eNOS and compromised utilisation of L-arginine due to an increase in arginases and asymmetric dimethylarginine (*ADMA*). As a result of these effects, there is a decrease in NO bioavailability leading to vascular endothelial dysfunction, the early feature of atherosclerosis

include the decrease in intracellular calcium levels and smooth muscle relaxation [24–26]. However, some actions of NO can be independent of the sGC/cGMP/PKG cascade; these include changes in cyclic adenosine monophosphate (cAMP) signalling [27] or the deleterious production of peroxynitrite radical ($ONOO^-$) [28–30]. In fact, elevated concentrations of NO can react with O_2^- that results in the formation of $ONOO^-$, a potent oxidant with the potential to disrupt protein structures by nitrating their tyrosine residues [31] (Fig. 26.2). Therefore, NO can also modulate the

activity of several proteins either by nitrosylation of their thiol residues, by nitration of tyrosine or by oxidation [26]. Furthermore, NO has been reported to inactivate NADPH oxidase by antagonising its assembling process, thereby inhibiting ROS generation [32]. However, in physiological settings, NO-induced activation of sGC remains the most important pathway in mediating NO responses [24].

26.3 Action of NO in the Vasculature

Numerous vasculoprotective actions of NO have been reported and are reviewed elsewhere [33]. Briefly, in addition to its vasodilating effect, the anti-atherosclerotic actions of NO include inhibitions of atherogenesis [34], thrombocyte aggregation [35] and VSMC proliferation [36–38] and migration [39]. NO may also antagonise the physiological and pathophysiological effects of growth factors and vasoactive peptides such as epidermal growth factor (EGF) [36], platelet-derived growth factor (PDGF) [40] and basic fibroblast growth factor (bFGF) [39] by interfering with some of the signalling events induced by these factors [34, 37, 39, 41, 42] (Fig. 26.1). Indeed, NO has been reported to inhibit protein synthesis and c-Fos expression in response to endothelin-1 (ET-1) [43–45] and angiotensin II (Ang II) [46]. Early reports showed that NO was able to suppress Ang II-induced activation of three mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase 1/kinase 2 (ERK1/ERK2), p38MAPK and c-Jun N terminal kinase (JNK) [47] as well as the non-receptor tyrosine kinase Pyk2 [48] in cardiac fibroblasts. In addition, Ang II-induced proliferation of VSMC was found to be attenuated by leptin via NO-mediated signalling [49]. Not surprisingly, due to an eventual reduction of NO bioavailability in hypertension, this effect of leptin was attenuated in VSMC isolated from 10-week-old spontaneously hypertensive rats [49].

26.4 NO Bioavailability and Vascular Endothelial Dysfunction

Multiple lines of evidence support that the processes that lead to either a reduction in NOS substrate L-arginine, modulation of endothelial NOS (eNOS) activity or expression or direct quenching of newly synthesised NO, may account for vascular endothelial dysfunction via their influence on NO bioavailability. It was shown that L-arginine supplementation in monkeys reversed endothelial dysfunction induced by hypercholesterolemia, supporting strongly that a depletion of the NOS substrate could result in altered NO synthesis and contribute to pathologies related to atherosclerosis [50]. It was further revealed that ROS such as hydrogen peroxide and peroxynitrite, as well as oxidised lipoproteins, could induce the expression and the activity of arginase in aortic endothelial cells via the RhoA/Rho kinase pathway amongst other unspecified pathways [51–54]. Consistent with a potential role of arginine deficiency in impaired endothelial function, hyperglycaemia has

been reported to enhance arginase activity [55]. By metabolising L-arginine into urea and ornithine, arginase contributes to a decrease in arginine levels resulting in diminished NO biosynthesis and has been implicated in the pathogenesis of vascular dysfunction in T2DM, hypertension and ageing [56–60]. Consequently, arginase inhibitors were shown to improve endothelium-dependent vasorelaxation in patients afflicted with T2DM and coronary artery disease [61] as well as to alleviate hypertension associated with T2DM and metabolic syndrome [62, 63]. Furthermore, in addition to their direct influence on arginine degradation, ROS have also been shown to induce the accumulation of methylated arginine (asymmetric dimethylarginine (ADMA)), endogenous competitive inhibitors of L-arginine binding to the eNOS [64, 65]. ADMA was demonstrated to be upregulated in diabetes mellitus, in association with increased levels of ROS [66, 67]. Indeed, some antioxidants exert their beneficial effects on vascular function via their ability to modulate the level of ADMA [68–70]. However, arginases and ADMA are also able to induce ROS generation through their interaction with eNOS [71, 72]. Therefore, their role as mediators of ROS-dependent impairment in NO bioavailability in endothelial dysfunction remains unclear.

Since BH4 is a key cofactor responsible for the catalytic activation of eNOS activity, impairment in BH4 levels has been suggested to play an important role in regulating the bioavailability of NO [73]. Consistent with this, transgenic over induction of BH4 synthesis has been shown to preserve NO-mediated endothelial function in diabetic mice [74] and to reduce atherosclerosis in apolipoprotein E-knockout ($ApoE^{-/-}$) mice [75]. Also, BH4 supplementation was shown to reverse endothelial dysfunction in healthy subjects subjected to transient hyperglycaemia [76] as well as in diabetic patients [77], suggesting that BH4 depletion may also account for endothelial dysfunction in T2DM. ROS such as superoxide and peroxynitrite are able to rapidly oxidise BH4 bound or not to eNOS leading to BH4 catabolism and depletion [78]. In addition, oxidation of BH4 results in the formation of dihydrobiopterin (BH2), which binds to eNOS and generates superoxide anion but not NO [79, 80]. Moreover, oxidative stress-mediated eNOS uncoupling can also occur via direct S-glutathionylation of eNOS [81–83]. In addition, ROS can decrease NO bioavailability by directly quenching free NO to form peroxynitrite [84]. Thus, both substrate and cofactor deficiency and excessive ROS levels can modify NO bioavailability and impair endothelial function leading to atherosclerotic vascular disease (Fig. 26.2).

26.5 Hyperglycaemia, Insulin Resistance and NO System

Diabetes is a major risk factor for vascular disease such as atherosclerosis, and hyperglycaemia has been suggested to contribute to vascular endothelial dysfunction-associated vascular diseases. Hyperglycaemia has also been shown to induce the generation of ROS by activation of NADPH oxidase system. ROS, by their ability to activate multiple signalling pathways linked with cell growth and proliferation and

by modifying NO bioavailability, can contribute to vascular endothelial dysfunction as outlined in the previous section. In addition, insulin has been reported to increase eNOS gene expression and protein activity resulting in increased NO bioavailability and is known to exert vasodilatory actions [85–88]. Insulin has also been shown to activate eNOS by inducing its phosphorylation on the serine residues, Ser^{615} and Ser^{1177} [89]. Consistent with this, it was reported that loss of insulin-mediated vasodilation in VSMC isolated from insulin-resistant diabetic Goto-Kakizaki rats could be reversed by overexpressing a constitutively active form of protein kinase B (PKB) [90]. Thus, diabetic atherosclerosis has been attributed to a defect in PI3-K/PKB/eNOS pathway. In contrast, a group reported that constitutively active PKB failed to stimulate the catalytic activity of eNOS immunoprecipitated from human coronary endothelial cells incubated in high glucose and high glucosamine [91]. It was suggested from these studies that in high glucose conditions, some other mechanisms may directly affect eNOS activity in a PKB-independent fashion. Nevertheless, additional reports have suggested that in addition to the induction of eNOS phosphorylation in response to insulin, insulin also induces an increase in L-arginine transport in endothelial cells, providing higher levels of substrate for NO synthesis [92, 93]. Interestingly, this effect on L-arginine is abrogated by PI3-K/PKB inhibition reinforcing the role of PKB in insulin-dependent modulation of endothelial function. Accordingly, obese and insulin-resistant Zucker rats subjected to L-arginine supplementation exhibited an increase of approximatively 85 % in NO release in comparison with their littermates that were not supplemented with L-arginine [94].

Although enhanced bioavailability of NO is beneficial for improving endothelial functions, excessive production of NO via the activity of iNOS has been suggested to be deleterious in the vasculature [95–97]. In fact, heightened levels of iNOS expression are observed in obese and diabetic states and account for aberrant PI3-K/PKB signalling, insulin resistance and impaired endothelial function [98–100]. Thus, in insulin-resistant states, increased iNOS expression could be an additional mechanism underlying endothelial dysfunction in diabetes or obesity.

26.6 PKC and NO System

Hyperglycaemia and ROS have been shown to activate protein kinase C (PKC) isoforms mainly via diacylglycerol formation [101–103]. Studies have suggested that the PKC isoforms mediate vascular complications by directly activating NADPH oxidase leading to higher ROS generation. Recent reports have shown that activation of PKC-β in endothelial cells blunts PKB phosphorylation in response to insulin and vascular endothelial growth factor [104]. Studies in insulin-resistant Zucker fatty rats reported that inhibition of PKC-β protects against endothelial insulin resistance by preserving insulin-mediated PKB phosphorylation and subsequent NO release [104]. In addition to their modulatory role in the insulin/NO pathway, PKC-β isoforms have also been demonstrated to cause an inhibitory phosphorylation of eNOS

on $Thr^{495/497.}$ By maintaining a sustained phosphorylation of eNOS on $Thr^{495/497}$, PKC-β antagonises agonist-induced eNOS activation and subsequent NO release [105, 106]. Consistent with that, an increase in NO bioavailability was observed following PKC inactivation in endothelial cells [107]. Furthermore, eNOS uncoupling towards ROS generation has recently been shown to be stimulated by PKC via Thr^{497} phosphorylation of eNOS in endothelial cells reinforcing the role of PKC in the impairment of endothelial function by modulating NO bioavailability [108].

The evidence of the pro-atherogenicity of PKC-β is reinforced by studies where atherosclerosis in $ApoE^{-/-}$mice is significantly decreased by genetic deletion or ruboxistaurin-mediated pharmacological blockade of PKC-β [109, 110]. PKC-β mediates atherosclerosis via the induction of the early growth response gene (EGR-1) and the matrix metalloproteinase-2. Blockade of PKC-β also reduces the lesion size by lowering the levels of pro-inflammatory proteins and macrophages [109, 110].

26.7 Dyslipidaemia and Regulation of NO System

Dyslipidaemia is associated with vascular endothelial dysfunction and has been suggested as a contributing factor in the pathogenesis of atherosclerosis. Free fatty acids (FFA) are produced from the metabolism of triglycerides and were reported to inhibit insulin-induced NO production resulting in impaired vasodilation [111]. It was found that hypertriglyceridaemia directly impairs endothelial function by stimulating the production of endogenous ADMA known to antagonise NO synthesis by competing with L-arginine [112]. Accordingly, clinical studies reported a decrease in endothelial NO release in obese patients exhibiting elevated plasma levels of ADMA [113, 114]. High levels of FFA can also affect NO bioavailability by impairing PI3-K/PKB/eNOS route in endothelial cells [115, 116]. Additionally, in response to FFA, induction of iNOS production and pro-inflammatory markers has been reported to disrupt NO system resulting in endothelial dysfunction [117, 118]. Moreover, calcium and its downstream effector proteins are potent activators of PKB/eNOS/NO pathway [119], and an attenuation of calcium signalling in endothelial cells exposed to FFA has been reported [120]. Consequently, FFA overload in endothelial cells contributes to eNOS uncoupling by altering calcium-induced eNOS activation [120]. Thus, in the dyslipidaemic state, both altered substrate availability and impaired PI3-K/PKB/eNOS signalling can alter NO bioavailability and contribute to the progression of atherosclerotic vascular disease (Fig. 26.2).

26.8 Concluding Remarks

NO is a well-studied vasoprotective agent and has been suggested to play a protective role in vascular disease by antagonising the physiological and pathological effects of growth factors and vasoactive peptides whose levels are enhanced in vascular diseases. Thus, a reduction in NO bioavailability via substrate or

cofactor modulation may be one of the mechanisms that could contribute to the pathogenesis of atherosclerosis. In addition, eNOS activity can be modulated by post-translational phosphorylation events catalysed by protein kinases such as PKB and PKC. The activity of these kinases can be modified by ROS, vasoactive peptides and growth factors during the pathogenesis of atherosclerosis. Currently, efforts are being directed to investigate whether improved availability of eNOS substrate/cofactor and/or modulation of protein kinase signalling pathways could serve as potential therapeutic approaches in the treatment of atherosclerosis.

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Chapter 27
Cardioprotective Role of Omega-3 Polyunsaturated Fatty Acids Through the Regulation of Lipid Metabolism

Kayode A. Balogun and Sukhinder K. Cheema

Abstract Cardiovascular disease (CVD) is ranked as the number one cause of death worldwide. The causes of CVD are defined by interplay between genetics and environmental factors; this contributes to the complexity of the pathophysiology of CVD. In spite of the advancement in medical science and drug discovery, the prevalence of CVD is still on the rise. The most important environmental factor in the pathogenesis of CVD is nutrition, especially the role of dietary fats. There are numerous reports supporting the cardioprotective effects of omega (n)-3 polyunsaturated fatty acids (PUFAs); however, there are also controversial reports. Given the complexity and physiological variation of the human population, it is pertinent to consider the various factors that could potentially affect the metabolism and hence the health benefits of n-3 PUFA before a strong recommendation can be made. The focus of this chapter is on the cardioprotective effects of n-3 PUFA, with particular emphasis on the regulation of lipid and lipoprotein metabolism, and factors such as age, sex and epigenetic modification that could potentially affect the health benefits of n-3 PUFA. This chapter also summarizes the emerging paradigm of the connection between CVD and neuropsychiatric disorders; it presents the propensity of n-3 PUFA to facilitate a therapeutic connection between these two diseases through a common pathway of neurotrophin signalling.

Keywords Atherosclerosis • BDNF • Cardiovascular disease • Dietary fats • Gene expression • Inflammation • Lipids and lipoproteins • n-3 PUFA • Neurotrophins

27.1 Introduction

Cardiovascular disease (CVD) is a disorder of the cardiovascular system; it includes hypertension, coronary heart disease, stroke, cardiac arrhythmia and heart failure. According to a World Health Organization (WHO) report, 30 % of all the

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deaths in 2008 were caused by CVD, and it was projected that more than 23 million people will die yearly from CVD by 2030 [1]. It was formerly thought that CVD was a disease of affluence and only rampant in the western society. However, the prevalence of CVD is fast on the rise in the developing countries as well [2]. CVD constitutes a huge socio-economic burden with an impact of $403.1 billion in the USA and €169 billion in the European Union in 2006 [3]. The burden of CVD is further complicated by the reduced age of onset, with projected deaths of 6.4 million people between the ages of 30 and 69 as a result of CVD by 2020 [4]. At the age of 60, 50 % of the population will be diagnosed with some type of cardiovascular disorder including atherosclerosis [5]. Studies have identified a number of pathological events associated with the morbidities of CVD; these factors include oxidative stress [6], dyslipidaemia [7], hyperglycaemia [8,9], hyperinsulinaemia [10] and upregulated markers of inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6). Dyslipidaemia and the homeostatic regulation of lipid and lipoprotein metabolism are central to the onset of CVD, where low-density lipoprotein (LDL) cholesterol remains the primary target for lowering blood lipid levels. However, cardiovascular events still occur despite maintaining optimal levels of LDL cholesterol, indicating the need to focus on other factors as well. Therapies have also focussed on increasing the levels of high-density lipoprotein (HDL) cholesterol, the "good cholesterol," and lowering blood triacylglycerol (TG) levels. Lifestyle modifications, especially the diet, play an important role in the onset as well as prevention of CVD. Genetic composition also predisposes to dyslipidaemia, obesity and diabetes mellitus, while nutrition, exercise and smoking are the best studied environmental factors that contribute to the pathogenesis of CVD [11].

Nutrition as an environmental factor is very crucial in the development of CVD, most importantly dietary fatty acids. Dietary fats fall under the main categories of saturated fatty acids (SFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA). High intake of SFA is generally considered to promote the development of CVD, while both MUFA and PUFA have been shown to be cardioprotective [12,13]. While the human body is capable of synthesizing SFA and MUFA, humans lack the enzymes to synthesize PUFA [14]; thus, PUFAs are essential fatty acids and must be consumed in the diet. Over the past years, there has been a drastic change in the western diet; this was promoted by the industrial revolution and modern food processing techniques [15] and the birth of modern-day agriculture leading to the production of vegetable oils highly rich in omega (n)-6 PUFA [16]. This led to an increased intake of n-6 PUFA in the western diet and an overall reduction in the dietary consumption of n-3 PUFA [16]. It has been speculated that these changes in nutritional quality could be responsible for the majority of chronic diseases prevalent in the western societies, including CVD [17]. The importance of both n-3 and n-6 PUFA has been greatly studied in the pathophysiology of CVD; the focus of this chapter will mainly be on the cardioprotective effects of n-3 PUFA, with particular focus on factors related to the beneficial effects of n-3 PUFA.

27.2 Metabolism of Essential Polyunsaturated Fatty Acids

The two major essential fatty acids are linoleic acid (LA) of the n-6 PUFA class and α-linolenic acid (ALA) of the n-3 PUFA class [18]. LA is abundant in vegetable oils such as safflower and corn oils, while the essential n-3 PUFA, ALA, is rich in walnuts and flaxseed oils [14], which are plant-derived sources. The nomenclature of the essential fatty acids is based on the position of the first double bond from the methyl end of the fatty acid chain; n-3 PUFAs have their first double on carbon number 3 while that of n-6 PUFA is on carbon number 6 from the methyl end [14]. The parent 18-carbon LA and ALA acids can undergo a series of enzyme-catalyzed desaturation and elongation steps using desaturase enzymes to produce highly unsaturated longer-chain arachidonic acid (AA) in the n-6 PUFA pathway and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the n-3 PUFA pathway [14,19]. The conversion of ALA to EPA and DHA, the marine-derived n-3 PUFA, is inefficient with the conversion rate in men estimated to be approximately 0–1 % and ~9 % in women [20]. Studies have shown that the desaturation and elongation processes favour the conversion of ALA to EPA and DHA over the conversion of LA to AA [21]. However, a high consumption of dietary LA could shift the pathway in favour of the production of longer-chain n-6 PUFA (Fig. 27.1). The metabolism of n-3 and n-6 PUFA also involves the oxygenation of 20-carbon AA and EPA by cyclooxygenases (COX) and lipoxygenases (LOX) to produce eicosanoids, which are the signalling

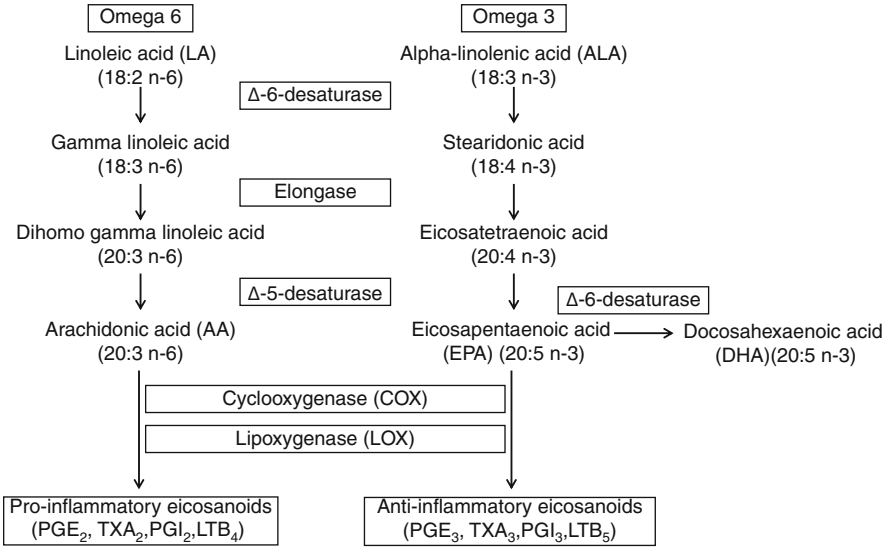

Fig. 27.1 Pathways for the synthesis of long-chain omega-6 and omega-3 polyunsaturated fatty acids. Leukotriene B (*LTB*); prostaglandin E (*PGE*); thromboxane A (*TXA*), prostacyclin (*PGI*)

molecules of physiological and therapeutic importance; these include prostaglandins (PG), thromboxanes (TX) and leukotrienes (LT). Eicosanoids from AA are proinflammatory and prothrombotic and generally promote atherosclerosis [22]. On the other hand, eicosanoids derived from EPA have been shown to be anti-inflammatory and antithrombotic and promote good health [23]. It is therefore imperative to maintain a nutritional balance between n-6 and n-3 PUFA for optimal body function. Over the years, there has been a decline in the consumption of n-3 PUFA in the western diet forcing the ratio of n-6 to n-3 PUFA in the western diets to be approximately 20–30:1 which is relatively higher than the 1:1 ratio on which we evolved [24]. This decline has been suggested to be responsible for the prevalence of CVD (Fig. 27.2).

27.2.1 n-3 PUFA and Cardiovascular Disease

The scientific inquiry into the health benefits of n-3 PUFA originated from the Bang and Dyerberg's observation of the Greenland Inuit [25]. They observed that the Greenland Inuit had lower concentrations of plasma TG, LDL and total cholesterol (TC) as compared to the Danish control; these differences were ascribed to the high-fish diet of the Inuit. n-3 PUFAs such as EPA and DHA occur predominantly in fish oil, and an inverse relationship between fish consumption and incidence of CVD has been reported in a meta-analysis of 200,575 subjects [26]; other clinical studies have also corroborated these findings [27,28]. Furthermore, it has been

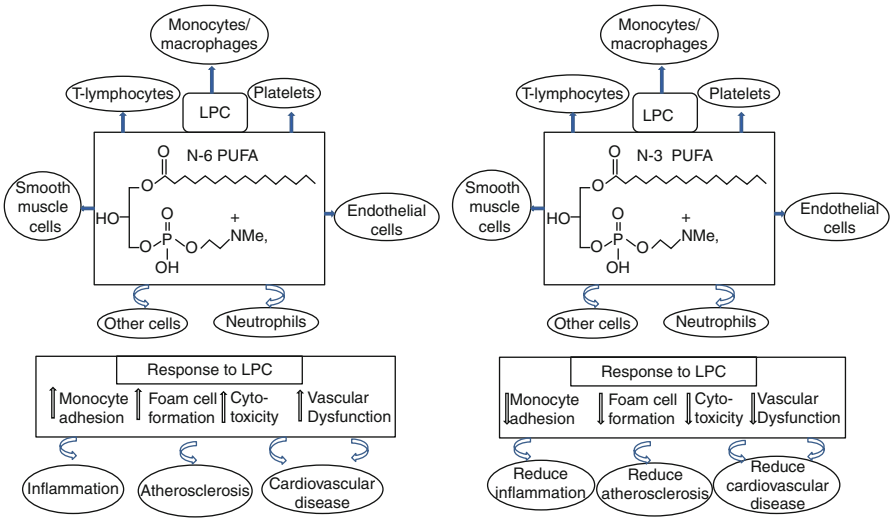

Fig. 27.2 Potential atheroprotective mechanisms of omega (n)-3 polyunsaturated fatty acid (*PUFA*)-enriched lysophosphatidylcholine (*LPC*)

reported that Americans exposed to a high-fish diet had a significantly lower risk of coronary heart disease [29]. Dietary supplementation of n-3 PUFA (>2 g/day) has been shown to alleviate symptoms of dyslipidaemia, improve endothelial function and resolve inflammation associated with the development of CVD [30–32]. There are also evidence supporting the anti-inflammatory, antithrombotic, anti-atherogenic and antiarrhythmic properties of n-3 PUFA [33]. The North American intake of n-3 PUFA is approximately 130–150 g/day [33,34]. With the documented health benefits of n-3 PUFA, the consumption of two fatty fish servings per week for the prevention of CVD was recommended by the American Heart Association [35]; this is estimated to provide EPA and DHA of approximately 450–500 mg/day [35,36]. There is no universally recognized recommendation for the consumption of n-3 PUFA due to dietary variations in different countries. However, most countries and organizations have made different recommendations based on the recognized health benefits of n-3 PUFA. Some of these recommendations accounted for gender, age and health status; however, the common theme among the different recommendations is the n-6 to n-3 PUFA ratio of approximately 5:1 (Table 27.1). The health benefits of n-3 PUFA depends on its availability in the body and its accretion to body tissues; hence, the omega-3 index which is the percentage of the erythrocyte highly unsaturated n-3 PUFA (EPA + DHA) can be considered as a possible risk factor of cardiovascular irregularities [37]. An omega-3 index of 4 % represents low cardioprotective effects, while an index of 8 % signifies relatively high cardioprotection [38]. The premise for this was that the fatty acid composition of the blood can be used as surrogate for the fatty acid composition of the cardiac muscle [39].

27.3 Cardioprotective Mechanisms of n-3 PUFA

Several mechanisms have been proposed by which n-3 PUFA can prevent CVD; the three main mechanisms are (a) regulation of lipid and lipoprotein metabolism, (b) alteration of membrane dynamics and production of bioactive lipids and (c) reduction of inflammation. The following sections focus on the involvement of n-3 PUFA in the regulation of these pathways.

27.3.1 Cardioprotective Effects of n-3 PUFA by Regulating Lipid and Lipoprotein Metabolism

Alterations in lipid metabolism underlie the pathology of diseases such as CVD and diabetes mellitus; thus, the regulation of lipid metabolism is crucial for maintaining physiological function. The following subsections highlight the importance of n-3 PUFA in regulating lipid and lipoprotein metabolism and the associated mechanisms.

Table 27.1 Omega-3 polyunsaturated fatty acid international intake recommendation

Source	Date	n-6:n-3 ratio	Other specific recommendations (%en=% of daily energy intake)
National Nutrition Council of Norway	1989	None	0.5 % en n-3 LCPUFA (1–2 g/day)
NATO Workshop on n-3/n-6	1989	None	0.8 g/day EPA/DHA (0.27 %en)
Scientific Review Committee of Canada	1990	5:1–6:1	n-3 PUFA at least 0.5 %en
British Nutrition Foundation Task Force	1992	6:1	EPA 0.2–0.5 %en: DHA 0.5 %en
FAO/WHO Expert Committee on Fats and Oils in Human Nutrition	1994	5:1–10:1	Consider pre-formed DHA in pregnancy
UK Committee on Medical Aspects of Food Policy (COMA)	1994	None	Fish twice/week, one of which should be oil, minimum intake EPA/DHA 200 mg/day
Ad Hoc Expert Workshop	2000	None	EPA + DHA 0.3 %en:0.65 g/day minimum
France: AFFSA, CNERNA and CNRS	2001	5:1	500 mg n-3 LCPUFA/day: DHA 120 mg minimum
US National Academy of Science/Institute of Medicine	2002	None	130–260 mg EPA + DHA/day
American Heart Association	2002	None	If no CHD, eat (oily) fish twice/week; if CHD consume 1,000 mg n-3 LCPUFA/day; if high triglycerides, take 2–4 g per day, under medical supervision
UK Scientific Advisory Committee on Nutrition (SACN)	2004	None	Fish twice/week, one should be oily, min intake EPA/DHA 450 mg/day
ISSFAL	2004	None	500 mg n-3 lcPUFA/day
Australia and New Zealand Government Recommendations	2005	None	n-3 LCPUFA men 160 mg/day; women 90 mg/day
Superior Health Council of Belgium	2006	None	A minimum of 0.3en% EPA + DHA for adults
Health Council of the Netherlands	2006	None	To achieve the dietary reference intake of 450 mg of n-3 PUFA from fish a day, it is necessary to eat two portions of fish a week, at least one of them being oily fish (such as salmon, herring or mackerel)

The table shows a summary of the omega-3 polyunsaturated fatty acid intake recommendation worldwide composed by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) 2010. http://www.issfal.org/statements/pufa-recommendations/recommendations-by-others
LCPUFA long-chain polyunsaturated fatty acids, *CHD* coronary heart disease

27.3.1.1 n-3 PUFA and Serum Lipoprotein Metabolism

The transport of dietary fats from the intestine to the liver and movement of cholesterol to peripheral tissues in mammals are facilitated by lipoproteins [40]. Lipoprotein

particle is composed of lipids and apolipoproteins (apo) responsible for its structural integrity [41]. Lipoproteins are categorized according to their particle density and size; the least dense lipoproteins are the chylomicrons followed by very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL and HDL [41]. The densities of these lipoproteins are defined by the relative concentration of lipids to proteins. The major types of lipoproteins and their properties are given in Table 27.2. During lipid metabolism, ingested dietary fats are transported from the intestine in form of chylomicrons. The TG in the circulating chylomicrons is metabolized by lipoprotein lipase (LPL), transforming them into chylomicron remnant, which is cleared by the hepatic LDL receptor and the LDL receptor-related protein; the released fatty acids are transported to the adipose tissue where they form TG and are stored [43]. The liver synthesizes cholesterol and fatty acids which are packaged and transported in VLDL. Similar to chylomicron metabolism, VLDL also undergoes hydrolysis by LPL to produce free fatty acids which are once again transported to the adipose tissue for storage as TG. VLDL loses its lipids and transforms to IDL which can be cleared by the liver or further metabolized by LPL resulting in a loss of apo-E to produce LDL. LDL contains apo-B 100 and is the main transporter of plasma cholesterol and can be cleared by LDL receptor on the membrane of the liver. LDL has been said to carry the "bad cholesterol," an excess of which could be highly atherogenic. Conversely, HDL is produced both in the liver and intestine from precursor apoA-1. Lipid poor apoA-1 acquires lipid by the action of ATP-binding cassette transporter (ABCA1) to form nascent HDL particle [44]. HDL is further lapidated by the action of ABCG1 from lipid acquired from TG-rich lipoproteins. Lecithin cholesterol acyltransferase (LCAT) esterifies the cholesterol in the HDL, thereby forming mature HDL [45]. HDL is involved in reverse cholesterol transport which is responsible for carrying cholesterol from peripheral tissues to the liver for excretion; this makes HDL functionally an atheroprotective. Figure 27.3 shows a schematic representation of the lipoprotein metabolic pathway.

TG is transported in circulation by lipoproteins, primarily VLDL and chylomicrons; the concentration of plasma TG affects the concentration of plasma lipoproteins. TG is associated with atherogenic lipoproteins such as VLDL and LDL; n-3 PUFA reduces TG concentration chiefly by reducing hepatic VLDL production [46]. This also leads to an increased conversion of VLDL to LDL [47], which explains the increase in LDL cholesterol concentration upon supplementation with n-3 PUFA [46]. Individuals supplemented with n-3 PUFA have been shown to have an increase in LDL cholesterol concentrations which is a risk factor of CVD [31,48]; however, the increase in LDL is towards a less atherogenic large buoyant LDL particle. The effects of n-3 PUFA on lipoprotein concentrations have been controversial. The current consensus is that n-3 PUFA improves the quality of lipoproteins profile to a less atherogenic subclass without affecting their concentrations [49]. Studies have shown that small dense LDL is capable of infiltrating the arterial wall and prone to oxidation, making them more atherogenic compared to the large buoyant LDL particles [50]. n-3 PUFA has been shown to increase the concentration of less atherogenic large LDL particles [51]; this is facilitated by a decrease in TG concentration which causes an increase in LDL particle size as a result of an increase in hepatic VLDL clearance [52].

Table 27.2 Properties and functions of lipoprotein classes

Lipoproteins	Density (g/mL)	Apoproteins	Composition (%)				Lipid delivery method	Function
			Protein	TG	Chol	Phosp		
Chylomicron	<0.95	B-48, C, E	2	90	5	3	Lipoprotein lipase hydrolysis	Transport of dietary TG from intestine to hepatic and extrahepatic tissues
VLDL	0.95–1.006	B-100, C, E	6	60	20	14	Lipoprotein lipase hydrolysis	Transport of TG from liver to extrahepatic tissues and precursor of IDL
IDL	1.006–1.019	B-100, E	18	20	40	22	Receptor-mediated hepatic endocytosis and conversion to LDL	Precursor of LDL
LDL	1.019–1.063	B-100	21	7	50	22	Receptor-mediated endocytosis by the liver and extrahepatic tissues	Primarily transports cholesterol from the liver to extrahepatic tissues
HDL	1.063–1.210	A	44	5	25	26	Transfers cholesterol to IDL and LDL	Responsible for reverse cholesterol transport from extrahepatic tissues to the liver

Adapted and modified from reference [43]
VLDL very-low-density lipoprotein, *IDL* intermediate-density lipoprotein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* triglycerides, *Chol* cholesterol, *Phosp* phospholipids

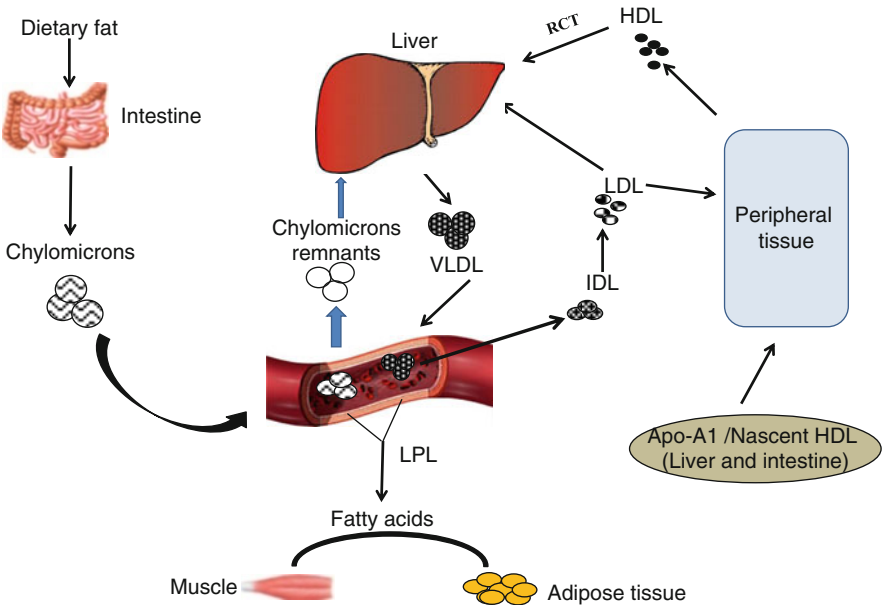

Fig. 27.3 Lipoprotein metabolic pathway. *VLDL* very-low-density lipoprotein, *IDL* intermediate-density lipoprotein, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *LPL* lipoprotein lipase, *Apo-A1* apolipoprotein A1, *RCT* reverse cholesterol transport

High circulation TC level is also a risk factor for the development of CVD [53]. n-3 PUFA regulates TC concentration by downregulating the expression of sterol regulatory element-binding protein (SREBP), thereby suppressing the expression of 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase, the key enzyme of cholesterol biosynthesis [54]. Liver X receptor (LXR) also prevents cellular cholesterol accumulation by upregulating the expression of 7-α-hydroxylase, cytochrome P450 [CYP7A], an enzyme involved in bile synthesis, thus converting excess cholesterol into bile [55]. High-density lipoprotein (HDL) is involved in reverse cholesterol transport and has been colloquially referred to as the carrier of good cholesterol. There are reports showing an increase in HDL cholesterol concentration upon supplementation with n-3 PUFA [56]. HDL exerts its cardioprotective effect mainly through reverse cholesterol transport, which is the removal of excess cholesterol from extrahepatic tissues to the liver for excretion. The functionality of HDL depends on its ability to remove cholesterol which is known as cholesterol efflux capacity [57]. HDL is also a heterogeneous lipoprotein with different particle sizes each with different cholesterol efflux capability [58]. HDL-2 and HDL-3 are the most studied classes of HDL, and they differ by size and functionality with HDL-2 showing the most cholesterol efflux potential [59]. n-3 PUFA has been reported to increase the concentration of larger and buoyant HDL-2 particles without affecting the total HDL cholesterol concentration [60], thereby increasing cholesterol efflux which has cardioprotective implication.

27.3.1.2 n-3 PUFA and the Regulation of Genes Involved in Lipid Metabolism

Abnormal concentration of lipids known as dyslipidaemia is a major independent risk factor of CVD [61]. Hypertriglyceridaemia is an independent risk factor for the development of CVD [62]. Fish oil has been shown to be potent at treating hypertriglyceridaemia [63]. It has been reported that 3–4 g/day EPA and DHA resulted in 25 % reduction of TG levels in normolipidaemic individuals and 35 % reduction in TG in individuals with hyperlipidaemia [31,35]. The mechanism underlying the TG-lowering effects of n-3 PUFA has been explained by the involvement of n-3 PUFA in the regulation of genes involved in lipid metabolism; such genes include SREBP, all forms of peroxisome proliferator-activated receptors (PPARs), retinoid X receptor-alpha (RXR-α) and LXR-α. The retinoid X receptor (RXR) heterodimerizes with LXR and regulates the activity of SREBP1-c by binding to the LXR response element in the SREBP1-c promoter region, thereby suppressing its expression [64]. SREBP1-c is the key controller of lipogenesis; its inhibition would downregulate the expression of fatty acid synthase and acetyl-CoA carboxylase, thereby preventing fatty acid synthesis required for TG synthesis. Another classic cardioprotective mechanism of n-3 PUFA in the reduction of circulating TG is by stimulating fatty acid β-oxidation. n-3 PUFA reduces TG concentration by increasing the β-oxidation of nonesterified fatty acids (NEFA), a substrate for TG synthesis [65]. n-3 PUFA also regulates the expression of PPARα which upregulates acetyl coenzyme A oxidase, a rate-limiting enzyme in fatty acid catabolism, which further stimulates β-oxidation [66].

27.3.2 Cardioprotective Effects of n-3 PUFA by Altering Membrane Dynamics and Production of Bioactive Lipids

Membrane fluidity is influenced by the incorporation of long-chain n-3 PUFA into membrane phospholipids [67,68], which could alter the functions of transmembrane proteins and their interaction with extracellular ligands [69]. These alterations indirectly affect signalling pathways and other physiological functions. Furthermore, the fatty acid on the *sn*-2 position of membrane phospholipids could be cleaved by the action of phospholipase A_2 (PLA_2) to produce a free fatty acid and lysophosphatidylcholine (LPC) which are both bioactive molecules [70]. The released 20-carbon AA and EPA from the membrane phospholipids undergo oxidation catalyzed by cyclooxygenases (COX-1 and COX-2) and lipoxygenases (LOX-5, LOX-12, LOX-15) to produce bioactive lipid intermediates and hormone-like substances known as eicosanoids [38]. AA is a precursor to series-2 prostaglandins and series-4 leukotrienes; these are generally proinflammatory, vasoconstrictive and pro-aggregatory and generally promote CVD [22]. On the other hand, series-3 prostaglandins and

series-5 leukotrienes produced from EPA are anti-inflammatory and prevent the development CVD [23]. AA-derived eicosanoids include proinflammatory PGE_2 (vasodilator), TXA_2 (vasoconstrictor), PGI_2 (platelet aggregator) and LTB_4 (chemotactic factor), while EPA-derived eicosanoids include anti-inflammatory PGE_3 (vasodilator) and PGI_3 (inhibit platelet aggregator), and LTB_5 and TXA_3 are less active than AA-derived eicosanoids [14,71] (Fig. 27.1).

Cardiac arrhythmia is a major event of CVD, and this involves the electrophysiological control of cardiac muscle activities [72]. n-3 PUFA has been shown to control cardiac arrhythmia by regulating Na^+, Ca^{2+}, K+ channels and ion pumps [72]. n-3 PUFAs are relatively safe; however, they have been shown to influence platelet function and could affect the bleeding time. n-3 PUFAs increase the concentration of $PG1_2$ or prostacyclin, a vasodilator and platelet inhibitor [73]; this also leads to a reduced formation of the platelet activator TXA_2 (11). Furthermore, n-3 PUFAs suppress the production of platelet-activating factor (PAF), also a platelet activator [73]; this consequently increases bleeding time and reduces ADP, epinephrine and collagen-stimulated platelet aggregation in individuals supplemented with n-3 PUFA [74]. Although n-3 PUFAs have been shown to affect bleeding time, the changes in bleeding time are within the normal range and are not associated with any bleeding complications. Studies that supplemented n-3 PUFA within the range of 3–6 g/day to healthy subjects and patients with cardiovascular diseases without any concomitant medication that prolongs bleeding time reported an increase in bleeding time, which was within the normal range [75]. Other studies that administered up to 6 g/day n-3 PUFA saw no significant difference in bleeding time [76,77].

DHA and EPA produced from membrane phospholipids can also be oxygenated to produce a novel class of inflammation-resolving compounds known as resolvins and protectins which are also cardioprotective [78]. The resolution of inflammation involves a decrease in proinflammatory mediators, clearance of leukocytes and the transition of the cells back to a non-inflammatory state [79]. Inflammation-resolving lipid mediators are produced based on the parent fatty acid and the presence or absence of aspirin [80]. The expression of COX-2 is upregulated during acute inflammation [81], and in the presence of aspirin, COX-2 is acetylated thereby inhibiting the formation of prostaglandins [80]. Acetylated COX-2 can catalyze a series of reactions using EPA and DHA leading to the formation of resolvins (resolution phase interaction products). Resolvins are oxygenated anti-inflammatory and immunoregulatory products of the metabolism of EPA and DHA. The resolvins and protectins elicit their beneficial effects in the picomolar and nanomolar range both in vivo and in vitro [82,83]. EPA is oxygenated to produce the E-series resolvins, while DHA produced resolvins or protectins of the D-series. Both the D- and E-series resolvins are formed by 15-LOX in leukocytes and aspirin-acetylated COX-2 in vascular endothelial cells [84], while protectins are formed from DHA by the oxygenation of 15-LOX in leukocytes and other cells [23,85]. Resolvins exhibit their anti-inflammatory properties by inhibiting the transmigration and infiltration of neutrophils mainly by initiating apoptosis [83] which is important in the resolution of inflammation. Protectins on the other hand prevent inflammation by blocking the recruitment and action of neutrophils, inhibiting the secretion of TNF-α and

altering the activities of COX-2 in both in vivo and in vitro settings [86]. Protectin and resolvins are capable of resolving inflammations associated with atherosclerosis, mainly by downregulating the expression of inflammatory proteins such as MCP-1 and IL-8 [87].

The type of the released fatty acid from the membrane phospholipids depends on the dietary fatty acid composition. We have previously shown that consuming a diet high in n-3 PUFA alters the fatty acid composition of membrane phospholipids such as phosphatidylcholine (PC) and phosphatidylethanolamine (PE), thereby resulting in increased release of cardioprotective n-3 PUFA such as free EPA and DHA [42]. n-3 PUFAs have also been shown to cause an increase in the n-3 PUFA composition of lysophosphatidylcholine (LPC), which is also a product of the enzyme hydrolysis of membrane PC [42]. LPC is biologically active and regulates several metabolic and physiological pathways by acting as a signalling molecule [88]. LPC is generally considered atherogenic in nature [89]; however, the biological and metabolic functions of LPC have been suggested to depend on the acyl chain length and degree of unsaturation [90]. Fish oil intake was found to increase plasma and tissue concentrations of LPC enriched with EPA and DHA [42,90,91]. The consumption of fish oil in subjects with impaired glucose metabolism significantly increased plasma LPC-EPA [92], and LPC was found to enhance insulin secretion [93]. LPC with DHA is also known to possess anti-inflammatory properties with overall cardioprotective effect [88]. Furthermore, LPC containing n-3 PUFA has been shown to promote cholesterol efflux from macrophages consequently increasing the overall reverse cholesterol transport which has a cardioprotective implication [94]. Figure 27.2 summarizes the potential of n-3 PUFA-enriched LPC to act as an anti-atherogenic molecule. Overall, there is plenty of evidence that enrichment of membrane n-3 PUFA content has the ability to modify metabolic and physiological functions, thereby inducing cardioprotective effects.

27.3.3 Cardioprotective Effects of n-3 PUFA by Reducing Inflammation

Atherosclerosis is defined as the pathological thickening of the arterial wall as a result of invading white blood cells, which is the major underlying process for the development of CVD [95]. The development of atherosclerosis encompasses a cycle of inflammatory processes and is now recognized as an inflammatory disease [96]. Atherosclerosis develops from the oxidation of LDL chiefly by reactive oxygen species. The oxidized LDL triggers a sequence of inflammatory responses resulting in an increased expression of adhesion molecules such as vascular cell adhesion molecule 1 (V-CAM-1), intercellular adhesion molecule 1 (ICAM-1) and E-selectin by the endothelial cells. A chain of chemical reactions lead to the recruitment of monocytes which later differentiate in macrophages; these macrophages take up the oxidized LDL and become lipid laden to form foam cells. The foam cells continue to grow and rupture leading to a huge deposit of cholesterol and fatty streaks on the endothelial wall. More macrophages are then recruited upon rupture

of the foam cells, and the cycle continues which could eventually lead to end-stage CVD [97] (Chap. 25).

Studies have reported the ability of n-3 PUFA to reduce the expression of adhesion molecules on macrophages [98] and endothelial cells [99], thereby preventing the atherosclerotic plaque progression. n-3 PUFAs also prevent CVD by maintaining vascular endothelial function. The adhesion molecules secreted by endothelial cells are actively involved in platelet adhesion and leukocyte recruitment during inflammation, which are major players in atherogenesis [23]. These adhesion molecules are activated by proinflammatory cytokines such as TNF-α, IL-6 and IL-8, and n-3 PUFA has been shown to decrease the expression of these cytokines.

The expression of adhesion molecules on the endothelium is also promoted by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), a proinflammatory transcription factor [100,101]. NF-kB is involved in a number of cellular responses including inflammation and immune response to infection. Activation of NF-kB leads to a sequence of reactions that promote inflammation and consequently atherogenesis. The activated form of NF-kB has been found in atherosclerotic vessel walls that promotes the formation of atherosclerotic lesion [102]. n-3 PUFA downregulates the expression of NF-kB to suppress inflammation [103]; this reduces the markers of atherosclerosis and enhances vascular function [104]. n-3 PUFA has also been found to impede the translation of genes involved in inflammation by inhibiting NF-kB. Furthermore, EPA was found to inhibit the expression of TNF-α, a classic proinflammatory cytokine by preventing the movement of NF-kB into the nucleus [105]. NF-kB also upregulates the expression of inflammatory cytokines such as IL-6, IL-2 and TNF-α; n-3 PUFAs have been shown to reduce these cytokines. The expression of PPARs, an important class of nuclear receptor proteins involved in the regulation of inflammation and lipid metabolism, has also been shown to be directly regulated by n-3 PUFA [106]. PPAR forms heterodimer with retinoid X receptor (RXR); the PPAR/RXR heterodimer binds to the peroxisome proliferator response element (PPRE) on the target gene to elicit its regulatory role [23]. PPARα and PPARγ inhibit NF-kB, thereby blocking the production of potent inflammatory cytokines. PPARα has also been shown to exhibit its cardioprotective effect by blocking the production of cellular adhesion molecules, leading to a significant reduction of inflammation [106]. Moreover, as mentioned previously, n-3 PUFA can also alleviate inflammation resulting from atherogenesis by producing anti-inflammatory eicosanoids and docosanoids from EPA and DHA, respectively [107].

27.4 Potential Reasons for Controversies in the Cardioprotective Effects of n-3 PUFA

There are numerous reports on the beneficial health effects of n-3 PUFA; however, there are also controversial reports on the cardioprotective efficacy of n-3 PUFA. A recent systematic review and meta-analysis on the association between n-3 PUFA supplementation and risk of CVD revealed that n-3 PUFA was not associated with

lower mortality from cardiovascular events [108]. Furthermore, a recent study reported no significant effect on markers of CVD after 6-year supplementation with n-3 PUFA [109]. These controversies could be due to differential effects of n-3 PUFA based on sex, dose, duration of exposure and the type of n-3 PUFA used.

27.4.1 Sex, Age and the Cardioprotective Effects of n-3 PUFA

The most characterized factor affecting lipid metabolism is sex; this has been ascribed to a clear distinction in hormonal regulation between male and female [110]. Research evidence suggests that sex also plays a vital role in the development of CVD; it has been reported that men and women differ significantly in their circulating blood lipids and predisposition to CVD [111] (Chap. 21). Plasma TC has been shown to increase with age peaking at 50–59 years in men and at 60–69 years in women [112]; these sex-specific differences in blood lipid parameters have also been reported for plasma HDL cholesterol and TG [112]. The female hormone, oestrogen, is involved in lipid metabolic pathways; it is also responsible for the rapid transport of fat in women compared to men, and this partly accounts for the gender-specific risk of CVD [113]. These sex-specific differences have also been shown to affect the metabolism of n-3 PUFA, which would explain the overall sex differences in cardiovascular effects of n-3 PUFA. Studies have reported a higher tissue accretion of DHA in females compared to male [114,115], supported by the higher conversion rate of ALA to longer-chain EPA and DHA in women [114]. This is explained mechanistically by the sex-specific effect of the liver desaturase enzyme responsible for the conversion of ALA to EPA and DHA [115]. Interestingly oestrogen has also been shown to affect tissue distribution of n-3 PUFA with females showing a higher accretion which further explains the differences observed between male and female [116]. Although controversial, the role of oestrogen in LDL metabolism has been reported; oestrogen decreased the circulating concentration of atherogenic LDL [117]. We have also observed an interaction between n-3 PUFA and sex in a rodent model, where female mice showed a lower concentration of plasma LDL cholesterol concentration in response to high-n-3 PUFA diet compared to male mice [118]. There are also sex differences in the concentration of HDL particles between men and women [113]. More importantly, cholesterol efflux capacity is sex specific and is higher in males than in females in response to high-n-3 PUFA diet [118]. The mechanism underlying the sex-specific effects of n-3 PUFA has been explained by the interaction between PPARα and oestrogen receptor. Studies have shown a stimulatory relationship between PPARα and oestrogen receptor, which is affected by n-3 PUFA [119,120]. There are also evidences of the sex-specific effect of PPARα on the regulation of cholesterol metabolism [121].

The effect of sex in the development of CVD cannot be overemphasized; however, beyond sex differences comes age. The prevalence of CVD is different between male and female, and this has also been shown to be affected with age [122]; this has been linked to age-dependent variation in cholesterol concentration between

male and female [123]. The plasma TC concentration increases with age [124] mainly because of the age-dependent decrease in the catabolism of cholesterol [124]. Furthermore, males and females have comparable plasma HDL cholesterol concentration at puberty after which the differences become apparent as they age [125]. There are also documented age effects on plasma concentration of TG concentration [122]. Recent evidence also supports the effect of age and n-3 PUFA on the concentration of plasma lipids and lipoproteins [118] (Chap. 21).

27.4.2 Dose and the Cardioprotective Effects of n-3 PUFA

To get the desired cardioprotective benefits from n-3 PUFA, it is imperative to administer the appropriate dosage. The recent systematic review and meta-analyses that discredited the cardioprotective effects of n-3 PUFA [108] considered studies that used a lower than the recommended dosage of n-3 PUFA; the mean intake of EPA and DHA in their study was approximately half the recommended dosage of 3 g/day to reduce the risk of CVD. The beneficial effect of n-3 PUFA on cardiovascular events has been shown to be dose dependent. Moertl et al. found a 2.5 % improvement in left ventricular ejection fraction (LVEF) in patients with coronary heart failure (CHF) after administering 1 g/day n-3 PUFA for 3 months; however, a 5.5 % improvement was recorded with a higher dose of 4 g/day of n-3 PUFA [126]. In the same cohort, only higher doses were seen to be effective at resolving inflammation and alleviating endothelial dysfunction, further emphasizing the importance of dose in the health benefits of n-3 PUFA [126]. Furthermore, studies have also reported the beneficial effect of n-3 PUFA dosage greater than 1 g/day at treating endothelial dysfunction [127]. To obtain a full cardioprotective effect of n-3 PUFA, a dosage in excess of the currently recommended 1 g/day will be required. The immunomodulatory effects of n-3 PUFA has also been shown to be dose dependent, with observable benefits within the range of 1.65 and 3.3 g/day [128]. The importance of dosage in the health benefits of n-3 PUFA has also been corroborated by animal studies with significant improvement from cardiovascular events observed at a higher dosage [129]. Several clinical trials have reported the beneficial effects of consuming fish and n-3 PUFA supplements, and a different dosage has been shown to be effective. In a clinical trial, subjects who were asked to consume 200–400 g oily fish per week or the equivalent of fish oil capsules (EPA 180 mg and DHA 120 mg) saw significant cardioprotective effects [27]. In another study, individuals who received approximately 882 mg of EPA and DHA (1:2) had up to 20 % reduction in risk of CVD [130] compared to those without n-3 PUFA supplements [131]. Analyses of prospective cohort studies have shown that the consumption of 25–500 mg/day EPA and DHA is sufficient to reduce the risk of CVD [132]; however, another study reported that the upper limit of 500 mg/day provided the most beneficial effect [133] and that even greater intake will confer additional protection [134]. It was also reported that 4 g/day reduced TG concentration by 25–30 %, and a dose response relationship was also observed [31]. Another study of 42

participants revealed a 45 % decrease in TG after supplementing patients with 4 g/day n-3 PUFA [135]. The cardioprotective benefits of n-3 PUFA have been well documented; however, the optimal dose remains to be established. There is no firm recommended dietary intake for n-3 PUFA; however, different international organizations have dietary recommendations (Table 27.1). The effective dose of n-3 PUFA to treat an underlying CVD ranges from 3 to 5 g/day, which can only be obtained by supplements [136].

27.5 n-3 PUFA, Epigenetics and CVD

It has been clearly stated that genetics and environment are the key players in the development of CVD; however, intertwined between the two is epigenetics. Over the past couple of years, the area of system biology has experienced an "-omic" revolution. This continues to shape our understanding of molecular biology with technologies in genomics, transcriptomic, proteomics, metabolomics and lipidomics. Epigenetics refers to the study of changes resulting from gene expression caused by factors other than changes in the genome. These changes result in long-term modification in the genome resulting in an alteration in transcriptional regulation of DNA [137]. In 1940, Conrad Waddington defined epigenetics as "the causal interaction between genes and their products, which brings the phenotype into being" [138]. Epigenetic changes occur mainly by DNA methylation and chromatin remodelling. Chromatin is remodelled through DNA methylation at the CpG site, converting cytosine to 5-methyl cytosine. DNA methylation reduces the transcriptional activity of the DNA, which results in the silencing of some genes. Noncoding RNAs known as microRNAs (miRNA) have also been shown to be involved in epigenetic modification. Epigenetic regulation has made its way into lipid metabolism, where a number of genes and proteins involved in lipid metabolism are capable of being subjected to epigenetic modification. PPAR, a protein with activities central to lipid metabolism, has been shown to be regulated by DNA methylation [139]. Acyl-CoA oxidase, the rate-limiting enzyme of the peroxisomal β-oxidation pathways, and directly regulated by PPARγ [140], was also shown to be regulated by DNA methylation [139]. LXR-α promoter region has been identified as a target for DNA hypermethylation during protein restriction, and its transcription is dependent on DNA methylation. Cholesterol metabolism has been shown to be regulated by miR-33 regulatory miRNA found in the gene coding for sterol regulatory element-binding factor-2 (SREBF-2), a vital regulator of cholesterol transport [141]. The miR-3 was also shown to repress the expression of ABCA1 gene, thereby attenuating cholesterol efflux via apolipoprotein-A1 [141]. Recent evidence suggests that n-3 PUFA could influence epigenetic modification. The role of DHA in one carbon metabolism and epigenetics has been reported [142]. Folic acid and vitamin B_{12} are the major players in one carbon metabolism which produces S-adenosyl methionine (SAM), a methyl group donor [143]. There are studies suggesting that n-3 PUFA in addition with folic acid and vitamin B_{12} increased plasma

homocysteine which could affect DNA methylation, in schizophrenic individuals [144]. It is proposed that n-3 PUFAs alter epigenetic DNA methylation where reduced dietary consumption of DHA decreases the concentration of PE [145], a chief methyl acceptor to form PC. A decrease in PE results in excess methyl group available for DNA methylation and altered expression of genes [146]. Furthermore, n-3 PUFA was shown to affect the epigenetic status of the hepatic *fad2* gene that codes for δ-6 desaturase, the rate-limiting enzyme in the synthesis of AA and DHA in C57BL/6 mice [147]. Although there are no available data in the literature that link the epigenetic regulation of n-3 PUFA to CVD, it would be plausible to think that there is a direct relationship between epigenetic modifications and the cardioprotective roles of n-3 PUFA, considering the fact that most of the genes and proteins regulated by n-3 PUFA have been shown to be targets of epigenetic modification. However, studies could be designed to ascertain the role of n-3 PUFA in epigenetic regulation.

27.6 Brain and Heart Connection in CVD and the Role of n-3 PUFA

The complexity of the cause of CVD warrants a greater understanding of its pathophysiology. Recent evidence suggests a relationship between cardiometabolic irregularities and neurocognitive decline [148]; this proposition is further strengthened by the similarities in events and timeline leading to the pathological decline of the brain and cardiac functions [149]. Individuals with neurological abnormalities often have vascular impairment [150]. n-3 PUFA is well established to be both neuroprotective [151] and cardioprotective [152]; however, the effects of n-3 PUFA on the causal relationship between these two conditions have not been elucidated. Emerging evidence reveals that certain trophic factors known as neurotrophins thought to be classic neurotrophic in function also possess metabotrophic properties [153]. The secretion of neurotrophins is not limited to the central nervous system; they are released in the peripheral system as well, where they have been shown to play a role in atherosclerosis and lipoprotein metabolism among others [154]. Interestingly, neurotrophins and n-3 PUFA share some functional similarities; in addition to their effects on neural and cardiovascular functions, there is a significant decrease in tissue accretion of n-3 PUFA with age [155], and also neurotrophins [156], and a consequent increase in the risk of cardiovascular and neuropsychiatric disorders. The most abundant and best characterized neurotrophin in the mammalian nervous system is the brain-derived neurotrophic factor (BDNF), and it is responsible for neuronal survival and differentiation in the nervous systems [157]. Approximately 80 % of the secreted BDNF comes from the brain; however, there is evidence of secretion in peripheral tissues although its peripheral effect has not been fully elucidated [158]. There are reports of the effects of BDNF in both neuropsychiatric and metabolic disorders suggesting a brain-body regulatory role of BDNF [159]. There are also evidences of the involvement of BDNF in inflammation which is a major

player in CVD [160]; low circulating BDNF concentration has been reported in patients with CVD and metabolic syndrome [156]. Mice expressing aberrant BDNF receptor trkb have been shown to develop cardiovascular abnormalities [161], and heterozygous knockout mice for BDNF are hyperphagic with the propensity to become obese and insulin resistant [162]. Laboratory findings have shown that the administration of BDNF improves glucose metabolism in diabetic mice models [163], and the circulating BDNF concentration is age and sex specific [156]. There is a reported inverse correlation between plasma BDNF and circulation blood lipid concentration such as TG, cholesterol and LDL [156,164,165]. BDNF has been shown to lower plasma nonesterified fatty acids, total cholesterol and blood glucose in mice [166]. With the reported cardioprotective and neuroprotective properties of BDNF and n-3 PUFA, it is not surprising that they both share a regulatory relationship. n-3 PUFA upregulates the expression of BNDF possibly through the phosphorylation of cAMP response element-binding protein, the transcription factor responsible for BDNF synthesis [167]. All evidence points towards our current speculation that the cardioprotective and neuroprotective effects of n-3 PUFA are centrally mediated by BDNF signalling.

27.7 Concluding Remarks

Dietary intervention remains the safest strategy to prevent the development of CVD; however, with the physiological variation in human population, it is impossible to make a robust general recommendation without considering human variability in response to dietary regimen. The cardioprotective properties of n-3 PUFAs have been under study over the years, with more supportive than confuting findings. This represents a very promising therapeutic option for the prevention and treatment of CVD; however, more studies need to be undertaken to understand the detailed mechanism of action of n-3 PUFA in light of the aforementioned effects of sex and age. Furthermore, it will be important to gain new insights into the neurological origin of CVD and the implication of n-3 PUFA in facilitating a central therapeutic option for the prevention and treatment of both neuropsychiatric and cardiovascular diseases.

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Chapter 28
Prevention and Treatment of Atherosclerotic Vascular Disease: Hypolipidemic Agents

Antonio M. Gotto Jr. and Henry J. Pownall

Abstract While the quality and quantity of lipids and lipoproteins provide a window on cardiovascular health, in some cases, they are also therapeutic targets that when treated can reduce or reverse the underlying cause of most cardiovascular disease (CVD), including atherosclerosis. We summarize in this chapter the current strategies and attendant mechanisms for reducing CVD risk. Clearly, for most patients, CVD risk can be reduced by the statin class of hypocholesterolemic drugs. However, even after receiving statin therapy, there is residual CVD risk for which current therapies are inadequate. In this context, we discuss the now unsupported "higher HDL-C concentration is better" approach, the reasons for its failure, possible new approaches that will reduce residual CVD risk, and the molecular mechanisms that give rise to a major CVD risk factor, metabolic syndrome in atherogenesis. We also describe the mechanisms and attendant CVD targets of the major classes of lipid-lowering drugs—statins, fibrates, niacin, bile acid sequestrants, ezetimibe, and n-3 fatty acids.

Keywords Dyslipidemia • Atherosclerosis • Cholesterol • Lipoproteins • Metabolic syndrome • Nutrition

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28.1 Introduction

28.1.1 Lipoproteins and Cardiovascular Disease (CVD)

Medical advances have made great inroads against CVD so that life expectancy at birth is at a record high and age-adjusted death rates are at a record low. Nevertheless, heart and cerebrovascular diseases account for 30 % of all deaths in the United States [1]. Thus, new diagnostics and therapies that complement those that are currently available are still needed. Although there are many modifiable CVD risk factors, there has been greater interest and success in approaches that reduce lipid and lipoprotein risk factors. Plasma cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride concentrations have been the major lipid-related therapeutic targets. Thus, therapies that reduce plasma total cholesterol, LDL-C, and triglyceride concentrations and raise plasma HDL-C concentrations have been designed and tested in randomized clinical trials.

28.1.2 Fredrickson-Lees Classification of Hyperlipoproteinemia [2]

Before genetics entered the lipoprotein world, lipid disorders were classified according to five phenotypes. Type I was defined by hypertriglyceridemia as elevated chylomicrons frequently due to a deficiency of lipoprotein lipase (LPL) or apo CII, its activator. Type IIa, familial hypercholesterolemia, is associated with elevated LDL-C and underlying LDL receptor deficiency. Type IIb, familial combined hyperlipidemia, presents as elevated LDL-C and very low-density lipoproteins (VLDL); the attendant defects are decreased LDL receptor and increased apolipoprotein (apo) B. Patients with familial dysbetalipoproteinemia, or type III, presented with an elevation of intermediate-density lipoproteins (IDL) due to a defect in apo E or its synthesis. In type IV familial hypertriglyceridemia, plasma triglycerides (TG) are elevated due to hypersecretion of VLDL or impaired VLDL processing and disposal. Increased VLDL production and low LPL underlie type V hyperlipoproteinemia, which manifests as elevated VLDL and chylomicrons. Subsequently, therapies that reduce plasma total cholesterol, LDL-C, and TG concentrations and raise plasma HDL-C concentrations have been designed and tested.

28.2 Clinical Trials of Lipoprotein CVD Risk Factors Reduction

28.2.1 LDL-C

Atherosclerosis, the underlying cause of most cardiovascular diseases (CVD)—stroke and heart attacks—is characterized by arterial wall thickening due to accretion of macrophages and their remnants, which contain cholesterol and TG, as well

as calcium in advanced CVD. Although atherosclerosis is associated with elevated plasma cholesterol concentrations, especially LDL-C, LDL modified by oxidation and other mechanisms promotes the conversion of macrophages to foam cells that are cholesterol-rich hallmarks of atherosclerosis. Thus, there were both epidemiological and mechanistic rationales for testing therapies that reduce plasma LDL-C. The Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) tested the efficacy of cholesterol lowering with the bile acid sequestrant cholestyramine vs. a placebo group [3]. The cholestyramine group experienced an average plasma LDL-C reduction of 20.3 %, which was 12.6 % greater than that of the placebo group. The reduction of LDL-C in the test group was associated with a reduction in the primary end points—CHD death and/or nonfatal myocardial infarction (MI). The cumulative 7-year incidence of the primary end point was 7 and 8.6 % in the cholestyramine vs. placebo groups.

The CPPT provided a compelling rationale for developing and testing more tolerable and more effective LDL-C-lowering drugs that worked through inhibition of cholesterol biosynthesis. The first were mevastatin and compactin, the same drugs isolated by two different groups from *Penicillium citrinum* [4] and *Penicillium brevicompactum* [5], respectively, which were never marketed because of adverse effects. In 1987, Merck, led by P. Roy Vagelos as president of research and Al Alberts as head of the statin program, marketed the first statin class drug, lovastatin, which traded as Mevacor. As awareness of the "bad" LDL cholesterol grew, the number of patients with elevated plasma LDL-C concentrations receiving lovastatin to reduce cardiovascular risk also grew. The value of lovastatin in primary prevention was tested in a large-scale clinical trial, the Air Force/Texas Coronary Atherosclerosis Prevention Study. Among 5,608 men and 997 women with average plasma LDL-C concentrations receiving lovastatin (20–40 mg/day), which reduced LDL-C by 25 %, or allocated to placebo and a diet low in saturated fat and cholesterol, the intervention group had less fatal or nonfatal MI, unstable angina, or sudden cardiac death; this study confirmed the benefit of plasma LDL-C reduction [6]. The efficacy and safety of lovastatin encouraged other pharmaceutical companies to develop their own version of statins, which also entered rigorous double-blind, placebo-controlled trials that provided additional information on the relationships between statin therapy, lipid lowering, and reduction in major coronary events.

The Scandinavian Simvastatin Survival Study (4S) [7] compared the effects of simvastatin vs. placebo and a lipid-lowering diet on mortality and morbidity in patients with angina pectoris or previous MI and serum cholesterol concentrations between 5.5 and 8.0 mmol/L over 5.4 years median follow-up. Simvastatin produced mean changes in total cholesterol, LDL-C, and HDL-C of −25, −35, and +8 %, respectively. Mortalities in the treated and control groups were 8 and 12 %, respectively, which corresponded to a relative risk of death in the simvastatin group of 0.70. Risk was also reduced in women and patients of both sexes aged ≥60 years. A subsequent analysis of 4S concluded that the reduction in major coronary events within the simvastatin group was correlated with on-treatment levels and changes from baseline in plasma concentrations of total cholesterol, LDL-C, and apo B, but less so with plasma HDL-C concentrations and not with plasma TG concentrations. These data further suggested that the benefits of simvastatin were determined mainly by change in LDL-C.

The Cholesterol and Recurrent Events (CARE) trial compared pravastatin (40 mg/day) with placebo over 5 years in 4,159 patients with a history of MI and mean plasma total cholesterol and LDL-C of 209 and 139 mg/dL, respectively [8]. The frequency of the primary end points, coronary death or recurrent MI, was lower in the pravastatin group (10.2 vs. 13.2 %). Also, in the pravastatin group, there was less coronary bypass surgery (7.5 vs. 10 %), angioplasty (8.3 vs. 10.5 %), and stroke (2.6 vs. 3.8 %). Pravastatin lowered the coronary event rates more among women than among men, as well as among patients with higher rather than lower pretreatment LDL-C levels. A subgroup analysis concluded that reduction of LDL-C concentrations to ~125 mg/dL was beneficial, but further reduction to <125 mg/dL did not add benefit [9].

The West of Scotland Coronary Prevention Study determined whether pravastatin (40 mg/day) vs. placebo reduced the combined incidence of nonfatal MI and death from coronary heart disease in 6,595 men, 45–64 years of age with a mean plasma total cholesterol concentration of 272 ± 23 mg/dL and without a history of MI [10]. Pravastatin lowered plasma total cholesterol levels and LDL-C concentrations by 20 and 26 %, respectively. There were 248 and 174 coronary events—nonfatal MI or death from coronary heart disease—in the placebo and pravastatin groups, respectively, and comparable reductions in the risk of nonfatal MI death from coronary heart disease and death from all cardiovascular causes. Subsequent analysis showed that the pravastatin treatment is proportionally the same independent of baseline lipid profile and that reduction of LDL-C reduces CHD risk with 24 % reduction being sufficient to produce the full benefit [11].

The Heart Protection Study tested simvastatin therapy in patients for whom clinical evidence did not dictate a specific treatment course. The study was important because it was large and inclusive enough to shed insights on the effects of several subgroups [12]. Those randomized to the simvastatin arm had lower total and vascular mortality, coronary events, strokes, and need for arterial revascularization compared to placebo. Moreover, within a diabetic subgroup, the risk of stroke and vascular death in the simvastatin arm was lower compared to placebo, with the reduction in the latter being similar to that of other high-risk patients without diabetes. Some subjects were randomized to a subgroup receiving a daily antioxidant cocktail comprising 600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily or to placebo. When the outcomes for the two groups were compared, there was no difference in all-cause mortality or deaths due to vascular or nonvascular causes and no differences in the numbers of nonfatal MI or coronary deaths, nonfatal or fatal stroke, or coronary or noncoronary revascularization. The authors concluded that among high-risk persons, antioxidant vitamins are safe but not medically beneficial.

In the pre-statin era, other therapeutic approaches to reduce LDL-C were used, but these have been supplanted by statins except for patients who are statin intolerant or unresponsive. One approach is bile acid sequestrants such as cholestyramine, cited above, which prevents reabsorption of bile acids in the gut. The liver must then convert more cholesterol to bile acids, thereby lowering LDL-C. Ezetimibe, which binds to an essential mediator of cholesterol absorption on gastrointestinal tract

epithelial cells, Niemann–Pick C1-like 1 protein, lowers plasma LDL-C concentration by inhibiting intestinal cholesterol absorption [13]. Ezetimibe is used in statin-intolerant patients or in combination with a statin to enhance LDL-C lowering. However, the combination therapy has not been tested for hard end points such as heart attack, stroke, or death, except in patients with chronic kidney disease. Moreover, one trial which compared statin combinations with ezetimibe and niacin found that taking a statin plus ezetimibe increased carotid intima–media thickness (CIMT), a surrogate measure of atherosclerosis, and was associated with more adverse cardiovascular events than treatment with a statin plus niacin, which decreased CIMT [14]. The results of a large-scale cardiovascular outcome trial comparing ezetimibe/simvastatin with simvastatin alone in patients with acute coronary syndromes will provide long anticipated data on the clinical efficacy of the combination therapy. Although stanols and phytosterols, plant-derived sterols, also inhibit cholesterol absorption and lower plasma LDL-C similarly [15–17], other studies have shown that elevated plant sterol concentrations are a CVD risk factor [18, 19]. Niacin and fibrates sometimes provide modest lowering of LDL-C concentrations but will be discussed in the context of HDL and TG concentration, for which they are more profound modulators.

Several other LDL therapies have been approved for specific patient populations. One of these is mipomersen, which is an antisense oligonucleotide for apo B, the major protein in LDL. Another is lomitapide, which inhibits the activity of microsomal TG transfer protein (MTP). Given that both apo B and MTP are required for the assembly of VLDL, both reduce its secretion. Furthermore, since VLDL is an LDL precursor, LDL-C is reduced [20–22]. Being independent of the LDL receptor, both drugs are appropriate treatments for homozygous familial hypercholesterolemia, and, not surprisingly, with diminished VLDL secretion, hepatosteatosis is a side effect of both drugs.

For the most part, statins are judged to be safe and effective. However, a meta-analysis uncovered a link between statin therapy and increased diabetes, especially in older patients [23]. Among 91,140 participants, statin therapy was associated with a 9 % increased risk for incident diabetes. Despite this finding, the authors concluded that the small risk of diabetes should not change clinical practice in patients with moderate to high CVD risk or existing CVD.

Recommendations for preventing CVD events have been summarized [24]. Patients are at increased risk of atherosclerotic CVD for a variety of reasons—mainly a past CVD event and CVD risk factors. Current recommendations are to adopt a healthy lifestyle, including smoking cessation among smokers, and to control blood pressure and diabetes. Statin therapy is advised for individuals likely to have a clear net benefit, including primary prevention for adults with diabetes. Rather than targeting specific LDL-C or non-HDL-C concentrations, statin therapy should be based on CVD risk, balanced against the potential for adverse effects, and matched to CVD risk level. (The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [25] and the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [26] are discussed in Chap. 2.)

28.2.2 HDL-C

Therapeutic reduction of LDL cholesterol levels results in decreased cardiovascular morbidity and mortality, yet residual risk remains unacceptably high [27]. Thus, researchers continued to look for other modifiable CVD risk factors that could be therapeutically targeted. One of these was plasma HDL-C concentrations. Early studies of Gofman [28] and a recent 29-year follow-up [29] showed a link between low plasma HDL concentrations and cardiovascular risk. These data also showed that the risk reduction by an increased HDL concentration was greater for the larger HDL_2 subfraction than for HDL_3. This conclusion was confirmed by the Framingham Heart Study, which showed that high HDL-C levels were associated with a lower CVD death rate [30]. Some interventions that increase HDL-C reduce CHD events. The Helsinki Heart Study [31, 32] and the Veterans Administration HDL Intervention Trial (VA-HIT) [33] of the fibrate gemfibrozil showed that an increase in HDL-C concentration was associated with reduced CHD events, although cardiovascular benefit was more strongly correlated with insulin resistance than HDL-C in VA-HIT. Also, moderate exercise and regular, moderate alcohol consumption increase the plasma HDL-C concentration nearly equally; however, addition of regular alcohol consumption does not add to the HDL-C-raising effect of moderate exercise [34]. Moreover, regular, moderate alcohol consumption is associated with reduced CHD incidence and mortality [35], an effect initially assigned to attendant increased HDL-C [36].

Despite evidence that raising HDL-C is a valid approach to CVD therapy, there are confounders. Although fibrates increase plasma HDL-C concentration, they are also highly hypotriglyceridemic. Alcohol via its terminal metabolite, acetate, also has profound effects on lipid metabolism. Acetate inhibits lipolysis in rat adipocytes [37] and reduces plasma nonesterified fatty acid concentrations in man [38]. Preprandial alcohol consumption inhibits the lipolysis of intestinally derived lipoproteins [39], an effect that is likely also mediated by acetate. The underlying molecular mechanisms for these effects are not known but may be related to the discovery that the G protein-coupled receptor 43 for which the ligand is acetate is highly expressed in adipocytes [40]. There is other evidence against the "raising HDL-C is better" hypothesis. Many patients with low HDL-C do not develop CVD, and vice versa. The very high plasma HDL-C concentrations found in patients with cholesteryl ester transfer protein (CETP) deficiency do not commensurately reduce CVD incidence [41]. To date, tests of CETP inhibitors have not shown reduced CVD events, although two large-scale trials are ongoing [42, 43]. Although the Coronary Drug Project showed that niacin reduced cardiovascular events and cardiovascular and all-cause mortality [44], this is not uniformly observed, and given the residual risk in patients who achieve their LDL-C targets, it was important to test whether the addition of niacin, which raises HDL-C, to a statin reduced residual risk. However, clinical trials have not shown that niacin reduces CVD events [45]. In the *A*therothrombosis *I*ntervention in *M*etabolic Syndrome with Low HDL/*H*igh Triglycerides: *I*mpact on *G*lobal *H*ealth Outcomes (AIM-HIGH) Trial, niacin

increased the HDL-C concentration (35–42 mg/dL) and lowered triglyceride (164–122 mg/dL) and LDL-C concentrations (74–62 mg/dL). However, at the end of 3 years, the trial was stopped for futility. Compared to the placebo group, there was no difference with respect to the primary composite end point of first event death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Although AIM-HIGH may have been underpowered, results from the larger *H*eart *P*rotection *S*tudy *2*–*T*reatment of *H*DL to *R*educe the *I*ncidence of *V*ascular *E*vents (HPS2-THRIVE) trial raise additional doubts regarding niacin [46]. In that trial, the addition of niacin and the flushing inhibitor laropiprant (prostaglandin D2 receptor type 1 antagonist) to statin therapy resulted in HDL-C changes that were less than expected, no evidence of clinical benefit, and significant toxicity. Subgroup analyses suggested benefit in European compared to Chinese participants, as well as in individuals with low baseline HDL-C and high triglyceride levels. Based on these results, it is unclear whether extended-release niacin added to a statin to raise low levels of HDL-C is superior to a statin alone in reducing residual risk.

Studies from human genetics have added evidence regarding the HDL-C-raising hypothesis. In the Copenhagen City Heart Study, patients with genetically elevated plasma levels of apo AI and HDL-C did not have a reduced risk for ischemic heart disease or myocardial infarction [47]. According to a Mendelian randomization study, an HDL-C-raising endothelial lipase variant was not associated with reduced myocardial infarction [48]. Finally, a 2011 study of the Cohort of Norway Population showed that controlling for HDL-C does not affect the magnitude of the negative relationship between alcohol intake and death from CVD, so HDL should not be implicated in the atheroprotective effects of alcohol ingestion [49]. Thus, many mechanisms and interventions that increase HDL-C are not atheroprotective (Chap. 25).

Given the failure of interventions that raise plasma HDL-C concentrations in a way that prevents atherosclerosis, other mechanistic strategies have been put forth and tested. However, their impact on CVD has been mixed, and current hypotheses focus in some cases not on the plasma lipoprotein concentrations but on lipoprotein quality and function, which depends upon how well HDL supports reverse cholesterol transport (RCT), the transfer of cholesterol from the arterial wall to the liver for disposal (Fig. 28.1) [50]. All nucleated cells synthesize cholesterol, an essential lipid in membrane biogenesis, but of the major organs, only the liver can dispose of it. More specifically, RCT begins with the transfer of macrophage cholesterol in the arterial subendothelium to apo AI and HDL; transfer of cholesterol along with phospholipids to apo AI is mediated by the macrophage plasma membrane ABCA1 transporter; cholesterol transfer to HDL is mediated by macrophage plasma membrane ABCG4 transporter. Both steps produce an early form of HDL, nascent HDL, that diffuses to the plasma compartment where in the second step, the cholesterol is esterified by lecithin-cholesterol acyltransferase (LCAT) producing a mature HDL. In the third and final step, the HDL lipids, cholesteryl ester, TG, and some phospholipids are selectively removed by hepatocytes, while the HDL apos are released into the extracellular space. Some newer therapeutic approaches have attempted to amplify one or more RCT steps with mixed results.

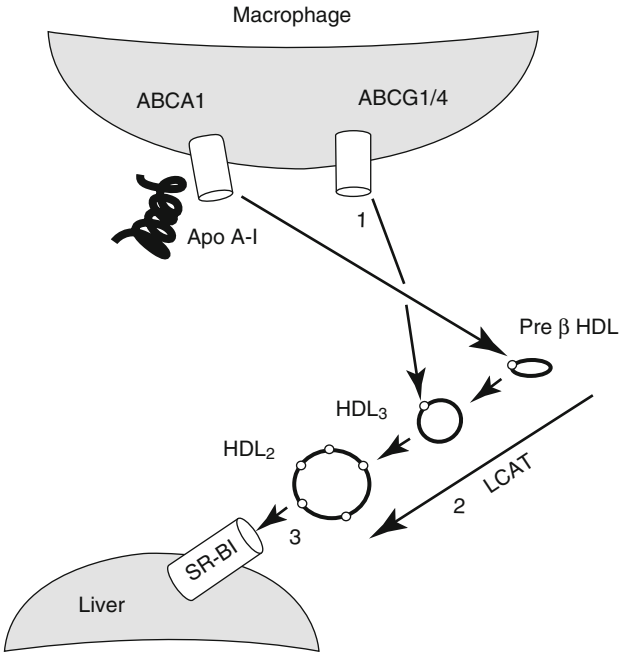

Fig. 28.1 RCT model showing (*1*) cholesterol efflux, (*2*) cholesterol esterification by LCAT, and (*3*) selective hepatic uptake of HDL lipids

One approach has been to increase the quality or plasma concentration of acceptors. Given that phospholipids are the essential cholesterol-binding molecule in HDL and the acyl donor in cholesterol esterification via LCAT, and that apo AI is the LCAT activator, researchers tested various reassembled (r) HDL. One of these was $rHDL_{Milano}$, which contains phospholipid and apo AI_{Milano}, a variant of apo AI found in an Italian family that was resistant to atherogenesis. Early studies were promising [51], but subsequent tests showed that $rHDL_{Milano}$ infusion remodels the arterial external elastic membrane but does not change lumen dimensions [52]. Infusions of delipidated HDL plasma increased pre-β-like HDL, which is thought to be atheroprotective and reduced α-HDL, the mature form giving a more cardioprotective plasma profile. However, intravascular ultrasound showed only a trend in atheroregression [53]. Other rHDL, apo AI variants, and apo AI mimetics have been tested for atheroregression. Some formulations (CSL-111, CSL-112, and ETC-216) mobilize cellular cholesterol and regress atherosclerotic plaques in animal models, even after only a few treatments [54]. Synthetic peptide analogs of apos also mediate cholesterol efflux [55]. An intrinsic problem with all of these infused agents that remove cholesterol from cells, be they peptides, rHDL, delipidated HDL, or lipid vesicles, is that they lack directionality and would likely remove cholesterol from all tissue sites, including the liver, the target of therapeutic disposal. Therefore, development of agents that selectively enhance macrophage cholesterol efflux will be a challenging task.

There have been various attempts to potentiate the second RCT step, cholesterol esterification via LCAT. This seems to be a sound approach; unlike free cholesterol, which moves reversibly between membrane and lipoproteins, its much more lipophilic ester cannot spontaneously transfer, thereby preventing effluxed cholesterol from transferring back to macrophages. However, the findings in population studies do not support this approach. A common LCAT variant found in patients with the lowest 2 % HDL-C was associated with a 13 % decrease in HDL cholesterol but not with increased risk of MI or other ischemic end points [56]. LCAT activity in CVD cases vs. controls has been compared; these studies revealed that high plasma LCAT activities did not predict reduced CVD risk [57], and other studies showed that plasma LCAT levels had little or no association with future CVD events [58]. Mature HDL is a poor LCAT substrate [59], and in normal subjects, the fraction of HDL cholesterol that is esterified is nearly invariant. Mice overexpressing LCAT have elevated plasma HDL-C but *more* atherosclerosis [60]. None of these findings support the hypothesis that simply increasing LCAT activity is a viable antiatherogenic therapy.

Studies in genetically altered mice suggest that the terminal RCT step, selective hepatic cholesterol disposal, might be an attractive therapeutic target. Selective uptake is mediated by scavenger receptor class B type I (SR-BI). Mice bearing the SR-BI transgene have reduced plasma HDL-C concentrations but less atherosclerosis, whereas mice in which the SR-BI gene has been ablated have elevated plasma HDL-C concentrations but more atherosclerosis [61–64]. These observations are, of course, the opposite of expectations based on the "high plasma HDL-C concentrations are better" hypothesis. Enhancement of the final RCT step, hepatic cholesterol disposal via SR-BI, is a promising strategy because this step provides RCT directionality.

There are several options. One could alter HDL structure in a way that enhances their hepatic disposal by multiple hepatic receptors. Given that apo E is a ligand for multiple receptors, apo E and its mimetics are attractive vectors for targeting lipoprotein-C for hepatic disposal. Mims et al. synthesized an analog containing all or part of the apo E receptor-binding domain [65]. These analogs also contained a diacyl moiety that irreversibly bound the peptides to lipoprotein surfaces, thereby guiding the lipoprotein to which it was bound to its receptor for endocytosis. Addition of some of these peptides to LDL enhanced its specific uptake and degradation by LDL receptor- and non-receptor-mediated mechanisms. Addition of the peptides to rHDL increased its affinity for the LDL receptor to that of apoE rHDL. Other apo E mimetics have also been tested. One of these, which consists of the receptor-binding region covalently linked to an amphipathic helix, reduces plasma cholesterol levels in mice and rabbits [66, 67]. Another possibility is the reaction catalyzed by streptococcal virulence factor, serum opacity factor (SOF), which disrupts HDL structure, giving among other products a cholesteryl ester-rich microemulsion (CERM) containing nearly all the cholesteryl esters of HDL and only apo E and its heterodimer with apo AII [68]. With its apo E and a high CE content, CERM is a target for hepatic uptake via multiple apo E receptors [69]. Intravenous injection of SOF into wild-type mice reduced plasma cholesterol via

hepatic uptake (−43 %) within 3 h; parallel studies with apo E-deficient, and with LDLR-deficient, mice revealed that CERM clearance requires apo E and that most of the hepatic clearance of CERM occurs via the LDLR [70]. However, these approaches are very preliminary and require additional optimization and testing to determine whether they reverse atherosclerosis in mice and other models.

28.3 Plasma TG and Metabolic Syndrome (MetS)

Hypertriglyceridemia, the elevation of plasma TG concentrations, can occur through several mechanisms. Genetic mutations that affect the hydrolysis of plasma TG can lead to severe hypertriglyceridemia. These include a deficiency of lipoprotein lipase (LPL), which hydrolyzes plasma TG associated with chylomicrons and VLDL, or the LPL activator protein, apo CII [71]. Conversely, rare mutations that decrease apo CIII levels are associated with lower TG levels and reduced risk of coronary heart disease [72]. Although isolated severe hypertriglyceridemia is associated with an increased risk of pancreatitis, its link with CVD appears to be associated with other factors that comprise MetS. MetS is defined as the coexistence of three or more of the following: hypertriglyceridemia, a low plasma HDL-C concentration, hypertension, hyperglycemia, and a large waist circumference. However, this cluster of lipid risk factors is also frequently associated with small, dense LDL, low LPL activity, elevated hepatic lipase activity, and hyperinsulinemia, which in association with hyperglycemia produces an insulin-resistant state. The risk factors have been mechanistically linked in a model of systemic steatosis [73], which begins with excess lipolysis within femoral–gluteal fat depots and leads to an excess plasma nonesterified fatty acid concentration (Fig. 28.2; *Step 1*). As a consequence, the excess fatty acids flow to other sites—to the liver (*Step 2*) where nonesterified fatty acids are converted to excess TG that is secreted as VLDL (*Step 3*) producing a hypertriglyceridemic state and to skeletal muscle (*Step 4*) where it impairs glucose disposal [74, 75] producing hyperglycemia and inducing insulin production followed by hyperinsulinemia. The plasma TG of elevated VLDL are exchanged for the cholesteryl esters of HDL_2 and LDL (*Step 5*) thereby making them TG-rich and cholesterol-poor; [76] this reduces HDL-C. Moreover, the TG-rich HDL and LDL are substrates for hepatic lipase (*Step 6*), which removes much of their TG and reduces them to their smaller forms, HDL_3, and small dense LDL. Finally, nonesterified fatty acids remaining after hepatic and muscle uptake are diverted to central depots (*Step 7*) resulting in a large waist circumference.

According to the model in Fig. 28.2, measures that reduce plasma nonesterified fatty acid concentrations would be expected to relieve MetS. These could include exercise, which reduces fasting and postprandial plasma TG concentrations while increasing HDL, particularly HDL_2 [77]. Fibrates are PPARα agonists that are hypotriglyceridemic, an effect that might be mechanistically linked to their in vitro

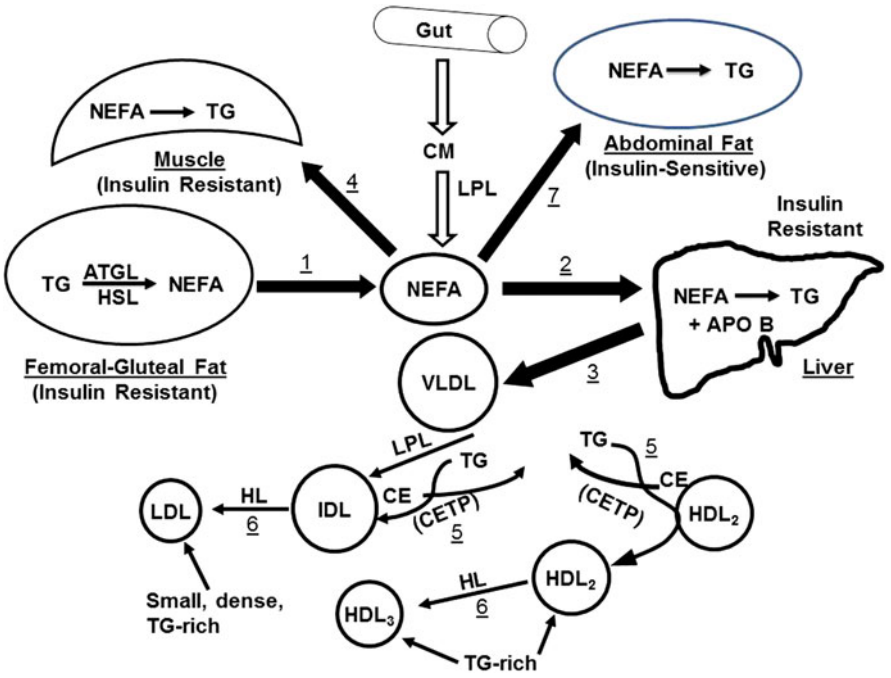

Fig. 28.2 Model of systemic steatosis stemming from excess lipolysis in femoral–gluteal fat depots: *ATGL* adipose tissue lipase, *HL* hormone-sensitive lipase, *CETP* cholesteryl ester transfer protein, *CM* chylomicrons, *IDL* intermediate-density lipoproteins, *TG* triglyceride, *NEFA* nonesterified fatty acids, *LPL* lipoprotein lipase. See text for details

enhancement of nonesterified fatty acid β-oxidation [78], which consumes intracellular nonesterified fatty acids, thereby diverting them from TG synthesis.

28.4 Dyslipidemic Therapies

28.4.1 HMG-CoA Reductase Inhibitors

The statin classes of drugs, which reduce cholesterol biosynthesis by inhibiting its rate-limiting enzyme, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, are by far the most widely prescribed hypolipidemic drugs. As cited above, numerous trials have supported plasma cholesterol lowering with statins. However, statins have another widely studied cardioprotective effect, modulation of endothelial function.

Endothelial nitric oxide synthase (eNOS) forms nitric oxide (NO), which when released into the vasculature has anti-inflammatory, antiplatelet, antiproliferative,

and anti-migratory properties in vessels [79]. Endothelial dysfunction is characterized by impaired endothelium-dependent relaxation due to reduced vessel wall NO bioavailability with subsequent increased oxidative stress and reduced vasorelaxation–vasoconstriction balance [80]. Thus, eNOS is central to the regulation of cardiovascular function. There is growing evidence that statins have salutary endothelial effects via increased eNOS activity in the context of atherosclerosis. For brevity, we will refer to statins generically rather than as a specific molecule even though they may elicit different effects if compared. The main endothelial effects of statins are as follows:

- Reversal of tumor necrosis factor-α-induced downregulation in eNOS activity by inhibiting HMG-CoA reductase and blocking isoprenoid synthesis [81]
- Induction of eNOS expression of LDL-exposed endothelial cells and inhibited lipid peroxidation [82]
- Prevention of induced vascular endothelial dysfunction in rats by increasing NO bioavailability [83]
- Prevention of induced vascular endothelial dysfunction in rats by enhancing the vascular NO generation, reducing the oxidative stress, and improving endothelial integrity and function [84]
- Prevention of ischemia–reperfusion-induced myocardial injury by upregulating myocardial eNOS expression [85]

In addition, rosuvastatin increased vascular endothelial nitric oxide production and subsequently attenuated myocardial necrosis following ischemia and reperfusion in the mouse [85]. Genetic ablation of the eNOS gene abrogates the cardioprotective effects of a statin, thus implicating statin effects on eNOS in the protective effect [86].

28.4.2 Fibrates

Fibrates reduce plasma TG concentrations, which has the effect of raising plasma HDL-C concentrations [76]. The primary effect of fibrates is likely to increase hepatic β-oxidation; this reduces the amount of fatty acids available for TG synthesis, which lowers the hepatic secretion rate and the plasma concentration. Fibrates activate PPAR (peroxisome proliferator-activated receptors), mainly PPARα, a nuclear receptor that modulates carbohydrate and fat metabolism. Following activation by fibrates and some other fatty acids, PPARα heterodimerizes with the retinoid X receptor (RXR) bound to the PPAR-response element and activates the expression of downstream genes that code for proteins involved in mitochondrial and peroxisomal β-oxidation. The mechanism, shown in Fig. 28.3, is as follows: Fibrates bind to a PPARα and RXR heterodimer that is associated with the PPAR-response element within the promotor on a DNA strand thereby activating transcription of downstream genes, including those that promote enhanced β-oxidation. Increased β-oxidation reduces intracellular fatty acid concentrations and in hepatocytes reduces production and secretion of VLDL-TG.

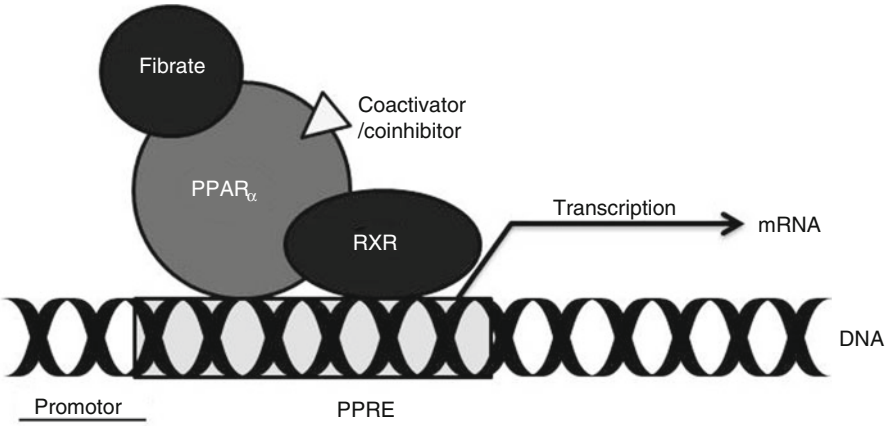

Fig. 28.3 Mechanistic model for the activity of fibrates. Fibrates bind to a PPARα and RXR heterodimer; the heterodimer binds to the PPAR-response element (*PPRE*) within the promotor for a specific gene thereby activating transcription of downstream genes

28.4.3 Cholesterol Absorption Inhibition

Ezetimibe lowers plasma cholesterol levels by inhibiting intestinal cholesterol absorption. Ezetimibe localizes to the small intestine brush border, where it binds to the Niemann–Pick C1-like 1, which mediates cholesterol absorption by gastrointestinal tract epithelial cells [13]. The reduced cholesterol absorption upregulates LDL receptors, mainly on hepatocytes, which increases LDL-C uptake thereby reducing plasma LDL levels. Although ezetimibe reduces LDL-C, it was not known to improve outcomes so that until ezetimibe is shown to have a clinical impact, it should be a second- or third-line agent [87].

28.4.4 Niacin

Niacin elicits its therapeutic effect by binding G protein-coupled receptors, niacin receptor 1 and 2, which are highly expressed in adipose tissue, but not in liver or intestine [88, 89]. Niacin receptor 1 inhibits cyclic adenosine monophosphate production and thus lipolysis in adipose tissue so that free fatty acids available for hepatic VLDL-TG production are reduced. As a consequence, the plasma product of VLDL hydrolysis, LDL-C, is also reduced. Reduced free fatty acids also suppress hepatic apo CIII expression and PPARγ coactivator-1b, thus increasing VLDL turnover and reducing its production [90]. The HDL-C-raising qualities may be due to reduced plasma concentration of TG no longer available for exchange for HDL-C. Notably, interest in niacin as a therapy was reduced by the AIM-HIGH Study, which was discontinued because of futility. Among atherosclerotic CVD patients

with LDL-C levels <70 mg/dL, there was no incremental clinical benefit from the addition of niacin to statin therapy, despite improvements in HDL cholesterol and triglyceride levels [91]. The flushing inhibitor, laropiprant, is sometimes recommended to improve niacin tolerance.

28.4.5 Bile Acid Sequestrants

Bile acid sequestrants (BAS, resins) include cholestyramine, colestipol, and colesevelam. The former, cholestyramine, was used to demonstrate that reduction of serum cholesterol reduces CVD events in the National Institutes of Health Lipid Research Clinics Coronary Primary Prevention Trial [3, 92]. Its success provided a compelling rationale for the pursuit of more convenient and powerful cholesterol-lowering agents such as the statins. The sequestrants bind to bile salts in the intestine and prevent them from recycling to cholesterol, which would ultimately appear in plasma. Lowering hepatic bile acid levels stimulates the diversion of cholesterol to bile acid synthesis, which in turn increases hepatic cell-surface LDL receptor expression thereby providing an additional plasma LDL-C-lowering effect.

28.4.5.1 n-3 Fatty Acids

Fish oils, which are long-chain polyunsaturated n-3 fatty acids, are hypotriglyceridemic agents that also increase blood clotting time and improve vascular function. While reducing plasma TG levels, fish oils also raise HDL-C by a mechanism that involves reduced exchange of plasma HDL-C for VLDL-TG [76]. Fish oils, mostly as eicosapentaenoic and docosahexaenoic acids, can have an indirect therapeutic effect via their conversion to resolvins, via the COX-2 pathway especially in the presence of aspirin. Resolvins appear to reduce cellular inflammation by inhibiting the production and transportation of inflammatory cells and chemicals to the sites of inflammation [93]. Protectins, which have anti-inflammatory, anti-apoptotic, and neuroprotective properties, are formed by the hydroxylation of polyunsaturated fatty acids. For example, oxygenation of docosahexaenoic acid produces protectin D1, which has been attributed with multiple salutary effects [94–97], which may provide vascular protection. Other studies showed that dietary fish oil prevents vascular dysfunction in rats, an effect that is associated with increased eNOS expression and reduced oxidative stress [98].

28.4.5.2 CETP Inhibition

Much of the reduction in plasma HDL-C concentrations occurs via the exchange of HDL-C for VLDL-TG, which is mediated by cholesterol ester transfer protein (CETP). Moreover, populations with a defect in CETP activity have very high

plasma HDL-C levels [99]. Thus, the negative correlation of plasma HDL-C levels and atherosclerotic CVD provided the impetus to inhibit this CETP activity pharmacologically. Several inhibitors were developed including torcetrapib and anacetrapib. Although the inhibitors increased plasma HDL-C levels [100], they were fraught with negative side effects (torcetrapib) [42] and/or did not improve CVD outcomes (dalcetrapib) [43]. Given that the occurrence of natural human CETP deficiency was not cardioprotective [101], the outcome did not surprise all.

28.4.5.3 Combination Therapy

Sometimes monotherapy with a statin is sufficient for reducing plasma LDL-C concentrations. However, combination therapy is an option for some patients in cases where high-statin doses are not tolerated and lower doses are not sufficient to bring LDL-C to target. In these instances, a combination of a statin and one of the other approved drugs—ezetimibe, fish oils, fibrates, or niacin—could be tried, with monitoring for efficacy.

The effects of lipid-lowering drugs on major plasma lipid analytes are given in Table 28.1, which also indicate possible side effects. Notably, the lipid-modifying effect is expected to be a function of dosing, formulation, and the specific drug within a class.

Nutrition Therapy

Nearly all recommendations for the control of plasma lipid concentrations include a dietary component. Recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) [102] and the American Diabetes Association [103] have shifted away from standard meal plans to eating patterns

Table 28.1 Effects of major lipid therapies on plasma lipoprotein concentrations

	Plasma lipid analyte[a]			
Drug/class	HDL-C	LDL-C	TG	Adverse effects
Statins	+	−−−	−	Myopathy, rhabdomyolysis, elevated liver enzymes, diabetes
Fibrates	+	−	−−−	Myopathy, rhabdomyolysis
n-3 fatty acids			−−	Increased blood clotting time, fishy taste
Niacin	+	−	−−−	Flushing
Ezetimibe		−		
Bile acid sequestrants	+	−		Constipation, fecal impaction
CETP inhibitors	+++			CVD outcomes unproven

[a]+ modest positive effect
+++ strong positive effect
−, −−, −−− respectively, modest, strong, very strong negative effects

that are individualized and based upon each patient's profile. This includes their health goals in the context of their personal and cultural preferences, health literacy, access to health-promoting foods, and the ability and commitment to changing eating patterns. There is an increased emphasis on appropriate portion size and reduced intake of processed nutrient-dense foods. In addition, ACC/AHA classifies the dietary recommendations according to the estimated certainty of a treatment effect that is weighed against a patient's risk–benefit balance. These classifications extend from treatments with compelling evidence of a treatment effect and a high risk–benefit ratio that would warrant a recommendation to the other extreme, treatments with little evidence of support and a minimal risk–benefit ratio for which the treatment may be considered but its effectiveness is not well established. In some cases, where there is at least moderate evidence-based certainty that there is no net benefit or that risks/harm outweigh benefit, the treatment would not be recommended.

28.5 Concluding Remarks

According to the studies of various interventions superimposed on statin therapy, there remains a need to reduce residual CVD risk. It may be time to think outside the proverbial box and explore other possibilities. The area of research that is most compelling for further investigation is the relationship between energy metabolism and atherogenesis. This includes more research into the metabolic pathways and mechanisms that underlie the cardioprotective effects of exercise and of moderate alcohol consumption, both of which raise HDL-C and reduce CVD risk. Identification of their attendant pathways and mechanisms is important because the CVD risk reduction may occur via mechanisms that are parallel to but do not involve pathways that increase HDL-C.

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Chapter 29
Prevention of Cardiovascular Disease: The Polypill Concept

Prem Pais, Deepak Y. Kamath, Alben Sigamani, and Denis Xavier

Abstract Primary prevention is recognized as the "holy grail" in combating the global burden of cardiovascular diseases (CVD) and will play an important role in achieving World Heart Federation's goal of reducing premature mortality from CVD by 25 % by 2025. Current primary prevention strategies, which focus on treating cardiovascular risk factors to set targets and individualizing treatments, are impractical for wide application at a population level. The "polypill" hypothesis of Wald and Law (2003) – that treating all people above 55 years of age with a fixed-dose combination of medication targeting at least two risk factors in a single pill could reduce CVD by 80 % – has generated both great hope and controversy. The concept is based on the premise that risk factors tend to cluster and that the level of risk is continuous with no inflection point. In addition, a once-a-day pill will likely improve patient medication adherence. Proof-of-concept trials have been undertaken and these have demonstrated initial successes and a few setbacks. Based on evidence from these studies, the polypill has been approved by regulatory agencies in some countries for secondary prevention. Large phase 3 primary prevention trials evaluating the efficacy of the polypill on clinical outcomes are underway. Today, there are at least five formulations of the polypill available. If the pivotal phase 3 trials prove to be successful in reducing clinical outcomes, a combination of the polypill strategy com-

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bined with a reorientation of the health system for effective delivery of the polypill could prove to be the most effective weapon in the armamentarium to achieve primary CVD prevention and reduce premature mortality from CVD.

Keywords Polypill • Statin • Aspirin • ACE inhibitor • Lifestyle modification • ACS • STEMI • LDL cholesterol • Diuretic • Beta-adrenergic blocker • Wald and Law polypill

29.1 Introduction

Noncommunicable disease (NCD) – mainly cardiovascular disease (CVD), cancers, chronic respiratory disease, and diabetes mellitus – is the major cause of death worldwide. Over 36 million people died from NCD (63 % of all deaths) in 2008. Of these deaths, 48 % were due to CVD and in 2010, 30 % of all deaths were due to CVD. In 2008, 80 % of all NCD deaths occurred in low- and middle-income countries (LMIC) and a higher proportion of deaths in these countries was premature (under 70 years of age) – 48 % as against 26 % in high-income countries (HIC) [1]. The fact that CVD deaths have been decreasing in HIC since the 1980s indicates that the disproportionate burden of this illness is only going to increase in countries which are strained for resources and bear a double burden of disease – persisting infectious disease, malnutrition, and maternal and child disease as well as increasing CVD.

For any disease, deaths can be reduced by saving lives of people who get the disease (reducing mortality rate) by better treatment of the disease or by preventing people from getting disease (reducing the incidence of disease) either for the first time (primary prevention) or from a recurrence if they survive an episode (secondary prevention). Over the last 50 years, great strides have been made in the treatment of acute coronary syndrome (ACS) with the introduction of coronary care units, management of acute arrhythmic cardiac arrest, and use of thrombolytics, beta-blockers, antiplatelets, and primary angioplasty. The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study estimated that a third of the 30 % reduction in mortality from acute ST elevation myocardial infarction (STEMI) in Canada and Western Europe between 1975 and 1995 was due to decreased hospital mortality and two thirds due to reduced incidence [2]. The two approaches, curative and preventive, are not mutually exclusive, yet it is clear that improved acute treatment is not enough. Almost 50 % of sudden cardiac death occurs in people with no prior overt heart disease.

Even with the best of treatment, 10 % of people with acute STEMI [3] and 25 % of people with stroke [4] will die within 1 month of the acute event. Almost 60 % of the survivors of stroke are left with significant disability (Rankin score $\geq$3 at discharge) [5]. Moreover, survivors of an acute coronary syndrome are at high risk of recurrent events and death (5 % in the first year after acute STEMI,

8.2 % after a non-STEMI [6], and 13 % in the first year after stroke) [7]. Thus, prevention both primary and secondary is of great importance. This is particularly so for LMIC where expensive curative services and logistics available to them such as ambulances are often suboptimal. In addition, many of the people in these countries cannot afford to access such care. In the CREATE (Clinical tRial of mEtabolic modulation in Acute myocardial infarction Treatment Evaluation) registry [8], a hospital-based registry of 20,000 subjects with ACS in India, the mortality in the poor was 50 % higher than in the rich mainly because of lack of access to appropriate treatment (time taken to reach hospital, type of hospital accessed, use of evidence-based drugs, thrombolytics, and percutaneous coronary intervention).

In this chapter, we discuss the strategy of the use of a multicomponent "polypill" in the prevention of CVD – the polypill concept. For the purpose of this chapter, a polypill is defined as a tablet/capsule containing multiple pharmacological components (at least a statin and an antihypertensive agent [9]) to reduce two or more risk factors for CVD.

29.2 Risk Factors for CVD

Prevention implies control of risk factors. The INTERHEART [10] and INTERSTROKE [11] studies, both large multinational case control studies of first acute myocardial infarction and stroke (with age- and gender-matched controls), have shown that nine common modifiable risk factors account for 90 % of the population attributable risk (PAR) for myocardial infarction and stroke (Table 29.1) and that this is consistent around the world. Prevention therefore calls for effectively addressing these risk factors by lifestyle changes and, where indicated, by drugs. How could this be done on a large scale at a population level?

Table 29.1 INTERHEART study [10] – the nine modifiable risk factors for myocardial infarction and their population attributable risk (PAR). Data is based on findings reported in Ref. [10]

Risk factors	OR	PAR (%)
Apo B/A1	3.2	49
Smoking	2.9	36
Psychological factors	2.7	33
Abdominal obesity	1.6	20
Hypertension	1.9	18
Diabetes mellitus	2.4	10
Fruits/vegetables	0.7	14
Physical activity	0.8	12
Alcohol	0.9	7

OR odds ratio

Over the last 15 years, we have learned important lessons on the relationship of risk factors to CVD, which are relevant to this question and pertinent to the polypill concept.

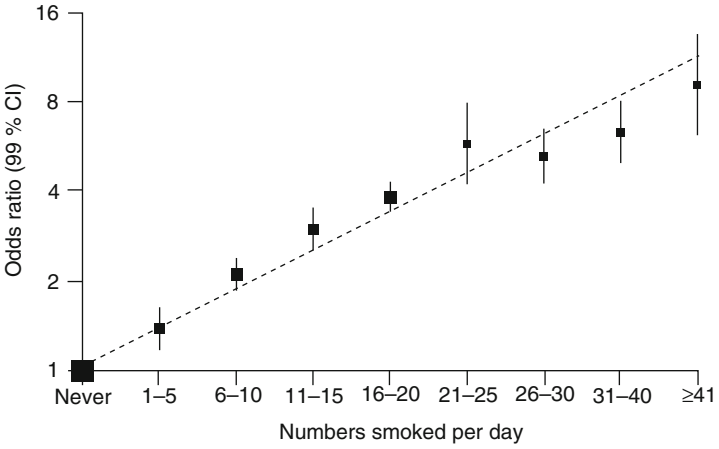
1. For any given risk factor, the level of risk for death or an event is continuous along the entire range without any specific inflection point. This has been shown for systolic and diastolic blood pressure [12, 13], LDL cholesterol [10], number of cigarettes smoked (Fig. 29.1), or even WHR (waist to hip ratio) [10]. Conversely, meta-analysis of clinical trials demonstrated that a unit reduction of blood pressure [14] or LDL cholesterol [15] will lead to a proportionate reduction of risk of death irrespective of the original level of risk, although the absolute risk reduction will vary.
2. Risk factors tend to cluster together. Thus, even if a person presents to the health system with one risk factor, e.g., hypertension, search for other common cardiovascular risk factors – tobacco use, abdominal obesity, diabetes mellitus, and hyperlipidemia – is required. In a population-based survey in India of 6,106 subjects, 77 % of those with hypertension, 68 % of those with prehypertension, and 46 % of those with normal blood pressure had additional cardiovascular risk factors [16]. Similarly, the Framingham Offspring Study showed that in those aged 18–74 years, less than 20 % of people had hypertension as an isolated risk factor [17].
3. When risk factors occur together, the increase in risk is multiplicative rather than additive. In the INTERHEART study, while the odds ratio for acute myocardial infarction for current tobacco smoking, hypertension, diabetes mellitus, and hyperlipidemia (apoB/A1 ratio, highest vs lowest quintile) was 2.87, 1.91, 2.37, and 3.25, respectively, the combination of all of them, which is not uncommon, carried an odds ratio of 42.3 [10] (Fig. 29.2).
4. Given the distribution of common risk factors in the population, choosing a cutoff level at one end of the distribution tail as a target for intervention is likely to miss most people who will get the disease as most of them in absolute numbers will have risk factor levels below this cutoff in the "normal" range [18] (Fig. 29.3). Geoffrey Rose pointed out this paradox over 30 years ago [19].

The implications of this behavior of risk factors is that it is prudent to treat the person at risk rather than specific cutoff levels of risk factors (the latest NCEP guidelines for management of hyperlipidemia [20] have recommended this as well) and to address multiple risk factors simultaneously rather than piecemeal.

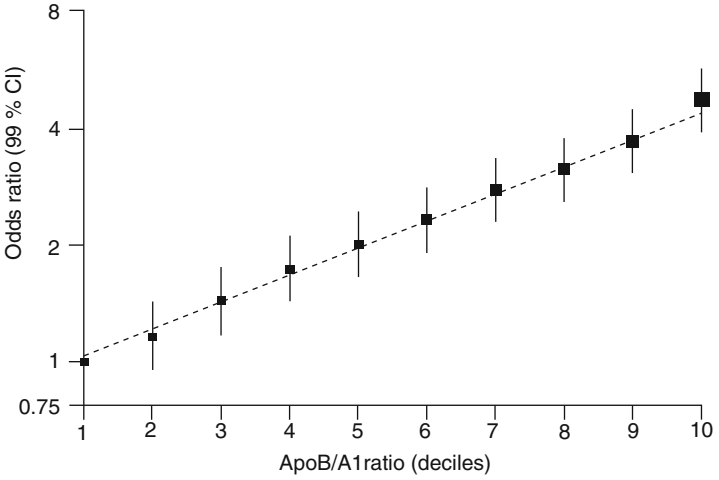
29.3 Levels of CVD Prevention

CVD prevention can be addressed at three levels – primordial, primary, and secondary.

Primordial prevention aims at preventing the development of risk factors in people and generally operates at the community or population level. Thus, in CVD



Number of controls	7,489	727	1,031	446	1,058	96	230	168	56
Number of cases	4,223	469	1,021	623	1,832	254	538	459	218
Odds ratio	1	1.38	2.10	2.99	3.83	5.80	5.26	6.34	9.16



Number of controls	1,210	1,206	1,208	1,207	1,210	1,209	1,207	1,208	1,208	1,209
Number of cases	435	496	610	720	790	893	1,063	1,196	1,366	1,757
Median	0.43	0.53	0.60	0.66	0.72	0.78	0.85	0.93	1.04	1.28

Fig. 29.1 Data from the INTERHEART study [10] showing the continuous relationship between the number of cigarettes smoked (*above*) and lipids as apoB/apoA ratio (*below*) on the one hand and the risk of an acute myocardial infarction on the other (Adapted with permission from Elsevier Ref. [10])

prevention, the objective of primordial prevention would be prevention of tobacco use and reduction of mean population blood pressure, lipid levels, and obesity. At the population level, a small reduction of a risk factor, e.g., systolic blood pressure or LDL cholesterol, while having little impact on the individual could substantially

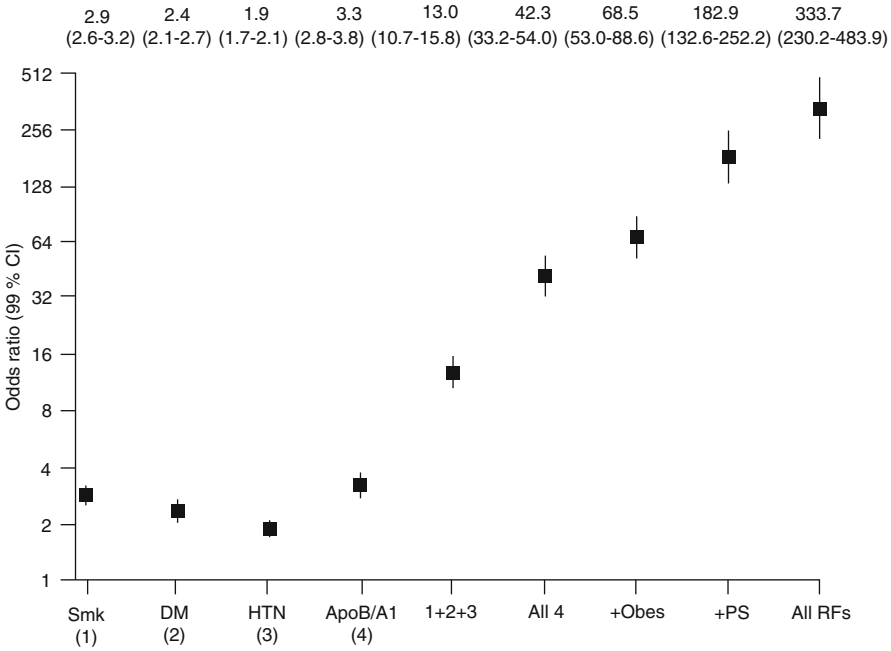


Fig. 29.2 Data from the INTERHEART study. While the odds ratios for acute myocardial infarction for current tobacco smoking, hypertension, diabetes mellitus, and hyperlipidemia (apoB/A1 ratio, highest vs lowest quintile) are 2.87, 1.91, 2.37, and 3.25, respectively, the combination of all of them, which is not uncommon, carries an odds ratio of 42.3 [10] (Adapted with permission from Elsevier Ref. [10])

reduce the burden of CVD at the country level. Primordial prevention has been described as one of the "best buys" in health promotion [21]. Primordial prevention largely requires action at the policy and political level through legislation and education through media.

An example of success in this strategy is the Polish experience [22] of using taxes and subsidies to reduce the consumption of butter, increase use of vegetable oils, and increase intake of fruits and vegetables with significant decrease in CVD mortality. Finland was one of the first countries to demonstrate the benefit of such prevention strategies [23].

Primordial prevention alone will not suffice, as it does not address individuals at high risk of disease who will need more intensive preventive measures. The current strategy for primary prevention involves identifying persons without CVD but at risk of getting it and treating them with both lifestyle modification and pharmacotherapy to reduce their risk factor levels to preset targets. Such a process involves screening asymptomatic individuals for level of risk (high risk, ≥20 % risk of event over 10 years; moderate risk, 10–19 % risk over 10 years; and low risk, ≤10 % risk over 10 years). This would involve measuring anthropometry (BMI and/or waist circumference), blood pressure, and usually lipids (although non-laboratory-based

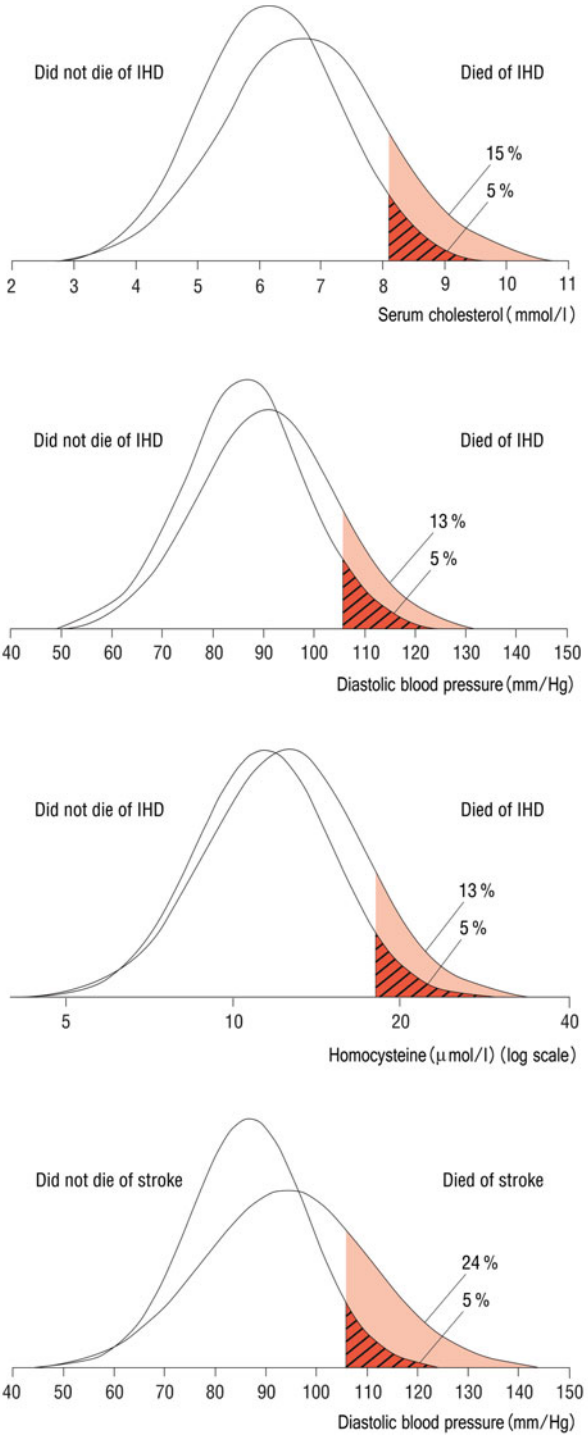


Fig. 29.3 Given the distribution of common risk factors in the population, choosing a cutoff level at one end of the distribution tail as a target for intervention is likely to miss most people who will get the disease as most of them in absolute numbers will have risk factor levels below this cutoff in the "normal" range [18] (Adapted with permission from BMJ Publishing Group Ltd Ref. [18])

risk scoring systems are also available). National policies and guidelines should be available to recommend at which level of risk, intervention with lifestyle modification, and pharmacotherapy is to follow. Such levels may vary from country to country. Therapies are targeted to lower blood pressure and lipids and, possibly, inhibit platelet function with use of multiple medications. Subsequent follow-up of the subjects is required with repeat measurements of risk factors and adjustment of medication to achieve the required target risk factor levels. Such a strategy is not practical on a large scale, which is required to address the epidemic proportions of the problem. In addition, this strategy fails to take into account the continuous nature of risk factors by setting specific levels of risk factors at which to intervene.

Secondary prevention on the other hand requires less effort and cost to identify people requiring intervention since such people have already had a symptomatic coronary artery disease (CAD) or stroke event. They can be identified at the time of the index event or at subsequent follow-up visits. Such people are also likely to be more motivated both for follow-up and to adhere to pharmacotherapy and lifestyle modification. Yet even here, such adherence is less than desirable. The PURE (Prospective Urban Rural Epidemiology) study showed that in the community among 5,650 subjects with prior self-reported CAD events and 2,292 with stroke, overall only 25 % were taking antiplatelet medication, 17 % beta-blockers, 20 % ACEI/ARBs, and 15 % statins. Even in high-income countries, the percentages of those on medication were unsatisfactory (62, 40, 50, and 67 %, respectively), while it was abysmal in low-income countries (9, 10, 5, and 3 %, respectively) [24]. Further, the EUROSPIRE III survey found that among patients in high-income countries in Europe after a CAD event, 17 % still smoked tobacco, 35 % were obese, 56 % had suboptimal blood pressure control, and 25 % had elevated cholesterol [25].

In 2002, the WHO advised strategies designed for control of CVD at the population level. These called for:

1. Education of policy makers and the public on the need for cardiovascular risk factor management.
2. Shifting from a single risk factor approach to comprehensive risk management.
3. Promotion of affordable approaches with rational resource allocation.
4. Promotion of evidence-based lifestyle measures (smoking cessation, healthy diet, weight control, and increased physical activity).
5. Use of cost-effective generic drugs. Subsequently, the World Health Assembly and the WHO accepted the prime importance of NCD and CVD control and defined national targets to achieve this goal. The four main targets are 25 % reduction in HTN, 30 % reduction in tobacco consumption, 30 % reduction in salt intake, and 10 % reduction in physical inactivity.

While lifestyle interventions are certainly of great importance and need to be maximally encouraged (Chap. 30) by governmental policies and media campaigns, they have generally not had a major sustained impact in reducing CVD events [26]. In people at moderate or greater risk and in those who have had a CVD event, pharmacotherapy is required. In situations where a large number of people need to be treated, the need for multiple tablets and the current requirement for screening and

treating risk factors to preset targets may not succeed. It is in such a scenario that we have to consider the polypill concept.

29.4 The Polypill Concept

Broadly, the polypill concept is that in view of the fact that a unit of reduction in a risk factor will result in a constant proportional reduction in risk of events independent of the initial value of the risk factor, reducing a range of risk factors using a combination pill in all subjects with moderate or greater risk will reduce cardiovascular events significantly and be cost-effective. This hypothesis was proposed by Wald and Law in their seminal paper in 2003 [18]. They proposed a single pill containing medications to reduce BP, lipids, and homocysteine as well as platelet aggregation. They further proposed that in view of the fact that age is the strongest risk factor, instead of screening the population for risk factors to identify those at "moderate" risk, such a pill could be given to all people who have had a cardiovascular event (secondary prevention) as well as to all people over the age of 55 years (primary prevention) since this age itself will put them at moderate risk. As will be discussed below, using a series of meta-analyses, they hypothesized that such a strategy could lower CVD events significantly – CAD events by 88 % and strokes by 80 %. About one in three people would directly benefit each on average gaining 11–12 years of life free of heart attack or stroke. In those aged 55–64 years, this increase of disease-free life could be as much as 20 years. The antihypertensive composition of the pill proposed by them consisted of half doses of three drugs to reduce side effects. They also proposed the use of out-of-patent medications to reduce cost. The polypill concept is just that a hypothesis that including in a single pill different component to address multiple risk factors would be effective. If proven, the polypill hypothesis could bridge the gap between evidence and practice by improving access and adherence to medication with the possibility of large benefits at low cost.

29.4.1 Constituents of the Wald and Law Polypill

The polypill proposed by Wald and Law was to contain a statin (simvastatin 40 mg or atorvastatin 10 mg) to lower LDL cholesterol (Chap. 28), aspirin 75 mg as an antiplatelet agent (Chap. 23), folic acid 0.8 mg to lower homocysteine, and three blood pressure-lowering medications (Chaps. 36 and 38) at half dose (a beta-adrenergic blocker, e.g., atenolol 50 mg; an ACE inhibitor/ARB, e.g., ramipril 5 mg; and a diuretic, e.g., hydrochlorothiazide 12.5 mg). The reasons for including three blood pressure-lowering drugs in lower doses are:

1. Each would act through a different pathway such that their effects on blood pressure lowering would be additive.

2. Side effects of each of the components would be different and not additive. Lower doses would reduce side effects, as these are dose dependent.
3. All the proposed constituents are no longer under patent and should serve to lower the cost of a polypill.

Wald and Law estimated that the statin in the pill (atorvastatin 10 mg or simvastatin 40 mg) would lower LDL cholesterol by over 1.8 mmol/L, which would be expected to lower CAD by 61 % and stroke by 17 %. The three antihypertensive components at the doses given should lower the diastolic BP by 11 mmHg resulting in reduction of CAD events by 32 % and stroke by 16 %. Aspirin should reduce IHD events by 32 % and stroke by 16 %. Using a series of meta-analyses, they calculated that such a pill could reduce CAD events by 88 % and strokes by 80 % (Table 29.2) [27, 28].

Since the publication of their paper, some of the assumptions made by Wald and Law have been questioned. Thus, clinical trials have shown the futility of folic acid supplements in reducing cardiovascular events [29]. This constituent is no longer considered for inclusion in the polypill. The value of aspirin in primary prevention of CVD is being questioned. The increased risk of bleeding due to aspirin may not be counterbalanced by the reduction of cardiovascular events in this population [30].

The polypill could have a number of potential benefits. It could decrease the cost of medication by, for example, reducing packaging and marketing costs as well as by using low-cost out-of-patent components. It could improve adherence by simplifying treatment regimens and make management by nonphysician health workers possible in select settings. These benefits could lead to greater efficiency of treatment, increased access, and equity and fewer medication errors on the part of the prescriber and the patient. On the other hand, there are potential risks. Formulation of a single pill with multiple components is not simple and may compromise bioavailability. The side effects of one drug may lead to discontinuation of all the components of the pill. While all the proposed components have been in use for secondary prevention and an effective combination pill could be used safely in

Table 29.2 Components of the polypill and estimated risk reductions achieved with individual components (Adapted with permission from BMJ Publishing group Ltd., Ref. [18])

Risk factor	Agent	Reduction in risk factor	% reduction in risk (95 % Cl)	
			IHD event	Stroke
LDL cholesterol	Statin	1.8 mmol/L	61 (51–71)	17 (9–25)
Blood pressure	3 classes of drugs at half standard dose	11 mmHg diastolic	46 (39–53)	63 (55–70)
Serum homocysteine[a]	Folic acid (0.8 mg/day)	3 μmol/L	16 (11–20)	24 (15–33)
Platelet function	Aspirin 75 mg/day	Not quantified	32 (23–40)	16 (7–25)
Combined effect	All	–	88 (84–91)	80 (71–87)

IHD ischemic heart disease
[a]The role of homocysteine as a modifiable risk factor is unclear

this setting, the basic tenet that a simple one dose pill could be effective and safe in the reduction of cardiovascular mortality and morbidity in primary prevention remains unproven.

To test the polypill concept, the following steps would be required:

1. Formulation of an effective multicomponent pill with pharmacokinetics and pharmacodynamics equivalent to those of the individual preparations
2. Demonstration in clinical trials of the pill's efficacy and safety in lowering risk factor levels in comparison to the individual components given separately
3. Testing the basic premise of the hypothesis that treating subjects at risk for the primary prevention of CVD with a fixed drug combination without being guided by risk factor levels would actually lead to a reduction in cardiovascular events and be safe

29.4.1.1 Available Polypills

Pills with different components have been formulated. One of the first such is the Polycap (Cadila Pharmaceuticals, India). It is also a formulation that has and is undergoing the most extensive testing. It has been licensed in India for secondary prevention of CVD and has been marketed in that country since 2010. Its composition is aspirin 100 mg, simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, and hydrochlorothiazide 12.5 mg. A second version (full strength) is yet to be licensed but is being tested for primary prevention in the large ongoing event-driven TIPS 3 (The International Polycap Study 3) study. The latter pill contains simvastatin 40 mg, ramipril 10 mg, atenolol 100 mg, and hydrochlorothiazide 25 mg, but no aspirin. Other examples of cardiovascular polypills to our knowledge are shown in Table 29.3. Of these, the Cadila Polycap and the Ferrer polypill have been licensed for secondary prevention of CVD in India and South America, respectively.

Table 29.3 Polypill formulations, components, and sponsor

Polypill formulations	Sponsor	Components
Polycap	Cadila Pharma, India	Simvastatin 20 mg, atenolol 50 mg, ramipril 5 mg, HCTZ* 12.5 mg
		Simvastatin 40 mg, atenolol 100 mg, ramipril 10 mg, HCTZ* 25 mg
Red Heart Pill	Dr. Reddy's Labs, India	Aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg ± HCTZ 12.5 mg
CardiaPill	CardioPharma, Inc., USA	Lisinopril, simvastatin, aspirin (strengths not available)
PolyIran	Alborz Darou, Iran Tehran University	Aspirin 100 mg, atorvastatin 20 mg, enalapril 2.5 mg, HCTZ 12.5 mg
	Pharmaceutical Co, Iran	
Ferrer	Ferrer Internacional, Spain	Aspirin 100 mg, simvastatin 40 mg, ramipril 2.5, 5, and 10 mg

*hydrochlorthiazide

29.4.2 Testing the Concept

Our group has been systematically testing the polypill concept utilizing the Polycap (Cadila Pharmaceuticals) referred to above in the following manner:

1. Bioavailability and PK/PD – Cadila Pharmaceuticals tested the bioavailability of both their formulations and demonstrated that their pharmacokinetics and pharmacodynamics are similar to that of the individual components [31].
2. The Indian Polycap Study (TIPS) [32] was a double-blind phase 2 randomized controlled trial testing the tolerability and efficacy of the Polycap. Its objectives were to demonstrate that the Polycap is equivalent to its components given separately in reducing blood pressure, heart rate (as a measure of beta-blockade), LDL cholesterol, and urinary thromboxane (a measure of platelet activity) as well as to test its adverse event profile and level of compliance compared to that of the individual components. In a multicenter (50 centers) trial in India comprised of 2,053 subjects aged 45–80 years without CVD but with one risk factor, the subjects were randomized either to the Polycap or to eight other arms with individual components – aspirin alone, simvastatin alone, hydrochlorothiazide alone, three arms with two BP-lowering drugs (atenolol-ramipril, hydrochlorothiazide-atenolol, and hydrochlorothiazide-ramipril), and two arms with all three BP-lowering drugs, one with aspirin and one without. Subjects received medication for 12 weeks. Compliance with the Polycap was similar to other arms (15 % discontinuation rate over 12 weeks) with the majority of discontinuations being for nonmedical reasons in this cohort of an asymptomatic primary prevention population. The reduction of platelet activity (urinary thromboxane) and beta-blockade (heart rate reduction) was similar with Polycap compared to aspirin and arms with atenolol, respectively. Blood pressure reduction was similar in the Polycap arm (7.5 mmHg systolic and 5.6 mmHg diastolic) compared to the arms with the three blood pressure-lowering arms (6.9 mmHg systolic and 5.0 mmHg diastolic) and was superior to arms with one or two blood pressure-lowering agents. Mean LDL cholesterol was reduced by the Polycap by 23 % (27 mg/dL) compared to arms with no simvastatin ($p<0.0001$). However, the reduction in LDL cholesterol was less when compared to the arms with simvastatin alone (27.7 % or 32 mg/dL reduction, $p=0.04$). The reason for this difference is unclear but suggests a reduction in activity of simvastatin when combined with other components in a single capsule. While the blood pressure reduction with Polycap was equivalent to the reduction in arms with three BP-lowering drugs with or without aspirin, it was less than the reduction hypothesized by Wald and Law of 19.9 mmHg systolic and 10.7 mmHg diastolic. This could reflect the population in the TIPS trial, which consisted of people at low to moderate risk with a mean blood pressure of 134/85 mmHg against the anticipated mean blood pressure of 150/90 mmHg in the Wald and Law paper. This finding is important, as a primary prevention population is likely to be similar to the subjects in TIPS. From the results of TIPS, the anticipated reduction of cardiovascular events in primary prevention would be less than that of Wald and Law anticipated, but still of considerable clinical and public health significance (Table 29.4).

Table 29.4 Comparative reductions in risk factors in the TIPS [32] trial compared to estimates by Wald and Law hypothesis [18]

	RF reduction	CHD	Stroke
LDL cholesterol[a]			
Wald and Law	1.74 mmol/L	61 %	17 %
TIPS	0.80 mm/L	27 %	8 %
Diastolic BP			
Wald and Law	11 mmHg	46 %	63 %
TIPS	5.7 mmHg	24 %	33 %
Platelet activity			
Wald and Law	–	32 %	16 %
TIPS	–	32 %	16 %
Homocysteine[b]			
Wald and Law	3 μmol/L	16 %	24 %
TIPS	–	–	–
Net effect			
Wald and Law		88 %	80 %
TIPS		62 %	48 %

[a]The Polycap contained 20 mg simvastatin as compared to the 40 mg in the Wald and Law proposed polypill

[b]Polycap did not contain folic acid because the benefit of folic acid had been disproved since the Wald and Law publication [29]

There have been other efficacy trials of polypill. The Programme to Improve Life and Longevity (PILL) trial [33] tested the Red Heart Pill (Table 29.3) in 378 people similar to those in TIPS. The trial reported reduction of systolic blood pressure by 9.9 mmHg and LDL cholesterol by 0.8 mmol/L with an estimated relative risk reduction of 46 %.

The Pilot PolyIran trial in a small sample of 475 residents of Kalaleh, Golestan, Iran, reported a lower but still significant reduction – systolic BP by 4.5 mmHg, diastolic BP by 1.6 mmHg, and LDL cholesterol by 0.4 mmol/L [34].

The results of TIPS suggest that the Polycap, while reducing blood pressure less than that hypothesized by Wald and Law, could still reduce risk of cardiovascular events by about half. Since its bioavailability and efficacy is demonstrated, it could be used for secondary and high-risk primary prevention where all the component drugs are indicated and baseline risk is high. Based on the results of TIPS, Polycap was licensed in India for secondary prevention of CVD and has been commercially available since 2010. The Ferrer polypill has also been similarly licensed in South America. Whether the polypill can be used for primary prevention irrespective of baseline risk factor level remains to be proven. The Wald and Law hypothesis of administering it to all people aged over 55 years seems difficult to test in a clinical trial. However, for people at moderate risk (10–20 % 10 year event rate), there is equipoise that can be tested in a practical trial.

29.4.3 Event-Driven Primary Prevention Trials with the Polypill

What would be an appropriate dose of components of a polypill to be used for a definitive event-driven trial of the polypill concept in primary prevention of CVD? This question arises because the reduction of blood pressure and LDL cholesterol in efficacy trials was less than Wald and Law had predicted. To demonstrate significant reduction of events in a lower-risk primary prevention population in a practical trial would require a sizeable reduction in risk factor levels since reduction in events is proportionate to the amount of reduction in risk factors. At the same time, any such pill should have an acceptable side effect profile and compliance. The TIPS 2 study addressed this question [35].

The TIPS 2 study was designed to evaluate the efficacy and tolerability of two capsules of Polycap (together containing full doses of three antihypertensive medications, 200 mg of aspirin and 40 mg simvastatin) compared to a single capsule (plus a matching placebo) given daily to patients with stable CVD in a placebo-controlled double-blind randomized clinical trial. After randomization, 518 patients with previous vascular disease or diabetes mellitus from 27 centers in India, after a two-phase run in a period over 2 weeks, received the study medication for 8 weeks. The study showed a significant incremental reduction in blood pressure (2.8 mmHg systolic and 1.7 mmHg diastolic) and LDL cholesterol (0.02 mmol/L). About 80 % of subjects receiving the full-dose regime achieved a BP of less than 140/90 compared to 58 % in the half-dose arm. In addition, the full-dose arm achieved a 3.8 point reduction in the Framingham Risk Score. Drug discontinuation rate was not significantly different in the two arms – 6.9 % in the half-dose arm and 7.8 % in the full-dose arm. There was also no difference in individual side effects except for symptomatic gastritis/dyspepsia possibly because the full-dose arm received 200 mg of aspirin instead of 100 mg. Based on the increased reduction of risk factors, it was estimated that the full-strength dosage could reduce CV events by a further 10 % approximately (Table 29.5). The findings of TIPS 2 led to the use of a full-dose preparation of the Polycap in the definitive TIPS 3 trial.

The International Polycap Study (TIPS) 3 and Heart Outcomes Prevention and Evaluation (HOPE) 3 are currently the only trials testing the polypill concept in an event-driven long-term placebo-controlled randomized controlled trial. TIPS 3 study [36] is using a single polypill with four components, while HOPE 3 [37] is using two pills – rosuvastatin 10 mg and candesartan/hydrochlorothiazide 16 mg/12.5 mg. Although not truly using a single multicomponent polypill, HOPE 3 does in fact test the concept of reducing blood pressure and lipids in a primary prevention population at moderate risk without set trigger or target levels of risk factors. The components of the Polycap being used in TIPS 3 are simvastatin 40 mg, atenolol 100 mg, ramipril 10 mg, and hydrochlorothiazide 25 mg. In view of the controversy on the benefit of aspirin in primary prevention, the Polycap in TIPS 3 does not contain aspirin. The latter is evaluated in a second arm versus matching placebo to test the question of the efficacy of aspirin in primary prevention of CVD (as well as in cancer reduction). The study also has a third arm testing the effect of vitamin D in fracture reduction. As far as CVD is concerned, the primary objective

Table 29.5 Projected theoretical relative risk reductions in CVD and the two strengths of the polycap using the approach of Wald and Law based on data from TIPS-1 and TIPS-2

	Low-dose polycap (based on TIPS-1)			Full-dose polycap (based on differences between full vs. low dose plus data from TIPS-1)		
		Projected reductions			Projected reductions	
	Reduction in risk factors	CHD, %	Stroke, %	Reduction in risk factors	CHD, %	Stroke, %
LDL cholesterol, mg/dl	−27.0	27	8	−33.6	33	10
Diastolic BP, mmHg	−5.6	24	33	−7.3	32	43
Combined effects of lowering LDL cholesterol and BP	NA	44	33	NA	54	49
Aspirin	NA	32	16	NA	32	16
Combined effects of lowering LDL cholesterol, BP and antiplatelet agents		62	48		69	57

Adapted with permission from AHA journals, Ref. [35]

of the study is to determine whether the Polycap compared to matching placebo reduces major CVD events (cardiovascular death, nonfatal myocardial infarction/stroke, heart failure, resuscitated cardiac arrest, and revascularization) and to determine whether aspirin reduces cardiovascular events compared to placebo. Subjects for the study are men and women aged over 55 years and 60 years, respectively, without CVD but with an INTERHEART risk score of >10 equivalent to an annual event rate of >1 %. Study subjects are randomized across three arms – one Polycap or placebo daily, 75 mg aspirin or placebo daily, or 60,000 IU vitamin D or placebo monthly. The study sample size is 5,000 subjects. To date, 1,700 subjects have been recruited from India and the Philippines. Results are expected in 2019. However, the results of HOPE 3 which has completed recruiting 12,705 subjects will be available by 2015 and will give the first definitive evidence of whether the polypill concept can work in primary prevention of CVD.

The Kanyini Guidelines Adherence with the Polypill (GAP) trial [38] in Australia aimed at assessing whether patients prescribed a polypill regime have improved adherence and risk factor reduction compared to usual care in secondary prevention of CVD. The trial used the Red Heart Pill (Dr Reddy's Lab) in two versions: Version 1 for postmyocardial infarction in which patients received aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg and Version 2 for poststroke patients substituted hydrochlorothiazide 12.5 mg for atenolol. The study randomized 623 patients who were followed for a median of 18 months. The trial reported a 49 % improvement in medication compliance (95 % CI 30–72) and a nonsignificant decrease in systolic blood pressure (1.5 mmHg) and of LDL cholesterol (0.08 mmol/L).

The UMPIRE (Use of a Multidrug Pill In Reducing cardiovascular Events) trial [39] employed the same combination pill as the Kanyini GAP trial in a randomized

open trial in people with or at high risk of CVD. The primary outcome measures were adherence to medication, systolic blood pressure, and LDL cholesterol. A total of 2,004 subjects from India and Europe (England, Ireland, and the Netherlands) were randomized either to usual care or to a polypill and followed for up to 24 months (at least 12 months). The polypill group received medication free of cost, while the usual care group were required to pay for their medications as per usual practice (note: 52 % in this group had to pay for medication). At the end of the study, adherence to medication improved by 33 % (from 65 % in usual care arm to 86 % in polypill arm, $p<0.0001$), mean systolic blood pressure declined from 131.7 mmHg in usual care arm to 129.2 mmHg in the polypill arm, and LDL cholesterol declined from 2.29 mmol/L in usual care arm to 2.18 mmol/L in the polypill arm ($p=0.0005$ in each case). The fact that half of the usual care group had to pay for their medication while all those in the polypill arm received it free of cost may have biased the results to some extent.

Following the Pilot PolyIran trial, a full-fledged PolyIran trial (a cluster randomized open trial) is comparing the use of a polypill versus usual care in primary and secondary prevention of CVD in adults aged 50–79 years in communities in Iran. The trial is ongoing.

A recent Cochrane review [40] of trials of polypills reported substantial heterogeneity between studies and uncertainty of benefit. This conclusion could have been because the review used clinical outcomes (mortality, nonfatal myocardial infarction, CABG, PTCA, stroke/TIA, carotid endarterectomy, and peripheral arterial disease) as primary measures, while the studies reviewed did not have clinical events as primary outcome. Secondly, the review combined primary and secondary prevention trials as well as comparisons against placebo, active control, and usual care. A second and hopefully more fruitful meta-analysis is ongoing (SPACE) [41].

29.4.4 Potential Role of the Polypill in Population-Based CVD Prevention

If the polypill concept works, it could open a door for large-scale population-based programs for prevention of CVD. Against a background of wide-scale rising of awareness of CVD and its risk factors by governments and media, programs could be set in place to screen populations above a certain age for risk. One method of identification of people at risk could be by using hypertension as a marker of risk. Screening for hypertension by blood pressure measurements could be made apart from physicians, by nonphysician health workers (NPHW), and by self-measurement by means of automated BP recorders in shopping malls and other public places. People detected to have hypertension could then be scored for risk for CVD using laboratory-based or non-laboratory-based scoring methods. Each country could decide on the level of risk at which pharmaceutical intervention would be provided. At the very least, all those with a previous CVD event should be included for intervention. NPHWs could be empowered to prescribe a polypill to those so

identified under supervision using well-designed protocols. Such workers could serve to screen the population by measuring blood pressure, promote healthy lifestyle, promote compliance to medication, and raise awareness of the symptoms of acute cardiovascular events. The HOPE 4 (Heart Outcomes Prevention and Evaluation) trial is a cluster randomized trial of such a model program of cardiovascular risk detection and treatment employing NPHWs and the polypill [42]. In the pilot phase of the trial, 50 urban and rural communities in Colombia and Malaysia will be randomized either to a cardiovascular risk detection and control program by NPHW or usual care. The NPHW will screen community households with people over 50 years of age for hypertension (known or measured). In the intervention arm, the NPHW will educate participants about CVD, its risk factors, and a healthy lifestyle and will initiate pharmacotherapy according to an algorithm including referral to a physician where indicated. The pharmacotherapy will be a standard Polycap (Cadila Pharmaceuticals, India) as used in TIPS 3 or a half-dose formulation. Outcome assessment of this phase will be at 12 months and will include blood pressure, CVD risk factors (lipids and glucose), safety and compliance to medication, and lifestyle and outcome events. This phase will be followed by a full-scale trial in 190 communities in 10 countries.

29.5 Concluding Remarks

In the issue of the BMJ in which the Wald and Law paper appeared in 2003, the editor described the paper as possibly the most important article published by the journal in more than 50 years [43]. Yet, over a decade later, the polypill concept remains a controversial hypothesis. Although a few polypills are now marketed in a few countries for secondary prevention of CVD, the promise of large-scale use in primary prevention is yet unfulfilled. There are a few reasons for the setback. An important one is the reluctance on the part of physicians and professional bodies to abandon the current practice of treating to target blood pressure or lipid levels and individualizing prescriptions. This hurdle will not be crossed until hard evidence can be documented that the polypill hypothesis works – that giving such a pill to a wide range of people at risk of CVD irrespective of baseline level of risk factors will in fact be effective in primary prevention of CVD. Such evidence is also needed by regulatory agencies if a polypill is to receive approval for primary prevention of CVD. Presently, the TIPS 3 and HOPE 3 trials will address the issue. Results from the latter will be available in mid-2015 and should provide the first evidence on whether or not the concept works. An additional issue to be addressed is the reluctance of the pharmaceutical industry to invest in a product (with low-cost out-of-patent components), which they feel does not hold much commercial promise. Eventually, if the polypill concept is proven by event-driven randomized clinical trials to have a significant impact on lowering cardiovascular mortality and morbidity, it will need to be used as a public health tool with governments devising strategies to use a polypill to halt the rising tide of cardiovascular disease.

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Part V
Hypertension

Chapter 30
Hypertension: Introduction, Types, Causes, and Complications

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Abstract Hypertension remains one of the most significant causes of mortality worldwide. It is preventable by medication and lifestyle modification. Office blood pressure (BP), out-of-office BP measurement with ambulatory BP monitoring, and self-BP measurement at home are reliable and important data for assessing hypertension. Primary hypertension can be defined as an elevated BP of unknown cause due to cardiovascular risk factors resulting from changes in environmental and lifestyle factors. Another type, secondary hypertension, is caused by various toxicities, iatrogenic disease, and congenital diseases. Complications of hypertension are the clinical outcomes of persistently high BP that result in cardiovascular disease (CVD), atherosclerosis, kidney disease, diabetes mellitus, metabolic syndrome, preeclampsia, erectile dysfunction, and eye disease. Treatment strategies for hypertension consist of lifestyle modifications (which include a diet rich in fruits, vegetables, and low-fat food or fish with a reduced content of saturated and total fat, salt restriction, appropriate body weight, regular exercise, moderate alcohol consumption, and smoking cessation) and drug therapies, although these vary somewhat according to different published hypertension treatment guidelines.

Keywords Blood pressure • Epidemiology • Lifestyle • Preventive medicine • Guidelines • Vegetables/fruits • Fish • Sodium restriction • Essential hypertension • Secondary hypertension • Combination therapy

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30.1 Introduction

Hypertension is defined as a persistence increase in blood pressure above the normal range of 120/80 mmHg. The prevalence of hypertension increases with advancing age. The persistent and chronic elevated arterial pressure causes marked pathological changes in the vasculature and heart. The blood pressure (BP) of ≥140/90 mmHg is a criterion by which the risk of hypertension-related cardiovascular disease is high enough and needs immediate medical attention. Hypertension is a major risk factor for coronary artery disease and its complications, heart failure, stroke, and renal insufficiency. Hypertension is preventable by medication and significant lifestyle modification.

It has been increasingly recognized that for the reliable assessment of BP and the accurate diagnosis of hypertension, not only office BP but also out-of-office BP measurement with ambulatory BP monitoring (ABPM) or self-BP measurement at home, are useful and important, as hypertension sometimes goes unrecognized and undetected. Although conventional office BP measurement currently remains the "gold standard" for screening, diagnosis and management of hypertension, ABPM, and home BP monitoring improve the prediction of cardiovascular risk in untreated and treated hypertensive patients [1]. An initially elevated office BP measurement must always be re-measured not less than twice over at least 4 weeks to make sure that hypertension is present. Medical personnel should also try to take at least two BP measurements, in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are very different. The average BP may be used if deemed appropriate.

In this chapter, we describe the types, causes, and complications of hypertension based on the latest hypertension treatment guidelines published by the European Society of Hypertension/European Society of Cardiology, the Joint National Committee, the Japanese Society of Hypertension, and the Canadian Hypertension Education Program Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension.

30.2 Causes

30.2.1 Primary (Essential) Hypertension

Comparisons of the decision to diagnose hypertension among the guidelines from six expert committees published since 2011 are shown in Table 30.1 [2–7]. The guidelines from the UK's National Institute for Health and Clinical Excellence (NICE) and the Japanese Society of Hypertension (JSH) 2014 differ from the others in that ambulatory recordings [3] and home BP monitoring [7] respectively are required to diagnose hypertension.

For most adults, high BP, called essential hypertension or primary hypertension, tends to develop gradually with aging. The incidence of hypertension in the

Table 30.1 Comparison of hypertension guidelines regarding definition of hypertension and blood pressure targets 2011–2014

Blood pressure, mmHg	NICE 2011 [3]	ESH/ESC 2013 [4]	AHA/ACC/CDC 2013 [6]	ASH/ISH 2013 [5]	JSH 2014 [7]	JNC 8 [2]
Definition of hypertension	≥140/90 and daytime ABPM (or home BP) ≥135/85	≥140/90	≥140/90	≥140/90	≥140/90 and home BP ≥135/85	Not addressed
In mild hypertension at low to moderate risk, lifestyle management without drugs can be considered	Not addressed	Not addressed	3 months	Some months	3 months	Not addressed
Initiate drug therapy in low-risk patients	≥160/100 or daytime ABPM ≥150/95	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90 for <60 years ≥150/90 for ≥60 years
Blood pressure targets						
Diabetes	Not addressed	<140/85	<140/90 Lower targets may be appropriate	<140/90	<130/80	<140/90
CKD with proteinuria	Not addressed	SBP <130 may be considered	<140/90 Lower targets may be appropriate	<130/80	<130/80	<140/90
Elderly	<150/90 for ≥80 years	SBP 140–150 for ≥80 years	<140/90 Lower targets may be appropriate	<150/90 for ≥80 years	<150/90 for >75 years, <140/90, if tolerated	<150/90 for ≥60 years

NICE the National Institute for Health and Clinical Excellence, *ESH/ESC* the European Society of Hypertension and the European Society of Cardiology, *AHA/ACC/CDC* the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention, *ASH/ISH* the American Society of Hypertension and the Internal Society of Hypertension, *JSH* the Japanese Society of Hypertension, *JNC-8* the Eighth Joint National Committee, *ABPM* ambulatory blood pressure monitoring, *BP* blood pressure, *CKD* chronic kidney disease, *SBP* systolic blood pressure

Framingham Heart Study showed that, for categories of participants <65 years and ≥65 years respectively, 5.3 % (95 % CI 4.4–6.3 %) and 16.0 % (12.0–20.9 %) of participants with optimal BP, 17.6 % (15.2–20.3 %) and 25.5 % (20.4–31.4 %) with normal, and 37.3 % (33.3–41.5 %) and 49.5 % (42.6–56.4 %) with high-normal BP progressed to hypertension within 4 years [8]. In a Japanese urban population, during 7 years of follow-up, there were 21, 63, and 137 cases of incident hypertension per 1,000 person-years in optimal, normal, and high-normal BP categories respectively. Compared with the optimal BP category, the adjusted hazard ratios (HRs; 95 % confidence intervals) for incident hypertension were 2.36 (2.07–2.70) and 5.11 (4.50–5.80) in the normal and high-normal BP categories, respectively [9]. Therefore, an annual medical examination is important for the prevention and early detection of hypertension.

Primary hypertension can be defined as elevated BP of unknown cause due to cardiovascular risk factors, resulting from environmental factors, including dietary factors and genetic factors, and interactions among these factors. Of the environmental factors that affect BP, diet plays a predominant role in BP homeostasis. Although the initiation of drug therapy in patients at a high level of risk should not be delayed, appropriate lifestyle modifications are recommended, not only to help treat hypertension, but also to prevent the development of hypertension and other CVD. Various hypertension guidelines represent the environmental risk factors of primary hypertension in slightly different terms. Each presents five to nine lifestyle modifications, based on the accumulated clinical and experimental evidence.

According to the 2013 European Society Hypertension and European Society of Cardiology Guideline for the management of arterial hypertension (ESH/ESC 2013) [4] the lifestyle section specifies:

1. Salt restriction to 5–6 g per day
2. Moderation of alcohol consumption to no more than 20–30 g and 10–20 g of ethanol per day in men and women respectively
3. Other dietary changes, including increased consumption of vegetables, fruits, and low-fat dairy products
4. Weight reduction to a BMI of 25 kg/m^2 and waist circumference reduction to <102 cm in men and <88 cm in women, unless contraindicated
5. Regular physical exercise, i.e., at least 30 min of moderate dynamic exercise 5–7 days per week
6. Smoking cessation, i.e., giving all smokers advice on quitting smoking and offering assistance.

The Japanese Society of Hypertension Guideline 2014 (JSH2014) [7] emphasizes that lifestyle modifications are important for preventing hypertension, both before and after the start of antihypertensive drug therapy. The JSH2014 lists the following seven items subsequent to it:

1. Salt reduction: the target of salt reduction <6 g/day
2. Dietary pattern: increased fruits/vegetables and fish (fish oil) intake and reduced cholesterol/saturated fatty acid intake

3. Weight control: the target body mass index (BMI) <25 kg/m^2
4. Exercise: primarily periodic (30 min or longer daily if possible) and aerobic exercise
5. Reduction of alcohol intake
6. Smoking cessation and avoidance of passive smoking
7. Others: avoidance of exposure to cold and the management of emotional stress

In addition to these recommendations, it is noted that comprehensive lifestyle modifications are more effective.

The Clinical Management of Primary Hypertension in Adults is a report issued by the National Institute for Health and Care Excellence (NICE) in 2011 [3]. This UK guideline suggests the following lifestyle interventions on the part of physicians:

1. Offer lifestyle advice both initially and then periodically to people undergoing assessment or treatment for hypertension
2. Ascertain patients' diet and exercise patterns as a healthy diet and regular exercise can reduce BP. Provide appropriate guidance and written or audiovisual materials to promote lifestyle changes
3. Relaxation therapies can reduce BP and people may wish to use these as part of their treatment. However, routine provision by the primary care team is not currently recommended.
4. Ascertain patients' alcohol consumption and encourage reduced intake if patients drink excessively, because this can reduce BP and has broader health benefits
5. Discourage excessive consumption of coffee and other caffeine-rich products
6. Encourage patients to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as this can reduce BP
7. Do not offer calcium, magnesium, or potassium supplements as a method of reducing BP
8. Offer advice and help to smokers on smoking cessation
9. Studies have found that group work is effective at motivating lifestyle changes. Inform people about local initiatives by, for example, healthcare teams of patient organizations that provide support and promote healthy lifestyle change

The 2014 Canadian Hypertension Education Program Recommendations for BP Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension (CHEP 2014) also provides the Prevention and Treatment Recommendations. In this section, there is a subsection on health behavior management, where they recommended the following measures:

1. Physical activity: prescribe the accumulation of 30–60 min of moderate-intensity dynamic exercise (e.g., walking, jogging, cycling, or swimming) 4–7 days per week in addition to the routine activities of daily living, and emphasize the ineffectiveness of higher-intensity exercise
2. Weight reduction: maintenance of a healthy body weight (body mass index of 18.5–24.9, and waist circumference <102 cm for men and <88 cm for women) for nonhypertensive individuals to prevent hypertension and for hypertensive

patients to reduce BP, encourage all overweight hypertensive individuals to lose weight, and use a multidisciplinary weight-loss strategy including dietary education, increased physical activity, and behavioral intervention.
3. Alcohol consumption: limit to two drinks per day, and consumption not exceeding 14 standard drinks per week for men and nine standard drinks per week for women (note: one standard drink is considered to be equivalent to 13.6 g or 17.2 mL of ethanol or approximately 44 mL [1.5 oz] of 80 proof [40 %] spirits, 355 mL [12 oz] of 5 % beer, or 148 mL [5 oz] of 12 % wine)
4. Dietary recommendation: eating more fruits, vegetables, low-fat dairy products, dietary and soluble fiber, whole grains, and protein from plant sources that have low saturated fat and cholesterol content (Dietary Approaches to Stop Hypertension [DASH])
5. Sodium intake: reducing toward 2,000 mg (5 g of salt or 87 mmol of sodium) per day
6. Potassium, calcium, and magnesium intake: nonrecommendation of supplementation
7. Stress management: more likely to be effective for individualized cognitive-behavioral interventions when relaxation techniques are used.

An Effective Approach to High Blood Pressure Control has been reported by a Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention [6]. This report recommends lifestyle changes for all hypertension patients as follows:

1. DASH diet [10]: consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat
2. Sodium restriction ($\leq$2.4 g/day)
3. Weight reduction: if BMI $\geq$25 kg/m^2
4. Exercise: at a moderate pace to achieve 150 min/week (i.e., 30 min/5 days/week)
5. Limit daily alcohol: no more than one drink (women) or two drinks (men)
6. Smoking cessation: counseling tobacco users on the health risks of smoking and the benefits of quitting strongly recommended.

These representative lifestyle improvement guidelines for hypertension can be summarized in the six following bullet points:

- Healthy diet (DASH diet, consume a diet rich in fruits, vegetables, and low-fat food or fish with a reduced content of saturated and total fat)
- Sodium restriction
- Weight reduction
- Regular exercise
- Moderate alcohol consumption
- Smoking cessation

The lifestyle modifications are present in all the guidelines regardless of the specific frame [11]. In addition, the health behavior recommendations that appear in the guidelines for the management of hypertension are very similar

to the recommendations appearing in the Guidelines for the Primary Prevention of Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association [12] and the European Stroke Organization (ESO) guidelines [13] for the primary prevention of stroke incidence.

Mechanisms of salt intake and elevated BP are an increase in extracellular volume and hence, in peripheral vascular resistance [14]. High salt intake has the ability to chronically increase renal sympathetic nerve activity and contribute to elevating BP [15]. The WHO Guidelines strongly recommend a salt intake of <5 g/day [16]. High salt intake and a high rate of salt sensitivity among the Japanese may contribute to their elevated BP [17]. The Japanese Guideline sets a target of restricting salt intake to <6 g/day, taking into consideration the current circumstances in Japan.

Vegetable and fruits are abundant in dietary fiber, potassium, magnesium, and antioxidant vitamins, the intake of which is inversely associated with BP [18–22]. High intake of fruits and vegetables reduces the risk of developing hypertension. The ESH/ESC 2103 recommends that patients with hypertension should be advised to eat 300–400 g/day of fruits and vegetables. The JSH2014 focuses on vegetables, recommending that patients with hypertension eat at least 350 g/day of vegetables.

Dietary n-3 polyunsaturated fatty acids (PUFAs) and fish oil have been shown to have a weak but significantly inverse association with BP [23, 24]. Even a small fish intake (30–60 g/day) was shown to reduce the risk of coronary heart disease and sudden cardiac death in Western countries (Chap. 27) [25]. The WHO CARDIAC (Cardiovascular Diseases and Alimentary Comparison) Study showed that the Japanese have one of the highest n-3 PUFA intakes and one of the lowest number of coronary heart disease mortalities worldwide [26]. The ESH/ESC 2013 guideline recommends that hypertensive patients eat fish at least twice a week.

Obesity and overweight are established risk factors for CVD, hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome [27]. A meta-analysis of studies estimated that each kilogram of weight loss reduced BP by 1.05 mmHg systolic and 0.92 mmHg diastolic [28].

Many prospective cohort studies have demonstrated that physical inactivity is associated with an increasing risk of hypertension [29, 30]. In a meta-analysis, eight randomized controlled trials showed that pedometer users significantly increased their physical activity, completing 2,491 more steps/day than controls [31]. Participants in this intervention decreased their systolic blood pressure (SBP) significantly by 3.8 mmHg.

Regular alcohol consumption can lead to an increase in BP [32]. A meta-analysis also showed the hypotensive effects of alcohol restriction [32]. In heavy drinkers, BP is increased after an abrupt reduction of drinking, but it can be subsequently reduced if the restriction is continued. In the ESH/ESC 2013, moderate daily alcohol consumption translates to no more than two drinks in men or one drink in women. In the JSH2014, drinking, in terms of ethanol intake, should be restricted to 20–30 mL (equivalent to 180 mL of sake (a Japanese alcoholic beverage), 500 mL of beer, 90 mL of shochu [distilled spirits], a double whisky or brandy, and two glasses of wine)/day or less in men and to 10–20 mL per day or less in women.

Cigarette smoking causes an acute pressor effect that may elevate BP [33]. It is reported that, in passive smokers, 24-h BP is high, and the incidence of masked hypertension is also high [34].

30.2.2 Secondary Hypertension

Some people have high BP caused by an underlying condition. This type of high BP is called secondary hypertension. Secondary hypertension tends to appear suddenly and to cause higher BP than primary hypertension. Various conditions and medications can lead to secondary hypertension, including:

1. Diseases such as adrenal gland tumors, thyroid problems, renovascular disease, kidney problems, and obstructive sleep apnea
2. Intoxication as found in acute alcohol abuse or chronic alcohol use, and in illegal drug use, such as cocaine and amphetamines
3. Iatrogenic routes caused by certain medications, such as birth control pills, decongestants, over-the-counter pain relievers, cold remedies, and some prescription drugs
4. Congenital anomalies leading to defects in blood vessels

30.3 Complications

30.3.1 High BP and Atherosclerosis

Elevated systolic BP is an important risk factor for carotid atherosclerosis [35]. There is an additive relationship between oral health disorders (severe periodontitis, gingival bleeding, lowest quartile of tooth number, and malocclusion) and risk of hypertension [36, 37]. A possible pathogenetic background of an association between periodontitis and BP would be oral inflammation, the role of the host immune response, the direct microbial effect on the vascular system and alterations in endothelial function (Chap. 26) [38].

30.3.2 Cardiovascular Disease and Hypertension

Hypertension is the most significant risk factor for incident stroke worldwide [39, 40]. The total population-attributable fractions of higher BP for CVD are approximately 30–50 % [41].

A review of major prospective cohort studies and an updated meta-analysis of >40 randomized controlled trials of BP lowering (including >188,000 participants and approximately 6,800 stroke events) showed that in the Asian Pacific region in addition to North America and Western Europe, each 10 mmHg reduction in systolic

BP is associated with a decrease in risk of approximately one-third in subjects aged 60–79 years [42]. In a meta-analysis of randomized controlled studies of subjects aged over 65 years, reducing BP to a level of 150/80 mmHg is associated with large benefit in stroke, CVD, and all-cause mortality [43]. SBP rather than diastolic blood pressure (DBP) reduction is significantly related to lower cardiovascular risk.

A meta-analysis of self-measurement of home BP has shown 1.24- and 1.20-times increased risks of a cardiovascular event and 1.33- and 1.30-times increased risks of incident stroke for high-normal conventional BP and mild hypertension respectively [44]. Among people with optimal, normal, and high-normal conventional BP, 5.0, 18.4, and 30.3 % respectively had masked hypertension (home BP ≥130 mmHg systolic or ≥85 mmHg diastolic). Compared with true optimal conventional BP, masked hypertension was associated with a 2.3-times increased risk of CVD [44].

30.3.3 Kidney Disease and Hypertension

Hypertension is a major cause of kidney disease and kidney failure [45]. In the Suita Study, the risk of CVD was higher in chronic kidney disease (CKD) patients with normal and high-normal BP than in non-CKD individuals in the same BP categories [46]. To prevent CVD, control of both BP and renal function is important, because of the mutual exacerbation of decreased kidney function and hypertension [47].

30.3.4 High BP and Diabetes Mellitus

Hypertension is a risk factor for the development and worsening of many complications in patients with diabetes mellitus. In an urban Japanese population cohort study, the subjects with high-normal blood pressure in any glucose category and the normal BP subjects with impaired fasting glucose levels showed increased risks of CVD [48]. These two groups of borderline disease subjects, i.e., subjects with prehypertension (normal and high-normal BP) and impaired fasting glucose comprised approximately 10 % of all population-wide subjects (30 or more years of age), and had a two-fold increased risk of a CVD event compared with the subjects with optimal BP and normoglycemia. Subjects with either borderline condition should be targeted for health guidance.

30.3.5 Metabolic Syndrome and High BP

Metabolic syndrome is a group of health problems that consists of abdominal obesity, elevated BP, hyperglycemia, hypertriglyceridemia, and hypo-HDL cholesterolemia. In a meta-analysis study that identified 87 studies and included 951,083 subjects, metabolic syndrome is associated with a two-fold increased risk of cardiovascular outcomes and a 1.5-fold increased risk of all-cause mortality [49].

30.3.6 Preeclampsia: High BP and Pregnancy

A meta-analysis of studies of pregnant women with chronic hypertension has recently shown that women with chronic hypertension had high pooled incidences of superimposed preeclampsia (25.9 %, 95 % confidence interval 21.0–31.5 %) (Chaps. 60 and 61) [50].

30.3.7 High BP and Erectile Dysfunction

A high incidence of erectile dysfunction was found in hypertensive patients from Spanish specialized care hypertension units. Sildenafil improved the score in the erectile function domain [51].

30.3.8 High BP and Eye Disease

In a meta-analysis of individual participant data, retinal arteriolar narrowing (per 20-μm difference) and venular widening (per 20-μm difference) were associated with 1.29- and 1.14-fold increased risks of hypertension respectively. These findings demonstrate the importance of microvascular remodeling in the pathogenesis of hypertension.

30.3.9 Hypertension and Dementia

A meta-analysis of six longitudinal studies showed that hypertension is associated with a 1.59-fold increased risk of incident vascular dementia [52]. The Hisayama study showed that mid-life and late-life hypertension are significant risk factors for late-life vascular dementia, but not for Alzheimer's disease [53]. Mid-life hypertension is associated with vascular dementia, regardless of late-life BP levels.

30.4 Principles of Treatment

The objective of treating hypertension is to prevent cardiovascular and renal diseases; thus, the goal of treatment for hypertension is not only to manage BP, but also to deal with the risk factors that hypertension and CVD share, including lipid disorders, glucose intolerance or diabetes, obesity, and smoking.

The basic two treatment strategies for hypertension are lifestyle modifications and drug therapies. In recent years, catheter-based radiofrequency denervation of renal arteries has emerged as a potential treatment for hypertension and is already in clinical studies in more than 80 countries (Chap. 42) [54, 55]. However, the beneficial effects on BP control as well as specific indications that promise a certain level of therapeutic effects are still under debate [56].

In this chapter, the treatment approach to hypertension is examined.

30.4.1 When Should Drug Treatment for Hypertension Be Started?

Lifestyle modifications should be initiated in all hypertensive patients before the initiation of drug treatment, and patients should also be assessed for target organ damage and existing CVD. Cardiovascular risk stratification includes the history of previous cardiovascular events such as stroke, transient ischemic attacks, dementia, coronary artery disease, heart failure, or peripheral artery disease, and asymptomatic organ damage, including left ventricular hypertrophy, carotid asymptomatic atherosclerosis, or chronic kidney disease (CKD). Age is also an important risk factor.

In mild (stage 1) hypertensive patients who are at a low to moderate risk, drug treatment could be delayed for a while: 3 months according to the guidelines from the American Heart Association, the American College of Cardiology, and Centers for Disease Control and Prevention (AHA/ACC/CDC 2013) [6] and from the JSH 2014 [7], and several months according to the American Society of Hypertension and the Internal Society of Hypertension (ASH/ISH 2014) [5].

Prompt initiation of drug treatment is recommended in patients with moderate to severe hypertension and/or when total cardiovascular risk is high because of organ damage, diabetes, CKD, or CVD. The guideline from NICE indicates higher levels of BP (≥160/90 mmHg) before initiating drug treatment in low-risk patients [3]. The ESH/ESC 2013 guideline recommends initiating drug treatment when SBP is ≥160 mmHg in elderly patients [4]. Also, the Eighth Joint National Committee (JNC-8) guideline has higher levels for initiating treatment in patients aged ≥60 (≥150/90 mmHg) [2]. The other three guidelines base the decision to start active drug therapy on a BP level ≥140/90 mmHg.

30.4.2 Treatment Goal of BP

In general, the treatment goal is widely accepted as BP <140/90 mmHg; however, there are different goals for particular subpopulations (Table 30.1).

30.4.2.1 Diabetes Mellitus

For hypertensive patients with diabetes mellitus, the targets are <140/90 mmHg in the guidelines with the exception of those in the ESH/ESC 2013 and the JSH 2014. In the ESH/ESC 2013 guidelines [4], the target diastolic BP is 5 mmHg lower (<140/85 mmHg), and in the JSH 2014 [7], the goals are much lower (<130/80 mmHg).

30.4.2.2 Nephropathy

For CKD patients without proteinuria, or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, the treatment goal is the same (<140/90 mmHg) in all six guidelines. In the ESH/ESC 2013 guidelines, SBP values of <130 mmHg may be considered when overt proteinuria is present. In the JSH 2014, the target is <130/80 mmHg when proteinuria (urine protein/ creatinine ratio >0.15 g/g creatinine) is present.

There are some post hoc analyses to support the notion that a lower BP goal is associated with a reduction in a composite cardiovascular outcome for diabetic patients [57, 58], and is related to improvement of renal outcomes for patients with proteinuria [59]. However, at this time, for hypertensive patients with diabetes and/or nephropathy, the evidence is insufficient to determine whether treatment to a lower BP goal (for example, <130/80 mmHg) significantly improved mortality or cardiovascular or cerebrovascular health outcomes compared with the goal of <140/90 mmHg. On the other hand, evidence from a meta-analysis suggests that the treatment resulting in a lower SBP might be effective in reducing the incidence of stroke [60] and thus in JSH 2014, the goals are much lower (<130/80 mmHg), taking into account the high risk of stroke in Japan [61].

30.4.2.3 Elderly

In elderly hypertensive patients (age >60 years; Chap. 31) too, BP control is associated with a favorable clinical outcome, and for hypertension with SBP ≥160 mmHg, there is solid evidence to recommend reducing SBP to between 140 and 150 mmHg [62–64]. It remains incompletely understood whether patients should be treated with a goal SBP <140 mmHg because none of the major trials of elderly hypertensive patients has achieved a mean SBP <140 mmHg in the active treatment group. In the JNC-8 guideline, a higher level (<150/90 mmHg) is recommended for those aged ≥60 [2]. ASH/ISH 2014 targets the same BP goal for those aged ≥80 [5] and JSH 2014 for those aged >75 [7].

30.4.3 Treatment with Antihypertensive Drugs

Drugs for the treatment of hypertension are commonly prescribed worldwide. Recently, a wider range of drugs has been developed, such as diuretics, angiotensin-converting enzyme inhibitor (ACE-I), angiotensin II-AT_1 receptor blocker (ARB),

beta-blocker, calcium channel blocker (CCB), etc. The choice of drugs is influenced by patient age, ethnicity/race, pregnancy, and other clinical conditions (e.g., diabetes mellitus, nephropathy, and coronary artery disease). In this chapter, initial drug choice, and considerations of the management of hypertensive patients with various other conditions, and of the subsequent order of additional therapy are examined. For more details on specific drug class, refer to Chaps. 35, 36, 37, 38, 39, 40, and 41.

30.4.4 Initial Choice of Drug to Start Treatment

When hypertension is the only or main condition, recommendations for the initial drug selection differ among the guidelines from the six expert committees published since 2011 [2–7]. A comprehensive comparison of the hypertension guidelines is shown in Table 30.2. In nonblack patients, the American Society of Hypertension and the Internal Society of Hypertension (ASH/ISH 2014) [5] recommends ACE-I or ARB for those aged <60; the National Institute for Health and Clinical Excellence (NICE) [3] recommends the same for those aged <55. The Japanese Society of Hypertension (JSH 2014) [7] and the Eighth Joint National Committee (JNC-8) [2] recommend ACE-I, ARB, CCB, or thiazide-type diuretics. The guideline from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC 2013) [6] recommend starting with a thiazide diuretic in most patients (alternatively ACE-I, ARB, or CCB).

For black patients, the three guidelines recommend CCB or thiazide diuretics as the initial drug, and the National Institute for Health and Clinical Excellence (NICE) [3] recommends CCB. The choice of the initial drug is different in some subpopulations.

30.4.4.1 Diabetes Mellitus

As stated in the American Diabetes Association (ADA) guideline [65], antihypertensive medication for hypertension and diabetes mellitus should consist of a regimen that includes renin–angiotensin aldosterone system (RAS) blockers, e.g., ACE-I or ARB. The intrarenal RAS is activated in diabetes [66, 67]; thus, RAS blockers should reduce intraglomerular pressure better than other drugs. In the guidelines from the ASH/ISH 2014 [5], the ESH/ESC 2013 [4], and JSH 2014 [7], ACE-I or ARB is specified as an initial choice, but not in the others.

30.4.4.2 Nephropathy

Albuminuria is well known to be a risk factor in hypertension, and reduction in the level of proteinuria seems to serve as a useful marker of successful therapy. Both ACE-I and ARB reduce proteinuria and slow the progression of CKD. Treatment

Table 30.2 Comparison of hypertension guidelines for initial drug selection 2011–2014

	NICE 2011 [3]	ESH/ESC 2013 [4]	AHA/ACC/CDC 2013 [6]	ASH/ISH 2013 [5]	JSH 2014 [7]	JNC 8 [2]
Nonblack	ACE-I or ARB for <55 years CCB for >55 years	Thiazide-type diuretic, beta blocker, ACE-I, or ARB	Thiazide-type diuretic for most patients	ACE-I or ARB for <60 years, CCB or thiazide-type diuretic for ≥60 years	Thiazide-type diuretic, CCB, ACE-I, or ARB	Thiazide-type diuretic, CCB, CCB, ACE-I, or ARB
Black	CCB	Not mentioned	Not mentioned	CCB, or thiazide-type diuretic	Not mentioned	CCB, or thiazide-type diuretic
Diabetes	Not addressed	ACE-I or ARB	ACE-I, ARB, CCB, beta blocker, or thiazide-type diuretic	ACE-I or ARB	ACE-I or ARB	Thiazide-type diuretic, CCB, ACE-I, or ARB for nonblacks; CCB, or thiazide-type diuretic for blacks
Kidney disease (including CKD)	Not addressed	ACE-I or ARB	ACE-I or ARB	ACE-I or ARB	ACE-I or ARB for patients with proteinuria	ACE-I or ARB
Beta blocker as first-line drug	No (step 4)	Yes	No (step 3)	No (step 4)	No (step 4)	No (step 4)
Initiate drug therapy with two drugs	Not mentioned	In patients with markedly elevated SBP	≥160/100	≥160/100	≥160/100	≥160/100

CCB calcium channel blocker, *ACE-I* angiotensin converting enzyme inhibitor, *ARB* angiotensin II-AT_1 receptor blocker

with ACE-I or ARB improves the renal outcome; however, there is less evidence favoring ACE-I or ARB for cardiovascular outcomes in patients with CKD, or for those aged >75.

Whichever drug is chosen first, almost all hypertensive patients with diabetes and/or nephropathy require more than one drug to achieve the target goal BP. To reach the goal, diuretics are sometimes needed.

30.4.5 Status of Beta Blockers in the Management of Hypertension

Beta blockers appear as the third- or fourth-choice drug in most guidelines, except for those in ESH/ESC 2013 [4], where beta blockers are included among the drugs suitable for the initiation of treatment. Beta blockers may not be as effective as the other major drug classes in preventing cardiovascular events in hypertensive patients [68], but they have strong clinical outcome benefits in patients with myocardial infarction and heart failure and are effective in the management of angina. In the guidelines from ESH/ESC 2013 [4], ASH/ISH 2014 [5], and JSH 2014 [7], use of a beta blocker is recommended to reduce mortality and hospitalization in patients with heart failure, coronary artery disease, or severe left ventricular dysfunction.

30.4.6 Combination Therapy as Initial Therapy, Choice of Second Drug

Monotherapy can reduce BP to the target in only a limited number of patients. Most hypertensive patients require a combination of two or more drugs; thus, the idea of starting with two drugs is gaining popularity. Initiation with a drug combination can be considered in patients at a high cardiovascular risk or with remarkably high BP (Table 30.2). A number of combination tables are now available, but combination therapy using antihypertensive drugs should be administered with attention given to the results rather than being applied automatically. An increasing number of trials have compared different combinations [69, 70] and found that the combination of two RAS blockers is not recommended and should be avoided [71]. In the guidelines from ESH/ESC 2013 [4] and JSH 2014 [7] combinations of a RAS inhibitor and a CCB, or a RAS inhibitor and a diuretic are preferred (Chaps. 36 and 41).

30.5 Concluding Remarks

Recently, new updated hypertension guidelines have been published in Western countries and in Japan. Under the new guidelines, hypertension should be treated by pharmacotherapy and/or nonpharmacotherapy (behavior modification). These

lifestyle modifications are universal regardless of the framework of the guideline: i.e., a DASH diet (rich in fruits, vegetables, and low-fat food or fish with a reduced content of saturated and total fat), sodium restriction, weight reduction, regular exercise, moderate alcohol consumption, and smoking cessation. Hypertensive patients should improve their lifestyle according to the hypertension guidelines, in addition to consulting a physician.

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Chapter 31
Pathophysiology of Hypertension

Michel Burnier and Grégoire Wuerzner

Abstract Hypertension is a rather simple phenotype characterized by an increase in systemic blood pressure above an arbitrarily defined threshold. Yet, the mechanisms leading to the increase in blood pressure are extremely complex and involved a wide variety of neurohormonal, renal, metabolic, and vascular factors. The causes of hypertension differ substantially in young children, in middle-aged men and women, and in the elderly. In children, hypertension is often the appearance of a renal or endocrine disease, whereas in adults, the large majority of patients with hypertension have an *essential* hypertension, a denomination reflecting that the mechanisms are not fully understood although some well-defined pathogenic factors have been described in patients with hypertension associated with diabetes mellitus, obesity, hyperaldosteronism, renovascular hypertension, or renal diseases. In the elderly, hypertension is strongly associated with factors leading to vascular aging and loss of arterial elasticity. The purpose of this chapter is to review the pathophysiology of hypertension in these different clinical situations in light of the recent literature.

Keywords Renal • Sodium handling • Hormonal systems • Inflammation • Estrogens • Immunity

31.1 Introduction

Cardiovascular diseases remain the most common noncommunicable cause of death in the general population in particular after the age of 40 years [1]. Among the factors that contribute to the development of cardiovascular diseases such as stroke, myocardial infarction, congestive heart failure, or renal and vascular complications, hypertension is undoubtedly the major, modifiable, independent risk factor in terms of prevalence, clinical impact, and attributable risk. According to the most recent

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Table 31.1 Trends in prevalence of hypertension according to age in the National Health and Nutrition Surveys

Age category (years)	1988–1991 (%)	1999–2000 (%)
8–17	7.3[a]	9.7[b]
18–39	5.1	7.2
40–59	27	30.1
>60	57–9	65.4

From Refs. [2] and [3]
[a]These data were obtained from 1988 to 1994
[b]These data were obtained from 1999 to 2006

data of the National Health and Nutrition Health Surveys conducted between 1988 and the years 2000–2006, the prevalence of hypertension is increasing slowly in adults as well as in children [2, 3] (Table 31.1). However, looking at these data, it appears that hypertension is still rather uncommon below the age of 20 and affects more than 50 % of subjects older than 60 years. This age effect on hypertension prevalence suggests that the pathophysiology of hypertension may differ substantially depending on the age at which the elevated blood pressure occurs and depending on the clinical comorbidities in which it happens. Indeed, there is a good evidence that the pathophysiology of hypertension developing in infancy is not comparable to that of hypertension diagnosed in the very elderly or in patients with chronic kidney disease or obesity. Yet, it is interesting to note that events occurring very early in life may influence the occurrence of hypertension later on. Thus, for example, it has been shown that changes occurring during the fetal period and the early years of development determine the blood pressure (BP) and the cardiovascular risk later on in life [4, 5]. Therefore, it may be useful to approach the pathophysiology of hypertension not as a unique global phenomenon but rather as a panel of mechanisms acting at different periods of life (Chap. 30). In this chapter, we shall review the pathophysiology of hypertension distinguishing hypertension in children, in middle-aged men and women, and in elderly taking into account the mechanisms associated with concomitant factors such as obesity, diabetes mellitus, or chronic kidney disease.

31.2 Pathophysiology of Hypertension in Children and Adolescents

Hypertension in childhood is defined as a BP above the 95th percentile taking into account age, sex, and height [6]. The prevalence of hypertension in children and adolescents is generally well below 10 % in the population, but the exact figure depends very much on the conditions in which BP is measured and on the number of visits [7]. Thus, in a recent survey of a large group of schoolchildren, we found that the prevalence of hypertension decreased from 11 to 2.2 % between the first and the third visits. The prevalence of elevated BP in children and adolescents is associated with an excess of body weight, a high heart rate, and the family history of

hypertension. However, the precise role of obesity in the recent increase in the prevalence of hypertension in childhood is debated [8].

In small children (<6–7 years), the detection of hypertension is commonly associated with the presence of a disease such as congenital renal abnormalities, a renal parenchymal disease, a coarctation of the aorta, or eventually a renal artery stenosis, endocrine diseases, and more rarely genetic alterations leading to hypertension [9] (Table 31.2). Hence, the pathophysiology of hypertension is linked directly to the mechanisms associated with the type of secondary hypertension. In congenital renal malformations or parenchymal renal diseases, the reduced glomerular filtration leading to a diminished capacity to excrete water and sodium plays an important role in the development of hypertension together with an activation of the renin-angiotensin and sympathetic nervous systems. In renal artery stenosis, the stimulation of the renin-angiotensin system by the stenotic renal artery contributes to BP elevation in order to maintain sodium balance at the expense of a high systemic BP. In young patients, a coarctation of the aorta induces hypertension through a dysfunction of baroreceptors associated with an intimal and medial hypertrophy of large and small vessels and a stiffening of the aorta. These changes can induce a vascular endothelial dysfunction, a reduced vasodilatory response to acetylcholine, and an increased vasoconstrictive response of peripheral vessels to catecholamines. For these reasons, hypertension tends to persist after correction of the coarctation.

The pathophysiology of endocrine-mediated hypertension depends on the type of hormone overproduction or absence. Glucocorticoid- and mineralocorticoid-induced hypertensions are mediated primarily by the sodium- and water-retention

Table 31.2 Common causes of hypertension in children between 1 and 10 years

First year	Coarctation of the aorta
	Renovascular disease
	Renal parenchymal disease
	Iatrogenic (medication, volume)
	Tumor
Infancy to 6 years	Renal parenchymal disease
	Renovascular disease
	Coarctation of the aorta
	Tumor
	Endocrine causes
	Iatrogenic
	Essential hypertension
Age 6–10 years	Renal parenchymal disease
	Essential hypertension
	Renovascular disease
	Coarctation of the aorta
	Endocrine causes
	Tumor
	Iatrogenic

Adapted with permission from Ref. [9]

properties of these steroids. In addition, direct effects of these hormones on cardiac, vascular, and renal tissues participate in the elevation of systemic BP. For example, glucocorticoids increase the synthesis of angiotensinogen and reduce the synthesis of prostacyclin resulting in a greater vascular reactivity to angiotensin II and catecholamines. Aldosterone has well-described profibrotic effects in the heart, kidneys, and vessels [10]. Hypertension is also a clinical characteristic of acromegaly. In that situation, hypertension is the consequence of the excess of growth hormones which leads to vascular hypertrophy but also to a hyperdynamic state, due to an activation of the sympathetic nervous system, and renal sodium retention [11]. Excess growth hormone and insulin-like growth factor 1 that characterize patients with acromegaly have been shown to be associated with enhanced renal and extrarenal epithelial sodium channel activity [12].

Monogenic forms of hypertension are more frequent among children with hypertension. As shown in Table 31.3, these forms of hypertension are due primarily to specific mutations in the kidney affecting sodium or potassium transport systems and leading most of the time to increased sodium reabsorption as the main cause of the elevation of BP [13]. In accordance with this mechanism, patients with monogenic hypertension have a good BP response to diuretics.

In older children (>10 years), secondary forms of hypertension tend to become less frequent although their incidence remains higher than in adults. However, essential hypertension becomes more prominent in adolescents and its pathophysiology is probably closer, if not similar, to that of young and middle-aged adults as discussed below.

As discussed before, birth weight appears to be an important determinant of BP and hypertension in children and adolescents as suggested in the *Barker's hypothesis* [4]. According to this hypothesis, the link between birth weight and hypertension is a low number of glomeruli and an incomplete renal maturity [5]. However,

Table 31.3 Most common forms of monogenic hypertension

Syndrome	K	pH	Renin	Aldo	Transmission	Gene	Treatment
GRA	Low/N	High	Low	High	Autosomal dominant	Chimeric gene CYP11B1/11B2	Spironolactone, amiloride, glucocorticoids
Liddle's syndrome	Low/N	High	Low	Low	Autosomal dominant	β and γ subunit of ENaC	Amiloride, triamterene
AME	Low/N	High	Low	Low	Autosomal recessive	11β-HSD	Spironolactone
MR in pregnancy	Low	High	Low	Low	Unknown	Mutations of mineralocorticoid receptor	Delivery
Gordon's syndrome	High	Low	Low	Low	Autosomal dominant	WNK 1 and WKN4	Hydrochlorothiazide
HBS	N	N	N	N		Unknown	None

GRA glucocorticoid-remediable aldosteronism, *AME* apparent mineralocorticoid excess, *MR* mineralocorticoid receptor mutation, *HBS* hypertension brachydactyly syndrome, *ENaC* epithelial sodium channel, *WNK* with no kinase

other factors related to the low birth weight may contribute to BP elevation including an immaturity of the corticoid system, a glomerular hyperfiltration, and a renal tubular adaptation leading to an overexpression of some renal transporters.

Taken together, it is suggested that hypertension in childhood and adolescence has a specific pathophysiology. The mechanisms of hypertension in this age category are important to consider because increasing evidence suggests that hypertension in infants and adolescents is associated with early target organ damage [14] and persistence of hypertension in adulthood.

31.3 Pathophysiology of Essential Hypertension in Adults

BP is the main driving force that brings blood to all organs of the body; thus, the control of BP is critical for life. In this context, it is not surprising that the regulation of BP is a highly complex and sometimes redundant interplay between renal, neural, cardiac, vascular, and endocrine factors modulated by genetic and environmental factors.

31.3.1 Role of Kidneys in the Pathogenesis of Essential Hypertension

Regulating sodium and water excretion and hence extracellular volume homeostasis, the kidney plays a crucial role in BP control. Indeed, as proposed by Guyton (1990), BP and sodium homeostasis are closely related through the pressure-natriuresis mechanism which enables to stabilize BP around a set point [15]. If renal perfusion pressure increases, renal sodium output increases and extracellular fluid volume contracts so that BP returns to its baseline value. According to this hypothesis, hypertension results from a shift of the BP set point due to a defect of the pressure-natriuresis mechanism. The regulation of sodium excretion in the pressure-natriuresis phenomenon occurs essentially in the proximal segments of the nephron and changes in medullary blood flow are important for the pressure-natriuresis relationship. In addition, many endocrine factors such as the renin-angiotensin-aldosterone system, nitric oxide, and prostaglandins can shift the pressure-natriuresis to higher or lower set points. There is also a good evidence that sodium handling by the distal segments of the nephron is critical to the regulation of sodium balance in relation to changes in BP and that other factors such as the sympathetic nervous system, a local intrarenal inflammation, and the generation of reactive oxygen species (ROS) can modify the pressure-natriuresis relationship [16].

The contribution of the kidneys to the development of hypertension has been demonstrated nicely using cross-transplantation studies in animals. These studies have demonstrated that transplantation of a kidney of a hypertensive rat into a normotensive animal leads to the development of hypertension in this latter.

Conversely, transplantation of a normotensive kidney to a hypertensive rat normalizes BP showing BP follows the kidney [17]. More recent studies have used this technique in mice to investigate the role of the renin-angiotensin system in mediating the hypertension induced by cross-transplantation. These studies have demonstrated that AT_1 receptors in the kidney but also in the vasculature contribute equally to the development of hypertension [18]. Some results have also been gathered in human transplantation, but the evidence obtained in these studies is less convincing as more confounding factors could interfere with the interpretation of the results [19].

In support of the role of kidneys in the pathophysiology of hypertension, one should mention once again the description of monogenic forms of hypertension which are associated to mutations in renal transport systems influencing renal sodium reabsorption in various segments of the nephron [20]. In essential hypertension, polymorphisms of some of these transport systems such as the epithelial sodium channel, Nedd4, or alpha-adducin may actually contribute to generate hypertension [21] or eventually protect against hypertension [22], but the frequency at which this occurs remains unknown.

31.3.2 Sympathetic Nervous System and Renin-Angiotensin-Aldosterone System

There are also several neuroendocrine systems that increase BP and maintain the hypertension state in part through their effects on renal function. The two most important are undoubtedly the renin-angiotensin-aldosterone and the sympathetic nervous systems. As both systems are discussed in separate chapters (Chap. 35, Sympathetic and Renin-Angiotensin Activity in the Pathophysiology of Hypertension; Chap. 36, Drugs Targeting RAAS in the Treatment of Hypertension and Other Cardiovascular Disease) of the present book, we shall only briefly summarize some effects of these systems as potential causes of hypertension. The renin-angiotensin-aldosterone system (RAAS), which originates with the synthesis of renin from the juxtaglomerular cells of the kidney, participates in the pathophysiology of hypertension in multiple ways through its vascular, endocrine, central, and renal properties. In recent years, it became apparent that the RAAS exists not only as a circulatory system but also as a local tissue system. As reviewed by Kobori et al. [23], many components of the renin-angiotensin-aldosterone system have been localized within the kidney. Thus, in addition to being a potent vasoconstrictor and a growth-promoting peptide, renal angiotensin II controls BP through its effect on renal hemodynamic and glomerular filtration rate as angiotensin II modulates the tone of both afferent and efferent arterioles. Angiotensin II also modulates renal tubular sodium reabsorption at different sites along the tubule through direct and aldosterone-mediated effects on sodium transport. But angiotensin II also induces inflammation, cell growth, mitogenesis, apoptosis, migration, and differentiation, regulates the gene expression of bioactive substances, and activates multiple

intracellular signaling pathways, all of which may contribute to maintain a high BP and to promote the development of hypertension-induced complications. Interestingly, even a short-time exposure to angiotensin II may produce a long-term hypertension by provoking renal vascular lesions and a local inflammation [24, 25]. Of note, although an increased activity of renin-angiotensin-aldosterone system has been observed in many animal models of hypertension, not all hypertensive patients have an activated renin-angiotensin-aldosterone system; therefore, when measuring the activity of this system in hypertension, it should always be examined in the light of sodium intake as there is a strong interaction between sodium intake and the activity of the renin-angiotensin-aldosterone system.

Regarding the sympathetic nervous system, there is also abundant evidence that this system contributes to the regulation of BP and to the pathophysiology of hypertension [26]. Indeed, several animal models of hypertension are characterized by an increased sympathetic activity [27]. Moreover, in early stages of clinical hypertension, a combination of sympathetic hyperactivity and parasympathetic dysfunction has been observed in young subjects with an increased heart rate [28]. In the kidney, the sympathetic system has a major influence on renin secretion, renal hemodynamics, and tubular sodium handling [26]. The role of the sympathetic nervous system and of baroreflex control in the genesis of hypertension has led to the development of new interventional strategies to treat resistant hypertension (renal denervation, baroreflex sensitization) [29].

31.3.3 Prostaglandins

Another set of substances that regulate BP and may be involved in the genesis of hypertension are prostaglandins. Prostaglandins are the product of arachidonic acid metabolism [30]. Their production involves several steps: firstly, the release of arachidonic acid from membrane phospholipids under the action of phospholipase A_2; secondly, the catalysis of arachidonic acid by cyclooxygenases (COX 1, 2, or 3) to generate PGH_2; and thirdly, the generation of specific prostaglandins under the effect of prostaglandin synthases such as prostacyclin synthase leading to the formation of prostacyclin (PGI_2) or thromboxane synthase which generates thromboxane A_2 (Fig. 31.1). This cascade leads to the synthesis of several prostaglandins with multiple biological properties, including vascular, renal, and inflammatory effects. Phospholipase A_2 is activated by a variety of stimuli, including angiotensin II, norepinephrine, and bradykinin.

Prostaglandins act mainly near their sites of release because they are degraded rapidly by local metabolism into inactive products. At the vascular level, prostaglandins can produce either a vasoconstriction (thromboxane A_2, $PGF_2\alpha$) or a vasodilatation (PGE_2, prostacyclin). One important property of vasodilatory prostaglandins is their ability to modulate the vasoconstriction induced by potent vasoactive substances such as angiotensin II. In the normal adult kidney, both COX-1 and COX-2 are constitutively expressed. COX-1 is expressed in the glomerulus, the afferent

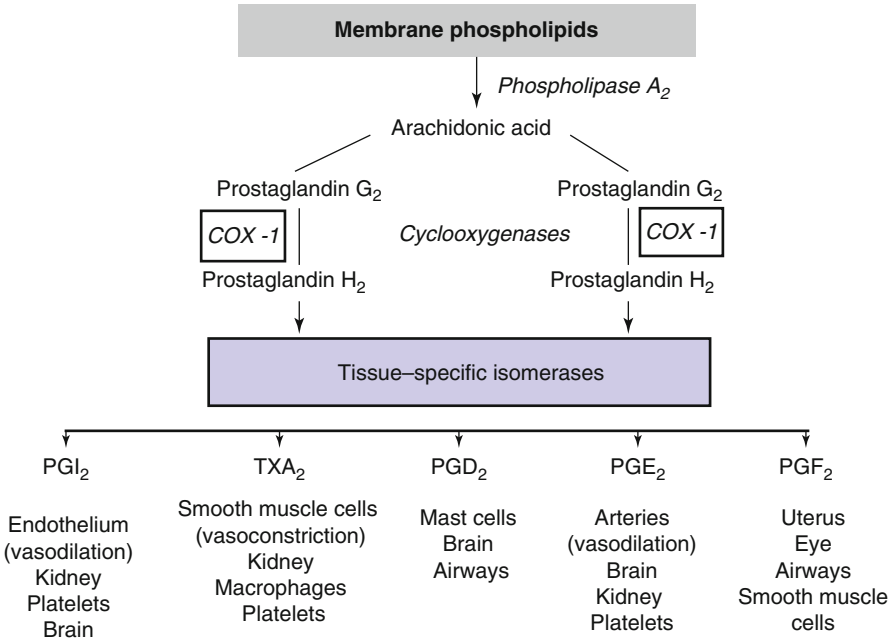

Fig. 31.1 Metabolism and systemic effects of prostaglandins. Schematic representation of the metabolism of prostaglandins and their effects on various tissues. Note that some prostaglandins can affect vascular tone and hence blood pressure through vasodilating prostaglandins (PGI_2 and PGE_2) as well as through the vasoconstrictor effect of thromboxane A_2 (TXA_2)

arteriole, and tubular cells, and COX-2 has been expressed in the afferent and efferent arterioles, the podocytes, the macula densa, and some tubular and interstitial cells. Intrarenal prostaglandins participate actively in the regulation of renal perfusion and glomerular filtration rate. They are also implicated in the maintenance of sodium, potassium, and chloride homeostasis and in the regulation of renin secretion [31, 32]. The impact of prostaglandins on vessels, renal electrolyte balance, and renin secretion may be of particular relevance to the genesis of hypertension [33]. Indeed, data have demonstrated that mice deficient in the PGI_2 receptor are resistant to the development of renovascular hypertension, a renin-dependent form of hypertension [34].

In hypertensive patients, a deficiency in vasodilatory prostaglandins has been reported [35], and an increase in thromboxane A_2 has been found in essential hypertension [36]. These observations lead to the hypothesis that there might be an imbalance between anti- and pro-hypertensive prostaglandins in hypertension. The potential role of prostaglandins in hypertension is further emphasized by the observation that selective and nonselective COX-1 and COX-2 inhibitors increase BP, favor sodium retention, and may cause hypertension in some patients [37]. However, it appears that the hypertensive effect of nonsteroidal anti-inflammatory drugs is more frequent among hypertensive than normotensive patients. This would indicate

that prostaglandins act as a counter-regulatory mechanism to limit the increase in BP in hypertension and may not be a primary hypertensive mechanism [35].

31.3.4 Role of Vasculature in the Pathogenesis of Essential Hypertension

As observed by Folkow in the 1970s [38], when BP increases persistently, blood vessels undergo an adaptation characterized by a structural remodeling leading to an increase in wall:lumen ratio. This adaptation actually maintains a chronic increase in vascular resistance in established hypertension. Clinically, it appears that this vascular remodeling occurs very early in the course of the pathogenesis of hypertension probably even before BP has reached the hypertensive range [39]. Today, several investigators have actually confirmed using gluteal biopsies that there is indeed a remodeling of small arteries in hypertensive patients, that small vessel remodeling may have a major impact on target organs, and that antihypertensive therapy can reverse it [40]. The mechanisms involved in this remodeling imply essentially an increased vascular tone and an increased activity of the sympathetic nervous system, angiotensin II which causes a proliferation of smooth muscle cells, endothelin-1, and perhaps inflammatory processes [41]. At the cellular level, the matrix rearrangement appears to involve integrins and tissue transglutaminase, one of a family of transglutaminase enzymes, which includes factor XIII [42].

31.3.4.1 Nitric Oxide

The endothelial layer of the vascular wall produces several substances, which are closely involved in the regulation of the circulation and vascular wall homeostasis. Some of these substances are direct vasodilators such as nitric oxide, prostacyclin, and endothelial-derived hyperpolarizing factor, and some are potent vasoconstrictors such as endothelin-1 and thromboxane. Nitric oxide is formed by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine. Once formed, NO diffuses to the underlying vascular smooth muscle cells, activates soluble guanylyl cyclase, and produces vasorelaxation [43]. Three forms of NOS have been described: a neuronal NOS present in neural cells, an inducible NOS (iNOS), and an endothelial NOS (eNOS) present essentially in the endothelium. In the vessels, NO is released from endothelial cells in response to physical stimuli (shear stress and hypoxia) and by the stimulation of endothelial receptors such as bradykinin and muscarinic receptors. NOS activity can be inhibited using endogenous analogues of L-arginine such as asymmetric dimethylarginine or N-monomethyl-L-arginine (L-NMMA). Some of these analogues are increased in disease states, for example, in patients with chronic renal failure.

The potential role of NO in the pathophysiology of cardiovascular diseases including hypertension has first been evoked with the demonstration that acetylcholine, in the absence of endothelium, is a vasoconstrictor rather than a vasodilator

[44]. Following this seminal observation, numerous studies have demonstrated the crucial role of the endothelium in the regulation of cardiovascular homeostasis and have led to the concept of endothelial dysfunction. Thus, endothelial dysfunction of large and small arteries has been described in animal models of hypertension as well as in patients with essential hypertension [45–47]. Several mechanisms are discussed whereby endothelial dysfunction results in hypertension. Studies have suggested an impaired NO synthesis and release, but endothelial dysfunction may also be consecutive to an increased breakdown of NO as the vasorelaxing properties of NO are counteracted by oxidative processes in tissues. Superoxide anions are potent scavengers of endothelial-derived NO. Whether endothelial dysfunction is a primary or secondary event in hypertension has been discussed because an elevation of blood pressure per se can cause endothelial dysfunction [48]. However, a blunted endothelium-dependent vasodilatation has been observed in offspring of hypertensive parents suggesting that endothelial dysfunction can precede the development of hypertension and may play a primary role in the genesis of the disease [49]. Of note, transgenic mice deficient for the eNOS develop a systemic hypertension associated with an increased peripheral vascular resistance [50, 51]

The role of nitric oxide in the pathogenesis of hypertension is controversial [52]. Nitric oxide can contribute to the etiology of hypertension by various other mechanisms, one of them being the development of atherosclerosis. Indeed, NO has been reported to decrease monocyte and leukocyte adhesion to endothelial cells, to inhibit platelet aggregation and platelet-vessel wall interaction, to decrease the transport of lipoproteins into the vessel wall, and to inhibit vascular smooth muscle cell proliferation as well as some components of the vascular inflammation. Another pathway by which NO can affect blood pressure is the interaction with the renin-angiotensin system. Nitric oxide has indeed been found to suppress renin release by juxtaglomerular cells and hence to reduce the activity of the renin-angiotensin system and to participate in the regulation of renal hemodynamics [53]. As discussed previously, NO also interacts closely at the vascular level with endothelin to limit the vasoconstrictor effect of endothelin. Some of these interactions may actually lead to an increased vascular tone. At last, the activity of nitric oxide is related to other vasoactive compounds such as prostanoids and bradykinins.

31.3.4.2 Endothelin

Endothelin (ET) is a very potent endogenous vasoconstrictor produced by the endothelium and identified by Yanagisawa et al. in 1988 [54]. There are three isoforms of endothelin (i.e., ET-1, ET-2, and ET-3), but endothelin-1 is the only relevant peptide in humans. Endothelin is derived from pro-endothelin, which is cleaved into a big endothelin and then converted to the active endothelin-1 by an endothelin-converting enzyme. Several stimuli induce endothelin release by endothelial cells including shear stress, thrombin, angiotensin II, vasopressin, catecholamines, and hypoxia [55]. The effects of endothelin are mediated by two receptors, i.e., the ET-A and ET-B receptors. The ET-A receptor is widely distributed and it is the principal receptor located on vascular smooth muscle cells and cardiomyocytes. In these cells, activation of ET-A

receptors leads to an activation of phospholipase C, to an increase in intracellular calcium, and, hence, to cell contraction. The ET-B receptor is located on both vascular smooth muscle and endothelial cells. In endothelium cells, activation of ET-B receptors releases vasodilating substances such as nitric oxide (NO), prostacyclin, and adrenomedullin. In muscle cells, activation of the ET-B receptor induces a vasoconstriction (Chaps. 34 and 45).

If vasoconstriction is the hallmark of endothelin's action, several other biological properties of endothelin have been described. Thus, renal function appears to be particularly responsive to the effects of endothelin [56]. Administration of low doses of endothelin-1 in animals and humans has been shown to decrease glomerular filtration rate and renal blood flow through the stimulation of vascular smooth muscle cells and contraction of mesangial cells and to reduce urinary sodium excretion. Similarly, overexpression of endothelin in the mouse kidney has been associated with the development of glomerulosclerosis, the development of interstitial fibrosis, and the development of renal cysts but not hypertension suggesting a role of endothelin in the development of some renal diseases independent of the hypertensive effect. These effects appear to be mediated by the activation of ET-A receptors. However, endothelin-1 can also lower BP and produce a natriuretic response through the activation of ET-B receptors which have been localized on renal tubular epithelial cells [57]. Recent data suggest that the renal medullary endothelin system is important for BP regulation. Indeed, transgenic rats deficient in endothelin-1 specifically in the collecting duct develop hypertension [58]. In the normal guinea pig heart and in isolated cardiomyocytes, endothelin-1 had positive inotropic and growth-promoting effects [59]. At the vascular level, as mentioned earlier, endothelin may contribute to the remodeling of small and large arteries [60].

Experimental data have demonstrated that endothelin-1 interacts very closely with nitric oxide via activation of ET-B receptors on endothelial cells. Indeed, endothelin-1 promotes the release of NO and thereby maintains a balance between the vasodilatory effect of NO and the vasoconstrictor effect of endothelin-1 itself. There is also a close interaction between endothelin and the renin-angiotensin-aldosterone system [61]. Angiotensin II enhances the vascular responsiveness to exogenous endothelin-1 and increases the release of endothelin-1 and the expression of preproendothelin in endothelial cells.

The role of endothelin as a potential pathogenic factor in hypertension has been suggested using several experimental and clinical approaches [60]. In rats, knockout of the ET-B receptor is associated with the development of severe salt-sensitive hypertension [62]. In humans with essential hypertension, plasma endothelin levels are usually not elevated except in Afro-Americans [63]. However, circulating concentrations of endothelin may not necessarily reflect the tissue concentrations because endothelin acts as a paracrine/autocrine system. Nonetheless, elevated circulating concentrations of endothelin have been reported in some human and experimental forms of hypertension such as the mineralocorticoid-induced and renovascular hypertension in the rat and hypertension in renal transplant patients and patients with diabetes or chronic renal failure. There are also data suggesting that endothelin plays a role in the development of hypertension in pregnancy-induced hypertension [64, 65].

The best demonstration of the role of endothelin in hypertension in humans has come from the use of selective endothelin antagonists. Indeed, in recent years, several selective and nonselective non-peptide antagonists of ET-A and ET-B receptors have been developed and investigated. In mild to moderate hypertensive patients, the dual ET-A and ET-B receptor antagonist bosentan (500–2,000 mg) lowered BP as effectively as the angiotensin-converting enzyme inhibitor enalapril (20 mg) [66]. Similarly, a significant decrease in blood pressure was found with darusentan, a selective ET-A endothelin receptor antagonist, in patients with a mild to moderate hypertension [67].

31.3.5 Metabolic Factors in the Pathogenesis of Essential Hypertension

31.3.5.1 Obesity

Essential hypertension is a common feature in patients with obesity, metabolic syndrome, and diabetes. Indeed, in obese subjects, hypertension is diagnosed in up to 50 % of patients, and similarly about 50 % of type 2 diabetic patients are hypertensive at the time of diagnosis [68, 69]. The pathogenesis of hypertension in these metabolic disorders has some specificity and implies, in addition to the sympathetic and renin-angiotensin systems, other mechanisms such as hyperglycemia, insulin resistance, adipokines (leptin and adiponectin) play.

In obese patients with hypertension, the elevated BP is associated with sodium retention and rightward shift of the pressure-natriuresis relationship. This shift is due in part to a sustained activation of the renin-angiotensin system and an increased sympathetic activity but also to the physical compression of the kidneys by surrounding visceral fat and increased renal sinus fat [70]. Considering the role of the renin-angiotensin system in obesity-induced hypertension, aldosterone appears to be particularly important to mediate an increase in BP observed in obesity as well as in patients with metabolic syndrome. Indeed, higher plasma aldosterone levels have been measured in obese patients and patients with the metabolic syndrome [71]. In the study by Goodfriend et al. (2004), oxidative stress and oxidized fatty acids derived from linoleic acid stimulated aldosteronogenesis and thereby promoted sodium retention [72]. These oxidized fatty acids are essentially produced by visceral fat, an observation that confirms that visceral fat contains all the components of the renin-angiotensin system.

31.3.5.2 Leptin

Regarding the sympathetic nervous system in obesity, many factors contribute to increase its activity including angiotensin II, baroreflex sensitivity, hyperinsulinemia, and sleep apnea but also hypoghrelinemia and hypoadiponectinemia and leptin resistance. An interesting observation made in animal models of obesity is that sympathetic tone is only moderately increased and that not all organs

demonstrate an elevated sympathetic activity [73]. Thus, some studies have shown that sympathetic drive is increased in the kidney and muscle but not necessarily in the heart [73]. Moreover, visceral fat rather than subcutaneous fat appears to participate in the increased sympathetic nerve activity. Leptin and adiponectin, the two molecules produced by adipocytes, may actually contribute to an increase in BP observed in obese patients through their effects on the sympathetic and renin-angiotensin systems. Plasma levels of leptin are proportional to the fat mass. Leptin acts on a specific leptin receptor localized in the brain where its stimulation reduces appetite and increase energy expenditure, thus lowering body weight [74]. Mice deficient in leptin develop hyperphagia, obesity, and insulin resistance. Leptin has also pro-inflammatory properties, which may contribute to the high cardiovascular risk associated with obesity. The ability of leptin to increase BP has been suggested by studies in which leptin was infused either in the brain or peripherally. These leptin administrations actually activated the sympathetic nervous system and progressively increased BP, an effect that could be blocked by administration of an alpha- and beta-adrenergic blocker [75]. In obese humans and rodents, elevated levels of leptin have been measured but surprisingly anorexia is generally absent. Therefore, it has been suggested that leptin resistance explains this discrepancy and that this resistance is frequent in obesity. Thereafter, the observation in animals of dissociation between the ability of leptin to stimulate sympathetic tone and to increase BP and the finding of an absence of simultaneous reduction of appetite and body weight has generated the concept of *selective leptin resistance* [76] as shown in Fig. 31.2. The concept of leptin resistance has been reviewed recently and the mechanisms of this dissociation are discussed in details by Mark et al. [77]. Of note, the actual role of leptin in mediating the obesity-induced hypertension in humans remains highly controversial as many conflicting results have been published [77].

31.3.5.3 Adiponectin

Adiponectin is another complex molecule secreted by adipocytes which has been associated with metabolic and cardiovascular diseases including hypertension [78] (Fig. 31.2). This molecule is present in the plasma in three molecular forms (high-molecular-weight, low-molecular-weight, and trimeric forms). Adiponectin acts on two distinct receptors localized in various tissues (muscle, liver, endothelium) where it can mediate the effects on peroxisome proliferator-activated receptors (PPAR), AMP kinase activation glucose uptake, and beta-oxidation [78]. In endothelial cells, adiponectin has also been shown to increase NO production by regulating endothelial NOS activity [79]. In obesity, low levels of adiponectin have been measured suggesting that hypoadiponectinemia is associated with an increase in BP. In animals, there is a close relationship between angiotensin II and the sympathetic nervous system and adiponectin. In rats, angiotensin II infusion decreases plasma adiponectin levels and inhibition of the renin-angiotensin system increases adiponectin through the PPARγ nuclear receptor [78]. As noted earlier, adiponectin is closely related to the sympathetic system. An increased sympathetic tone is associated with a reduction of plasma adiponectin and this may influence BP. The

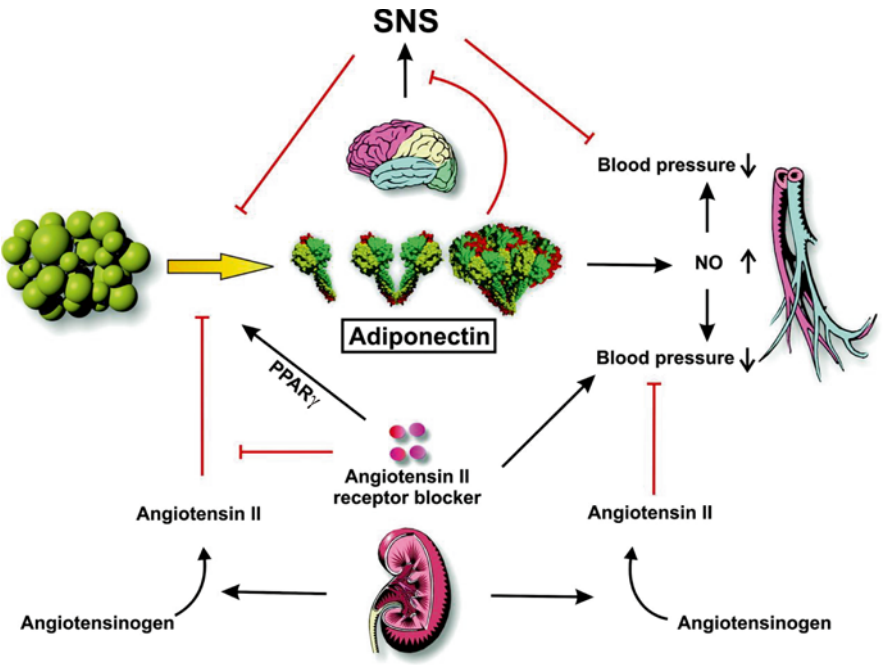

Fig. 31.2 Role of adiponectin in blood pressure control (Adapted with permission from Ref. [78]). Adipose tissue secretes three molecular forms of adiponectin into circulation. Adiponectin stimulates the production of NO, which is involved in the regulation of blood pressure. Renin secreted from the kidney cleaves angiotensinogen to produce angiotensin II. Angiotensin II plays an inhibitory role in adiponectin production. Angiotensin II AT_1 receptor blockers display pleiotropic effects on blood pressure control through receptor blocking and adiponectin stimulation. SNS overdrive increases blood pressure and inhibits the production of adiponectin. Also, adiponectin inhibits the activation of SNS through central actions. *Black arrows* indicate activation and *red lines* indicate inhibition

interaction between these two systems occurs in the periphery as well as in the brain and may be involved in the genesis of hypertension in obesity [80].

31.3.5.4 Insulin

Insulin is another hormone that is increasingly considered in the genesis of hypertension in obese patients and patients with the metabolic syndrome [81]. Hypertension, obesity, dyslipidemia, and glucose intolerance represent a cluster of risk factors which is called metabolic syndrome although this entity is often criticized. Insulin resistance in some peripheral tissues appears to be the main feature of metabolic syndrome. The peripheral insulin resistance is associated with an increased activity of the sympathetic nervous system and endothelin and a decrease in NO production [82]. Moreover, in the kidney, insulin has been shown to cause sodium retention, an effect which may further contribute to increased BP in this clinical context.

31.3.6 Other Hormonal Factors in the Pathophysiology of Essential Hypertension

In addition to the many system described above, several other hormonal factors may participate in the regulation of BP either through their vasodilating properties, which may be altered in hypertension, or through their vasoconstrictor effects. In this respect, one should consider natriuretic peptides, kinins, vasopressin, and dopamine.

31.3.6.1 Natriuretic Peptides

Natriuretic peptides were identified in the 1980s with the observation that rat atrial extracts had potent natriuretic and vasodilatory properties [83]. This original finding led to the identification of the atrial natriuretic peptide (ANP) and subsequently to the recognition of a family of four distinct natriuretic peptides: ANP (17 amino acids), BNP (32 amino acids), CNP (22 amino acids), and urodilatin (32 amino acids). ANP is synthesized and secreted predominantly by the atria. BNP was initially isolated from pig's and dog's brains but it is produced essentially by cardiomyocytes [84]. CNP has been localized in the brain and in the heart but also in several other peripheral tissues including the kidney, the adrenal glands, and the endothelium. ANP and BNP are released from the heart in response to changes in atrial or ventricular stretch. Plasma levels of natriuretic peptides are also influenced by the body position and the salt intake. Natriuretic peptides act by stimulating specific receptors (natriuretic peptide receptors A, B, and C). These receptors are widely distributed throughout the body including endothelium, smooth muscle cells, heart, adrenal gland, lung, brain, adipose tissue, and kidney [85]. Natriuretic peptides are degraded by the neutral endopeptidase [11, 24] and by a receptor-mediated clearance via the C receptor. Inhibition of neutral endopeptidase to increase plasma natriuretic peptides is today one approach to treat hypertension and heart failure in combination with a blocker of the renin-angiotensin system [86].

ANP and BNP possess diuretic, natriuretic, vasodilatory, and anti-hypertrophic, antifibrotic, antiproliferative, and anti-inflammatory properties. ANP also causes intravascular volume contraction as documented by increases in hematocrit and serum albumin when administered to binephrectomized rats [87]. ANP has an inhibitory action on aldosterone and renin secretion [88]. ANP and BNP antagonize vasoconstriction induced by norepinephrine or angiotensin II. There is also some evidence that the central effects of ANP contribute to fluid and electrolyte balance and to the regulation of systemic hemodynamics [89]. These central effects of ANP are mediated by an interaction between ANP and sympathetic tone in the brain stem.

Whether or not natriuretic peptides participate in the pathogenesis of hypertension is still debated. Experimentally, mice in which either the Pro-ANP or the ANP-A receptor genes were deleted developed hypertension [90, 91]. On the other

hand, mice overexpressing the ANP and BNP genes demonstrated a lower blood pressure than controls [92]. In rat models of hypertension, an altered ANP secretion in response to salt loading or to an increased atrial pressure has been observed suggesting a role of these peptides in hypertension [93]. In hypertensive patients, low to normal plasma ANP levels have been measured [94, 95]. However, some investigators have reported raised plasma ANP levels in patients with essential hypertension even though blood volume was generally not expanded in these patients. This observation may be explained by an increased central venous pressure owing to a greater venous return or to atrial distension in some hypertensive subjects. In offsprings of hypertensive parents, Ferrari et al. (1990) have reported a reduced ANP response to salt loading indicating ANP deficiency, which may be a predisposing factor to the development of hypertension [96]. A similar impaired ANP response to salt loading has been reported in Afro-Americans and in patients with salt-sensitive hypertension [97]. Today, several research groups are working on the role of genetic variants of the atrial natriuretic peptide gene to investigate the potential role of this peptide in the development of cardiovascular complications such as stroke or coronary heart disease [98, 99].

31.3.6.2 Kinins

The interest for kinins as effective mediators in cardiovascular control has grown with the development of angiotensin-converting enzyme inhibitors, which inhibit not only the generation of angiotensin II but also the degradation of bradykinin. The kallikrein-kinin system consists of proteases (kallikreins) that release kinins from kininogen, the precursor protein. Primarily, the liver synthesizes kininogen, but the mRNA for the high-molecular-weight (HMW) kininogen has been identified in endothelial cells. Kallikreins are present in plasma where they generate bradykinin from the HMW kininogen and in tissues, particularly in the kidney. Tissue kallikrein cleaves a low-molecular-weight kininogen to release *lys*-bradykinin (kallidin). Kallidin is then metabolized through an aminopeptidase into bradykinin. Kinins act by stimulating specific receptors (kinin B1, B2, and B3 receptors). The B1 receptor is involved in the chronic inflammatory and pain-producing response to kinins. The B2 receptor mediates most of the other actions of kinins. In the circulation and tissues, kinins are destroyed by aminopeptidases and carboxypeptidases. The dipeptidase kininase II (ACE) is the most important metabolizing enzyme within the cardiovascular and renal systems. The synthesis, activity, and release of renal kallikrein mRNA and protein levels are influenced by several hormonal systems including mineralocorticoids, glucocorticoids, testosterone, thyroxine, insulin, vasopressin, cathecholamines, and angiotensin II. Of note, renal kallikrein mRNA of females is twice that of males.

The very first clue that kinins could play a role in hypertension was published in the early 1930s when a reduction in urinary kallikrein excretion was found in hypertensive patients. Thereafter, little attention was given to this system. Later on, a similar observation was made in various groups of hypertensive patients

including African-Americans and patients with a low renin hypertension and in rats with hypertension [100, 101]. All genetic models of hypertension in the rat show abnormalities in the kallikrein-kinin system. With time, increased evidence for a role of kinins in blood pressure was reported. The B2 receptor knockout mouse receiving a high-sodium diet displayed a significantly increased blood pressure and renal vascular resistance, and reduced renal blood flow relative to the control mouse [102]. Similarly, selective B2 receptor blockade has been shown to cause a rise in blood pressure in various experimental models of hypertension in the rat [103, 104]. Conversely, overexpression of human tissue kallikrein lowered BP in mice [105]. More recent family studies have suggested that individuals with a greater urinary kallikrein excretion genotype were less likely to have one or two hypertensive parents and urinary kallikrein was recognized as a strong marker of a genetic component of essential hypertension [106, 107]. More recent data have suggested that the renal kallikrein-kinin system participates in the development of salt-sensitive hypertension and pharmacological interventions of this renal system may be a new pathway to lower BP in some individuals with hypertension [108].

31.3.6.3 Arginine-Vasopressin

Arginine-vasopressin (AVP) has been recognized as one of the most potent vasoconstrictor peptide in the body through the activation of V_1 vascular receptors. Moreover, vasopressin is a crucial determinant of fluid balance mediated by its activity on renal V_2 receptors. Vasopressin has long been known to play a role in blood pressure homeostasis in several physiological and pathological clinical conditions such as changes in posture, dehydration, hemorrhage, adrenal insufficiency, and heart failure [109]. More recently, the contribution of vasopressin to the progression of hypertension, diabetes, and chronic kidney diseases has been attributed to both V1 and V2 receptors, and there is some evidence that vasopressin could participate in the pathogenesis of some forms of hypertension [110].

When administered directly into the lateral or third ventricle of the brain, small doses of vasopressin V1 agonist induced a sudden rise in BP, which was not observed with a V2 agonist, and this effect may be due to an activation of sympathetic nervous system [89]. Elevated levels of vasopressin have been documented in several experimental rat models of hypertension including in the DOCA-salt-hypertensive rat, the SHR, and the Dahl salt-sensitive rat. However, the role of V2 receptors in these forms of hypertension remains debated [111–114]. In humans, the evidence for a role of vasopressin in the pathogenesis of essential hypertension is rather weak. In normotensive subjects and in hypertensive patients on a regular sodium diet, administration of an effective and selective V1 antagonist did not lower blood pressure [115, 116]. However, in patients with severe hypertension or malignant hypertension, the administration of a vasopressin receptor blocker was associated with a moderate decrease in blood pressure [117, 118].

31.3.6.4 Dopamine

Besides the abovementioned humoro-endocrine factors involved in the regulation of blood pressure, several other endocrine/autocrine systems can contribute to the development of hypertension. In recent years, evidence has shown that the intrarenal dopaminergic system contributes to BP regulation [119]. Data have been obtained in experimental and human studies indicating that abnormalities in dopamine production or dopamine receptor signaling can increase BP and augment the salt sensibility of BP. Particularly interesting observations have been made regarding the role of alterations in dopamine receptor function by GRK4, a G protein-coupled receptor kinase subfamily. Studies have demonstrated that the GRK4 gene locus is associated with the development of essential hypertension by promoting renal sodium reabsorption [120].

31.3.7 Is There a Role for Inflammation and Immunity in the Pathophysiology of Essential Hypertension?

Many of the pathogenic mechanisms discussed previously as causal in the early development and maintenance of an elevated BP in essential hypertension are actually associated with the induction of a micro-inflammation. This is the case, for example, of angiotensin II, salt, adipokines, and endothelial factors. These observations have revived the interest for inflammatory and immunological mechanisms in hypertension. In fact, historically, findings suggesting a role of immunity in the pathogenesis of hypertension have been published more than 30 years ago with the description of the role of the thymus in the development of hypertension in mice with a reduced renal mass and in the Lyon genetically hypertensive rat [121, 122].

As reviewed recently [123], many experiments were conducted in various models of hypertension such as the spontaneously hypertensive (SHR) or the deoxycorticosterone acetate-treated rat (DOCA) to investigate the impact on BP of transferring immune-competent cells or administering an immunosuppressive agent. In all these models, hypertension could be either induced or attenuated following an intervention on the immune system. These studies also focused the attention on the potential role of T cells in the pathogenesis of hypertension [124].

Today, the working hypothesis linking the immune system, inflammation, and the genesis of hypertension is based on the fact that hypertension-induced stimuli in target organs produce neoantigens, i.e., molecules that are normally not exposed to the immune system and generate an immune response (Fig. 31.3). Thus, factors like angiotensin II or salt, which cause a modest increase in BP initially, produce lesions in the vasculature or the kidney leading to the formation of neoantigens. These latter promote a T-cell activation and T cells penetrate the renal and vascular tissues. T-cell-derived signals such as IL-17 promote entry of other inflammatory cells such as macrophages. Consequently, inflammatory cells release cytokines that cause vasoconstriction and promote sodium and water absorption, ultimately increasing BP and causing sustained hypertension [124]. In this hypothetic model, some cytokines appear to play an important role as a

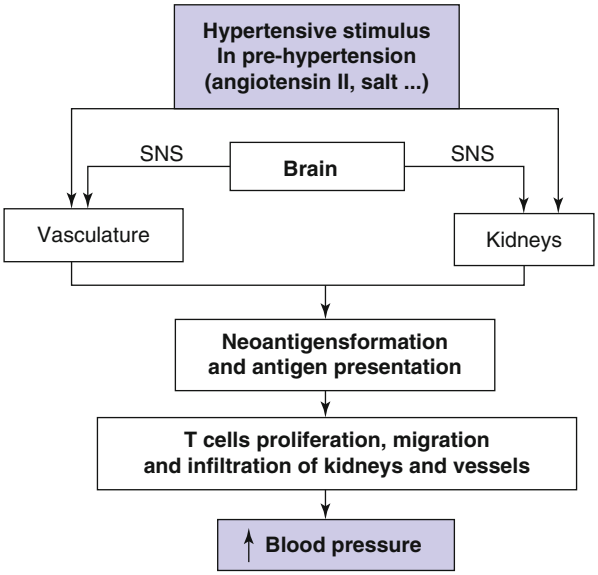

Fig. 31.3 Potential role of immunity in the pathogenesis of hypertension. Schematic representation of the potential role of immunity in the development of hypertension. Stimuli like angiotensin II or the sympathetic nervous system can induce small lesions in the vasculature and kidneys. This may lead to the formation of neoantigens from intracellular components. These latter will serve as antigens recognized by the immune system and will generate a cellular immune response which will develop against vessels and kidneys leading to an increase in blood pressure

promoter of hypertension, like interleukin-17, whereas other cytokines such as interleukin-10 may have a rather mitigating role to limit the increase in BP.

Taken together, the investigations of the role of immunity and inflammation in the genesis of hypertension are important as they might open new therapeutic approaches to treat hypertension.

31.4 Sex Differences in the Pathophysiology of Essential Hypertension

Epidemiologically, it is well recognized that men are at higher cardiovascular risk than women at least until women reach the time of menopause. Gender differences in BP may account for this finding as clear differences in BP with age have been demonstrated [125]. After the menopause, BP tends to increase in women and rejoin the levels of men [126]. This actually suggests that the pathogenic mechanisms causing hypertension may not be identical in males and females.

Similar sex differences in BP have been observed in animal models of hypertension as reviewed recently [127]. To investigate the role of sex hormones in the

development of hypertension in animals, several technical approaches have been used including castration of male, ovariectomy in females, or ovariectomy with estrogen replacement [127]. From these studies, it appears that testosterone plays a greater role than female sex hormones in the sexual dysmorphism. The main system mediating the effect of sex hormones on blood pressure is the renin-angiotensin system and to a lesser degree endothelin and nitric oxide [128]. There is also some evidence that the sex chromosomes per se are involved in sex difference in BP [129]. Thus, in male spontaneously hypertensive rats (SHR), the pressure-natriuresis relationship is shifted to the right and castration of male SHR has been found to restore it suggesting that androgens contribute to the higher blood pressure measured in males [130]. Androgen receptor blockade lowers blood pressure in male SHR to the level of female SHR [131], and the administration of testosterone to ovariectomized female SHR increases blood pressure [130]. This latter finding indicates that androgens play a role in the pathogenesis of hypertension that occurs after the menopause in some women. Thus, at the time of menopause, not only the loss of female hormones but also the relative change in estrogen/androgen ratio influences BP. Androgen receptors have also been localized in different parts of the renal tubule such as the proximal tubule in humans and the collecting tubule in rats [132, 133]. When injected in to rats, dihydrotestosterone, the main metabolite of testosterone, has been found to stimulate directly the proximal volume reabsorptive rate and hence to increase extracellular volume and blood pressure.

There is some evidence suggesting that female sex hormones (estrogens and progesterone) may protect against salt-induced changes in BP. When Dahl salt-sensitive (DS) rats receive a high-sodium diet, females become less hypertensive than male rats [134]. In this animal model, ovariectomy results in an accelerated development of salt-sensitive hypertension in females [134]. Interestingly, reversal of the diet to a low-salt intake reverses the hypertension in intact male and female DS rats, but this is not the case in ovariectomized female DS rats. The interpretation of this finding is that female sex hormones act to suppress sodium-dependent and sodium-independent increases in BP. A greater rise in blood pressure has also been reported in female SHR rats after ovariectomy [135]. More recent experimental data suggest that a loss of female hormones decreases the threshold of the hypertensive effect of salt [136].

Several studies have reported gender differences in various components of the renin-angiotensin cascade that could partially explain the gender differences in blood pressure [137]. In a normotensive population, a higher plasma renin activity (PRA) has been measured in men than in women regardless of age and ethnic heritage suggesting a higher risk of renal failure in males than in females [138]. Exogenous female sex hormones administered with oral contraception have also been shown to stimulate angiotensinogen production, which may lead to an increase in BP in some women [139]. Other studies have reported that PRA is higher in postmenopausal than in premenopausal women although PRA remains higher in men than in women for the same age [137]. In animals, the administration of testosterone to ovariectomized female rats increases PRA, which is lower in males after castration [140, 141]. Finally, in Sprague-Dawley rats, a positive linear correlation

between the levels of testosterone and plasma renin activity has been reported, suggesting that testosterone stimulates the renin-angiotensin system. In accordance with this observation, several studies have found that androgens, like estrogens, enhance renal angiotensinogen mRNA [140, 142]. Androgens also upregulate the expression and the affinity of AT_1 receptors for angiotensin II in male tissues [143].

Sexual hormones also affect the response to a stimulation of the renin-angiotensin system. Miller et al. (1999) have compared the renal hemodynamic response to the infusion of exogenous angiotensin II in young normotensive premenopausal women and in age-matched men and found striking differences [144]. Both groups exhibited an increase in blood pressure and a decrease in effective renal plasma flow with angiotensin II, but only men maintained their glomerular filtration rate (GFR) resulting in an increased filtration fraction. In women, the administration of angiotensin II decreased GFR leading to a reduction in filtration fraction.

Endogenous and exogenous female sex hormones have been found to influence systemic and renal response to salt in women [145]. In young normotensive women, whether or not under contraceptives, blood pressure is rather insensitive to salt, with a normal pattern of adaptation of renal proximal and distal reabsorption to changing salt intake [145]. In contrast, women become salt-sensitive after the menopause, which may explain the increase in blood pressure occurring at the menopause in some women. The renal hemodynamic response to salt and the regulation of sodium excretion is also modulated by female sex hormones.

Taken together, these data indicate that there are important differences in the pathogenesis of hypertension in male and females. These differences generate important clinical questions, which are still far from being resolved. For example, should therapeutic BP targets be the same in males and females? Does the BP-induced increase in cardiovascular risk similar in both sexes? These questions and the precise differences in the pathogenesis of hypertension deserve additional investigations to clarify the issues.

31.5 Pathophysiology of Hypertension in the Elderly (Chap. 30)

Hypertension is highly prevalent in subjects over 60 years of age. Indeed, in elderly and very elderly (>80 years), almost 60 % of subjects are hypertensive. However, hypertension in the elderly differs from that observed in younger subjects. Indeed, the main characteristic of hypertension in the elderly is an increase in systolic BP and a rather low diastolic (*isolated systolic hypertension*); hence, pulse pressure is increased. This hypertension phenotype develops as a result of reduced elasticity and compliance of central conduit arteries due to age-dependent arterial stiffening, development of atherosclerosis, and an accumulation of arterial calcium and collagen instead of elastin in arteries [146]. The remodeling of the arterial walls leads to an increased rigidity, which accelerates pulse wave velocity. Moreover, the remodeling is associated with an endothelial dysfunction, which further contributes to an increase in BP.

Among the pathogenic factors participating in the vascular remodeling, one has to cite the matrix metalloproteinase (MMP) family of enzymes [147]. Indeed, MMP9 and MMP2 plasma levels have been reported to positively correlate with BP and with the incidence of new cases of hypertension [148]. Conversely, animal studies have shown that inhibition of MMPs restore endothelial function and lower BP [149]. Another factor is the accumulation of calcium in the vascular wall. Usually, calcium load occurs in the tunica media and is linked to a change in the phenotype of smooth muscle cells, which behave like osteoclasts and retain calcium. A recent survey has shown an association between the presence of arterial calcifications and isolated systolic hypertension [150] (Chap. 4).

Another important factor to consider in the pathogenesis of hypertension in the elderly is salt intake (Chap. 30). Indeed, there is an association between BP and salt intake as assessed by urinary sodium excretion [151]. The association is stronger in hypertensive patients than in normotensive subjects, but it is also more pronounced in elderly subjects [151]. In the INTERSALT study, a high-salt intake was associated with a greater increase in BP with age [152]. The role of salt in mediating an elevation of BP in the elderly is not really a surprise. Indeed, elderly subjects are known to be more sensitive to a high-salt intake probably due to their age-related reduction in renal excretory capacity [153].

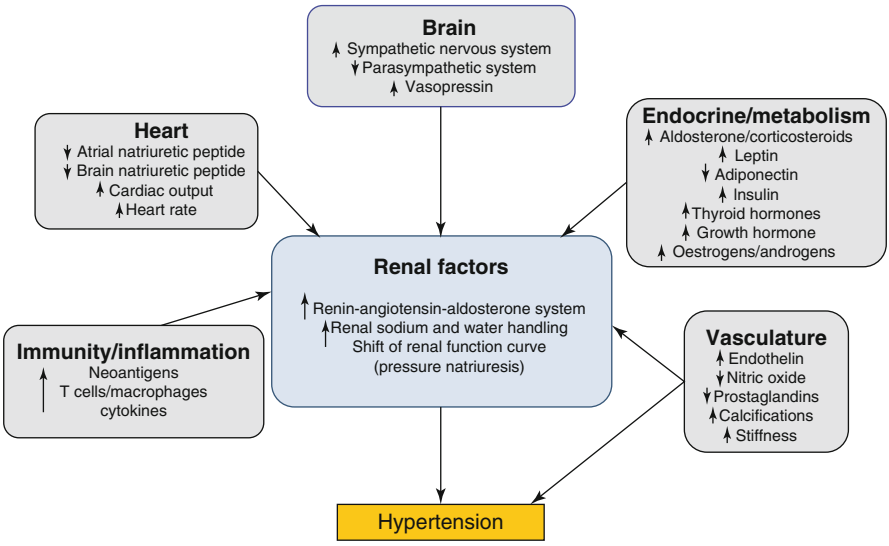

Fig. 31.4 Integrated scheme of the various factors potentially involved in the pathophysiology of hypertension. Stimulated or inhibited factors originating from the heart, the brain, the immune, and the endocrine systems act on the kidneys either to stimulate the renin-angiotensin-aldosterone system or to promote an increase in renal sodium reabsorption and hence a rightward shift of the pressure-natriuresis curve. This leads to an increase in blood pressure in order to maintain sodium balance. Note that the renal system plays a central role in the pathogenesis of hypertension

31.6 Concluding Remarks

The pathogenesis of hypertension is an extremely complex mosaic of neurohormonal factors as illustrated in Fig. 31.4. Their influence on blood pressure depends on many environmental factors as well as comorbidities and genetics. In this review, we addressed the major determinants of high BP in humans with respect to age and sex. We did not address the influence of genetic, nutritional, and environmental factors (such as calcium, potassium, magnesium, or air pollution) on blood pressure, which are discussed in separate chapters of this book. Due to space limitations, we also did not enter into all recent molecular mechanisms discovered in animal models of hypertension. Today, with the availability of transgenic mouse models, new molecules are regularly identified that appear to regulate BP. However, their exact role in the pathophysiology of human hypertension remains often unclear. Therefore, they deserve additional experimental and clinical studies.

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Chapter 32
Blood Pressure Genomics

Georg B. Ehret

Abstract Blood pressure genetics has been instrumental in understanding the pathways that regulate blood pressure and induce hypertension. Two types of approaches have been used with great success: First, studies of hypertensive families in which monogenic blood pressure elevation can be explained by mutations in one of a dozen genes identified so far. Unfortunately, the relevance of these rare familial variants is limited when predicting primary hypertension in the general population. Second, association meta-analyses based on genome-wide genotyping using large sample sizes that have so far yielded about around 60 common genetic variants predicting blood pressure with a small, but reproducible, impact on blood pressure in the general population. This chapter summarizes the current findings based on genome-wide association studies and outlines the conclusions that can be drawn when considering the variants identified in aggregate and gives an outlook of the challenges ahead.

Keywords Cardiovascular risk factors • Blood pressure • Complex trait genetics • Single nucleotide polymorphism • Genome-wide association studies

Abbreviations

BP	Blood pressure
DBP	Diastolic blood pressure
GWAS	Genome-wide association studies
ICBP	International Consortium for Blood Pressure GWAS
MAF	Minor allele frequency
SBP	Systolic blood pressure
SNP	Single nucleotide polymorphism
TOD	Target organ damage

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32.1 Introduction

BP is a classical quantitative trait, and both systolic (SBP) and diastolic blood pressure (DBP) are close to normally distributed in the general population [1, 2]. Elevated blood pressure is not a disease in itself, but hypertension (HTN) induces target organ damage (TOD) that is described in detail in other chapters of this book (Chaps. 29 and 30). TOD mainly occurs in the form of large- and small-vessel diseases that affect largely the heart structure and function [3–5], the arterial endothelium [6], kidney function and ultimately structure [7, 8], and the microvessels of the eye and the brain [9]. Proof of causality between BP and TOD is lacking for some of these associations [10]. BP is associated with cardiovascular risk in the general population in a graded manner; both SBP and DBP are predictive, and there is ample literature on the predictive advantages of the precise phenotype, including mean arterial pressure, pulse pressure, and newer indices, according to age and other characteristics [11–13].

32.2 The Spectrum of Genetic BP Variability

What is the underlying cause for the distribution of BP phenotypes in the population? Major environmental cofactors for BP are known and explain a part of BP variability and HTN, most prominent being age, BMI, and gender [14–16]. On the other hand, a substantial additional part of the BP variability is genetic; family and twin studies estimate the proportion of the blood pressure explained by genetics to be around 30–50 % [17–20]. For BP, as for other phenotypes, the estimates based on twin studies are somewhat larger compared to data based on family studies. Overall, the estimated variance explained by genetics is similar to many other cardiovascular phenotypes [18].

32.3 Types of Genetic Variants Underlying BP Variation

Several types of genetic variants exist in the human genome of which the most frequent and diverse are single nucleotide polymorphisms (SNPs), i.e., base changes at a single position. In recent large-scale DNA-sequencing experiments, 38 million SNPs have been validated [21]. Because of their great variability and abundance, SNPs are thought to carry a large proportion of genetic variability, but it is also important to recognize that SNPs have different frequencies in diverse populations and that most SNPs are rare as this is relevant to the genomics of HTN. The history of blood pressure genetics includes intense discussions since Pickering vs. Platt on the question of whether there are a few or many underlying genetic variants for BP [22].

For primary HTN, the genetic origin is clearly polygenic as genome-wide association studies (GWAS) have shown since 2009 [10, 23–26]. In these global genomic approaches, SBP, DBP, HTN, pulse pressure, and other phenotypes have been used, and the genetic variants discovered in these experiments are frequent genetic variants so far by design.

On the opposite extreme of the allele frequency spectrum, genetic variants of low frequency can be found that segregate in rare hypertensive families. These rare variants typically induce a marked elevation of BP [27]. Although it is very clear that extremely rare monogenic BP variants exist, the boundary between rare and frequent variants is blurred by familial BP variants that are not infrequent. It is also important to note that all monogenic HTN genes discovered so far act in two systems: electrolyte transport in the kidney and renin–angiotensin–aldosterone pathways [28].

32.4 Common Disease: Common Variant Hypothesis in the Age of Inactivity and Obesity

Population genetics arguments postulate that variants underlying common traits such as blood pressure elevation are frequent, as put forward by "the common disease–common variant hypothesis" [29]. A genetic variant that explains some fraction of a common trait today has arisen a long time ago in human history [30]. If the variant carries an evolutionary advantage, then the mutation has expanded to high frequency today and has at the same time helped to increase the prevalence of the phenotype or disease. Human evolution was overwhelmingly shaped by famine and pestilence, and the age of inactivity and obesity [31] is very recent on an evolutionary scale. It is current thinking that BP elevation was an advantage in the past when water and salt were scarce at times and what used to be an evolutionary advantage leads to disease today [32].

32.5 The Challenge to Find Variants for Primary HTN by Genome-Wide Association Studies (GWAS)

The challenge for many years has been to find reproducible genetic loci associated with primary HTN or SBP/DBP in the general population. A continuous phenotype is more precise and yields improved statistical power compared to the dichotomous phenotype HTN and is therefore preferred in many experiments [10, 25].

In GWAS, hundreds of thousands of SNPs are genotyped for each participant and an association statistic is computed between the genotype of each individual SNP and the phenotype [33]. The sheer number of tests performed using this technique has two important consequences: First, the technique could only be used successfully once microarrays that can interrogate large numbers of SNPs at

affordable prices became available [34], leading to the first published GWAS in 2005 [35–37]. Second, given the large number of tests, the significance threshold has to be adjusted for multiple testing. Generally, one million effective tests are conducted in genome-wide studies and a genome-wide significant p-value is therefore set at 5×10^{-8} or lower (Bonferroni-corrected alpha of 0.05). Consequently, large sample sizes are necessary. For the effect sizes typically observed for BP, samples of at least 10,000 participants, better 100,000 or more, are necessary to get to a reasonable statistical power, even if the allele frequencies are optimal [28].

32.6 Identification of BP Variants by GWAS

Since 2009, a number of large GWAS have been performed that have identified about 60 common genetic variants associated with one or several BP phenotypes (Table 32.1). It is important to emphasize that although the loci are named according to the genes in the vicinity of the most significant genetic variant, there is, with little exception, no direct proof which gene is causally involved in the BP elevation. Figure 32.1 shows the key characteristics of 29 of the variants depicted in Table 32.1 that were discovered by the International Consortium for Blood Pressure GWAS (ICBP) in 2009 and 2011 [10, 25, 26]. The reader can see that the effect size per risk allele is small, on average well below 1 mmHg for SBP. All variants are frequent with an average minor allele frequency of around 30 % in the ICBP experiments (Fig. 32.1).

Even collectively, 29 of the 60 variants described in Table 32.1 only explain 1–2 % of the phenotypic variability when their effect is analyzed together in the form of a genetic risk score [10] and a comprehensive testing of all 60 variants known so far is unlikely to yield very different results. Most of the variants are not in the vicinity of genes that were previously described to be linked to BP or HTN and therefore present potential new avenues to understand BP regulation.

32.7 Making Use of BP Loci Identified

Given the low phenotypic variance explained, genetic risk scores will not be very useful for risk prediction of HTN. But a number of other important uses can be made of collections of BP loci that are summarized here.

32.7.1 Identification of BP Pathways and BP Cell Types and Organ Systems

One important goal of BP genomics is the identification of pathways that can potentially be targeted with small molecules. Such pathway analyses have been attempted by the ICBP [10] and other groups. However, no single clear pathway could be

Table 32.1 Loci identified by blood pressure genome-wide association studies

Locus name	SNP	Chr	Position (hg18)	Phenotype	References
CASZ1	rs880315	1	11 Mb	SBP/DBP	[10]
MTHFR-NPPB	rs2272803	1	12 Mb	SBP/DBP	[10]
ST7L-CAPZA1-MOV10	rs2932538	1	113 Mb	SBP/DBP	[10]
MDM4	rs4245739	1	203 Mb	SBP/DBP	[10]
AGT	rs2004776	1	229 Mb	SBP/DBP/HTN	[10, 38]
KCNK3	rs1275988	2	27 Mb	SBP/DBP	[14, 39]
NCAPH	rs7599598	2	97 Mb	SBP/DBP	[39]
FIGN-GRB14	rs1446468	2	165 Mb	SBP/DBP	[10, 40]
STK39	rs6749447	2	169 Mb	SBP/DBP	[41]
PDE1A	rs16823124	2	183 Mb	DBP/MAP	[42]
HRH1-ATG7	rs2594992	3	11 Mb	SBP/DBP	[10]
ULK4	rs2272007	3	42 Mb	SBP/DBP	[10]
MAP4	rs319690	3	48 Mb	SBP/DBP	[10, 40]
MIR1263	rs16833934	3	165 Mb	DBP	[43]
MECOM	rs6779380	3	171 Mb	SBP/DBP	[10]
CHIC2	rs871606	4	54 Mb	PP	[40]
FGF5	rs1458038	4	81 Mb	SBP/DBP	[10]
SLC39A8	rs13107325	4	103 Mb	SBP/DBP	[10]
ENPEP	rs6825911	4	112 Mb	SBP/DBP	[24]
GUCY1A3-GUCY1B3	rs13139571	4	157 Mb	SBP/DBP	[10]
NPR3-C5orf23	rs12656497	5	33 Mb	SBP/DBP	[10, 24, 44]
EBF1	rs11953630	5	158 Mb	SBP/DBP	[10]
HFE	rs1799945	6	26 Mb	SBP/DBP	[10, 44]
BAT2-BAT5	rs2187668	6	33 Mb	SBP/DBP	[10]
ZNF318-ABCC10	rs6919440	6	43 Mb	SBP/DBP	[39]
RSPO3	rs13209747	6	127 Mb	SBP/DBP	[45]
PLEKHG1	rs17080102	6	151 Mb	SBP/DBP	[45]
EVX1-HOXA	rs17428471	7	27 Mb	SBP/DBP	[45]
CDK6	rs2282978	7	92 Mb	PP	[42]
PIK3CG	rs12705390	7	106 Mb	SBP/DBP/PP	[10, 40]
NOS3	rs3918226	7	150 Mb	DBP	[42, 44]
BLK-GATA4	rs2898290	8	11 Mb	SBP/DBP	[10]
NOV	rs2071518	8	121 Mb	PP	[40]
CACNB2	rs1813353	10	19 Mb	SBP/DBP	[10]
C10orf107	rs7070797	10	63 Mb	SBP/DBP	[10]
VCL	rs4746172	10	76 Mb	DBP, MAP	[42]
PLCE1	rs932764	10	96 Mb	SBP/DBP	[10]
CYP17A1-NT5C2	rs943037	10	105 Mb	SBP/DBP	[10]
ADRB1	rs2782980	10	116 Mb	SBP/DBP/MAP	[10, 40]
LSP1-TNNT3	rs661348	11	2 Mb	SBP/DBP/MAP	[10, 42, 44]
ADM	rs1450271	11	10 Mb	SBP/DBP	[10]
PLEKHA7	rs1156725	11	16 Mb	SBP/DBP/MAP	[10, 44, 45]

(continued)

Table 32.1 (continued)

Locus name	SNP	Chr	Position (hg18)	Phenotype	References
NUCB2	rs757081	11	17 Mb	SBP/PP/MAP	[42]
RELA	rs3741378	11	65 Mb	SBP/MAP	[42]
FLJ32810-TMEM133	rs633185	11	100 Mb	SBP/DBP	[10]
ADAMTS8	rs11222084	11	130 Mb	PP	[40]
HOXC4	rs7297416	12	53 Mb	SBP	[42]
ATP2B1	rs11105354	12	89 Mb	SBP/DBP/HTN	[10, 44]
SH2B3	rs3184504	12	110 Mb	SBP/DBP	[10]
TBX5-TBX3	rs35444	12	114 Mb	SBP/DBP	[10, 24]
FBN1	rs1036477	15	47 Mb	PP	[42]
CYP1A1-ULK3	rs936226	15	73 Mb	SBP/DBP	[10]
FURIN-FES	rs2521501	15	89 Mb	SBP/DBP	[10]
UMOD	rs13333226	16	20 Mb	SBP/DBP	[46]
NFAT5	rs33063	16	68 Mb	PP	[42]
PLCD3	rs7213273	17	41 Mb	SBP/DBP	[10]
GOSR2	rs17608766	17	42 Mb	SBP/DBP	[10]
ZNF652	rs12940887	17	45 Mb	SBP/DBP	[10]
JAG1	rs1327235	20	11 Mb	SBP/DBP	[10]
GNAS-EDN3	rs6026748	20	57 Mb	SBP/DBP	[10]

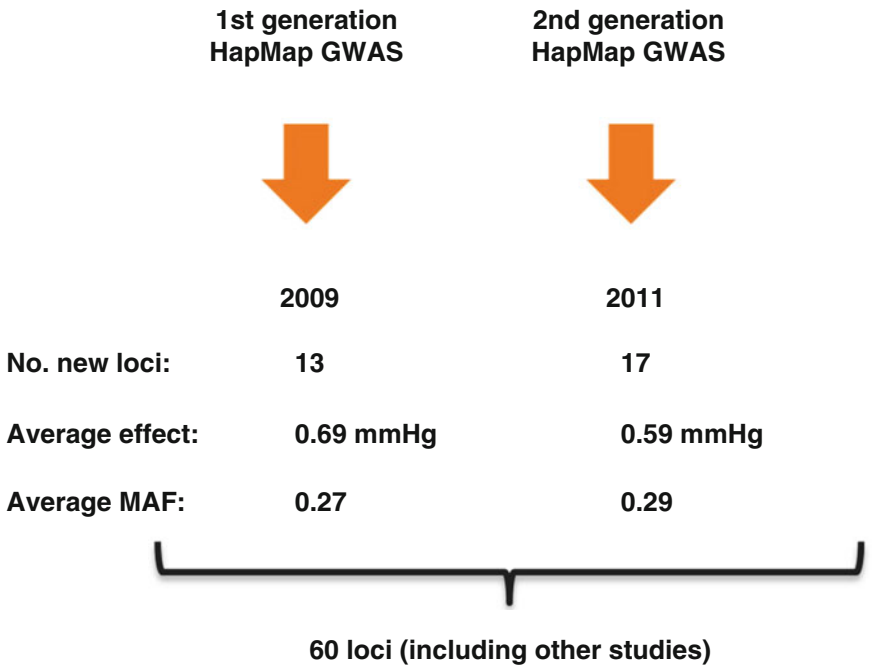

Fig. 32.1 Summary of key characteristics of two generations of large-scale GWAS of the International Consortium for Blood Pressure GWAS (effect sizes indicated for SBP)

identified so far. The difficulty might be due to the limited number of variants identified compared to other phenotypes (e.g., human height or blood lipids [47, 48]).

Another important step to identify BP pathways based on GWAS data is the analysis of eSNPs evidence at the GWAS BP loci, pointing to specific genes likely to be linked to the BP effect [49]. Large eSNP datasets are now available and are being applied to BP GWAS findings.

Another important effort are analyses of individuals of non-European origin and trans-ethnic mapping approaches using data from multiple ethnicities to better delimit a BP association signals and increase yield in discovery [45].

Using data on functional elements in the human genome that have been produced by different consortia (e.g., ENCODE project [50]), experiments can now be conducted to quantify enrichment of functional elements among GWAS findings. No such comprehensive analysis has yet been published, but several efforts are underway and there are interesting preliminary findings on the overrepresentation of DNase hypersensitive sites in microvascular endothelial cells among BP GWAS loci [51]. A diverse array of different experiments can be imagined based on these datasets and one of the beauties is that both the BP GWAS data and the data on the functional elements are publically accessible.

32.7.2 Identification of Directions of Effects in Mendelian Randomization Experiments

SNPs from loci associated with blood pressure levels in large BP GWAS have been tested for their impact on TOD. In participants of European ancestry [10], the International Consortium of Blood Pressure GWAS assessed the impact of a 29-SNP risk score on stroke, coronary artery disease, left ventricular hypertrophy, heart failure, and five measures of kidney function (kidney disease, microalbuminuria, creatinine, estimated GFR, urinary albumin/creatinine ratio). Although the genetic risk score predicted the brain and heart phenotypes with suggestive significance for heart failure, there was no prediction of any of the kidney phenotypes, suggesting potentially a chain of causality that might not be the commonly clinically assumed: subtle changes in kidney function might drive high BP more than high BP damages kidney function. This example shows how improved knowledge and detailed analyses of the impact of the relationships between genetic BP susceptibility and TOD can yield valuable information for improved understanding of pathophysiology.

32.8 Concluding Remarks

Over the last 5 years, primary HTN genomics has experienced a dramatic increase in knowledge, and the rhythm of discovery is still expected to increase. GWAS loci explain only a little of the genetic basis of BP so far, but partial progress has been

made and interesting secondary analyses, such as investigations of the causal relationships between BP and TOD, have already been performed.

The significance of past and future findings will be enhanced by the joint analysis of functional DNA elements and other secondary data. The rare allele spectrum of BP genomics is just now starting to be examined [52], and it is at least not impossible that rare, large effect size variables can be found for BP that might lead to novel therapeutic interventions similar to targeting PCSK9 (proprotein convertase subtilisin/kexin type 9) which promotes degradation of hepatic low-density lipoprotein receptor in dyslipidemia. Such findings might lead to novel therapies, which might improve BP control that is urgently needed.

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Chapter 33
Hypertension and Vascular Endothelial Growth Factors

Marcelo Rizzatti Luizon and Valeria Cristina Sandrim

Abstract The members of vascular endothelial growth factors (VEGF) are the principal regulators of angiogenesis and vascular biology. The specific growth factor of the endothelial cells is VEGF, which produces nitric oxide (NO) from endothelial cells causing vasodilation. VEGF-A, the best characterized and the most biologically active isoform, is critical for endothelial cell survival, inhibits apoptosis, increases vascular permeability, and stimulates vasodilation. VEGF-A is also a positive regulator of tumor growth and metastases. VEGF inhibitors are effective antiangiogenic agents used to treat cancer. However, hypertension is the most reported adverse effect of angiogenesis inhibitors interfering with VEGF signaling. Since VEGF stimulates vasodilation and NO, which plays a critical role in blood pressure control, VEGF may affect blood pressure regulation. Interestingly, a specific combination of polymorphisms in the *VEGF* gene (haplotype) is present more frequently in normotensive than in hypertensive subjects, and the same haplotype is found in subjects with higher plasma nitrite/nitrate levels (circulating markers of NO formation). This supports the hypothesis that impaired NO bioavailability contributes to clinical hypertension. Regarding hypertensive disorders of pregnancy, NO formation is inversely related to the antiangiogenic factors soluble VEGF receptor-1 (sFlt-1) and soluble endoglin levels in patients with preeclampsia, characterized by hypertension and proteinuria. Antihypertensive therapy may produce their effects by enhancing NO bioavailability, thus counteracting the impaired NO formation reported in these hypertensive disorders of pregnancy.

Keywords VEGF • Nitric oxide • Hypertension • Preeclampsia • Endothelial cells • Polymorphisms • Endoglin

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33.1 Introduction

VEGFs are the principal regulators of vascular biology and are critically involved in angiogenesis [1, 2]. Members of the VEGF family regulate vasculogenesis, angiogenesis, and vascular maintenance during embryogenesis and in adults. Because of their profound effects on blood vessels, VEGFs have received much attention regarding their potential therapeutic use in cardiovascular medicine [1].

VEGF was discovered as a tumor-derived soluble factor capable of inducing endothelial cell permeability [3] and angiogenesis [4]. Since that initial discovery, seven members of the VEGF family have been identified: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factors (PlGF) 1 and 2 [5]. The VEGF gene undergoes alternative splicing to form these multiple isoforms [6], and VEGF-A is the best characterized and the most biologically active isoform [7].

The downstream signals of VEGF are mediated by three tyrosine kinase receptors: VEGFR-1 (Flt-1), VEGFR-2 (Flt-1/KDR), and VEGFR-3 (Flt-4) [8]. VEGFR-1 and VEGFR-2 are expressed predominantly in endothelial cells, and their major biological effects are mediated through VEGF-A binding to VEGFR-2 receptors. Specific autophosphorylation of tyrosine residues on the activated receptor acts as docking and activation sites for numerous proteins that associate via their Src homology-2 domain [6, 9].

The binding of the different VEGF family members to these three high-affinity receptors on endothelium and downstream signaling cascades has been reviewed and discussed elsewhere [1, 6].

33.2 VEGF Roles and Signaling Pathways

VEGF binds to VEGFR-2 and initiates a tyrosine kinase signaling cascade that stimulates the production of factors that induce vasodilation, cell proliferation and survival, migration, and differentiation into mature blood vessels [10, 11]. Major signaling pathways include phosphoinositide 3-kinase (PI3K)-Akt/protein kinase B-mammalian target of rapamycin (mTOR) and activation of endothelial nitric oxide synthase (eNOS), leading to downstream release of potent vasodilators, including nitric oxide (NO) and prostacyclin (PGI_2) [12, 13]. VEGF also signals through phopholipase C, Raf-1, and mitogen-activated protein kinase, pathways that regulate endothelial cell survival, proliferation, migration, and permeability [14, 15]. The VEGF-A signal transduction pathway has been recently reviewed elsewhere [6, 16].

VEGF also binds to VEGFR-1. However, the biological function of VEGFR-1 is elusive, despite its wider expression pattern compared to that of VEGFR-2 [17]. VEGFR-1 has a weak kinase activity, but its binding to VEGF is tenfold greater than that of VEGFR-2. Accordingly, it has been suggested that VEGFR-1 is a negative regulator of VEGFR-2 [18]. The extracellular domain of VEGFR-1 exists as a soluble protein, named soluble Flt-1 (sFlt-1). In preeclampsia, a syndrome of pregnancy characterized by hypertension and proteinuria, placental production of soluble Flt-1 is increased [19, 20], where it might act as an endogenous VEGF inhibitor [6] (Chap. 61).

Although VEGF is critical for endothelial cell survival, inhibits apoptosis, increases vascular permeability, and stimulates vasodilation [21], it is a positive regulator of tumor growth and metastases. Increased VEGF expression correlates with tumor invasiveness, vascular density, and metastatic capacity [6].

33.3 VEGF Inhibitors-Induced Hypertension

VEGF inhibitors (VEGFIs) are effective antiangiogenic agents, increasingly being used to treat cancer [6]. This group of drugs includes anti-VEGF monoclonal antibodies (bevacizumab), intracellular VEGF receptor inhibitors (sorafenib, sunitinib, pazopanib), and the small VEGF inactivating molecules (VEGF trap) [22]. Hypertension is the most reported adverse effect of angiogenesis inhibitors interfering with VEGF signaling [23].

Many growth factors control angiogenesis, including VEGF (particularly VEGF-A) and its receptors (especially VEGFR-2), which play a major role via their effects on endothelial cell function [6, 24, 25]. Novel antiangiogenic cancer therapies, particularly agents that block VEGF signaling, have improved outcomes in patients with cancers and are now used as first-line therapies for some tumors [6]. Adverse effects during antiangiogenesis therapy were thought to be minimal, because the major target for VEGFIs, the endothelial cells, is physiologically quiescent. However, it became evident that hypertension was a serious unexpected cardiovascular adverse effect [26, 27].

The magnitude of VEGFI-induced hypertension is significant, with almost every clinical trial of VEGFIs reporting increased blood pressure (BP) as an adverse effect with up to 80 % of patients developing hypertension, often severe (>150/100 mmHg or hypertensive crisis) [6, 22, 28, 29]. Although the exact cause for VEGFI-induced hypertension is not known, inhibition of VEGF in the vasculature directly increases BP because hypertension develops acutely in response to VEGFIs and treatment cessation leads to BP normalization [6, 30]. An increased incidence of VEGFI-induced hypertension is expected due to the increased use of VEGFIs as anticancer therapies. Therefore, there is a need to better understand the mechanisms by which VEGFIs cause hypertension.

33.4 Genetic Markers of VEGF Inhibitors-Induced Hypertension

One widely accepted mechanism of VEGFI-induced hypertension focuses on the role of VEGF-A in NO regulation [31, 32]. NO is a potent vasodilator that plays a critical role in BP control. VEGF-A increases eNOS expression in a time- and concentration-dependent manner [33], and VEGF-A infusion causes rapid NO release and hypotension [34]. Conversely, inhibition of VEGF-A reduces eNOS expression, leading to vasoconstriction and hypertension in animal studies [35].

Several antiangiogenic agents were shown to induce hypertension, including bevacizumab [36, 37], a monoclonal antibody against VEGF-A, a key factor in inducing angiogenesis in tumors [38]. Hypertension is one of the most common side effects of bevacizumab therapy [37]. Since bevacizumab-induced hypertension is frequent, common genetic variation may play a critical role in susceptibility to hypertension. Variation in genes within the VEGF-A pathway has been proposed as potential biomarkers of bevacizumab-induced hypertension, given their importance as modulators of the NO and vasculature tone [37, 39]. Moreover, variation in genes associated to hypertension, such as the gene coding for eNOS (*NOS3*), may increase baseline BP and affect the susceptibility to bevacizumab-induced hypertension [37].

Genetic analyses of bevacizumab-induced hypertension were recently performed and single nucleotide polymorphisms (SNPs) were associated with bevacizumab-induced hypertension (Table 33.1). However, additional studies are warranted before considering the potential role for any of these SNPs in predicting the safety profile of bevacizumab [37]. A critical evaluation of the use of potential predictive biomarkers for bevacizumab has been reviewed elsewhere [38–40].

Table 33.1 SNPs and haplotypes associated with VEGF inhibitors-induced hypertension or elevations in blood pressure, with hypertension and with preeclampsia susceptibility in some candidate gene studies

Phenotype	Gene	SNP	OR	95 % CI	*P* value	Reference
Bevacizumab-induced hypertension	*EGF*	rs4444903	1.57	1.17–2.11	0.0025	[37]
	EGF	rs9992755	1.45	1.08–1.96	0.014	[37]
	WNK1	rs11064560	1.41	1.04–1.92	0.028	[37]
Sunitinib-induced hypertension						
Greater elevation in SBP	*VEGF-A*	A-C-G haplotype[a]	NA	NA	0.014	[42]
Greater elevation in MAP	*VEGF-A*	A-C-G haplotype[a]	NA	NA	0.036	[42]
Grade 3 hypertension	*VEGF-A*	A-C-G haplotype[a]	0.59	0.34–1.03	0.031	[42]
	eNOS	rs2070744	2.62	1.08–6.35	0.045	[42]
Protective effect against hypertension	*VEGF-A*	C-A-G haplotype[b]	NA	NA	0.0001	[50]
Protective effect against hypertension	*VEGF-A*	C-A-G haplotype[b]	0.30	0.08–1.18	0.047	[54]
Protective effect against preeclampsia	*VEGF-A*	C-G-C haplotype[b]	2.82	0.88–9.50	0.0047	[66]

CI confidence interval, *OR* odds ratio, *SNP* single nucleotide polymorphism, *SBP* systolic blood pressure, *MAP* mean arterial blood pressure, *EGF* epidermal growth factor, *WNK* WNK lysine-deficient protein kinase 1, *VEGF-A* vascular endothelial growth factor A, *eNOS* (*NOS3*) nitric oxide synthase 3 (endothelial cell)

[a]A-C-G haplotype: the combination of alleles for the SNPs rs699947 (−2578A>C), rs833061 (−460C>T), and rs2010963 (405C>G)

[b]C-A-G haplotype: the combination of alleles for the SNPs rs699947 (−2578A>C), rs1570360 (−1154G>A), and rs2010963 (−634G>C)

Sunitinib is a molecular tyrosine kinase inhibitor that exhibits potent antiangiogenic and antitumor activity. It is known to inhibit autophosphorylation in several drug targets, including the VEGF receptors [41]. Sunitinib is also associated with an increase in BP in a significant number of patients. Although hypertension induced by drugs targeting the VEGF pathway is usually manageable, a number of patients required dose reductions or even discontinuation of treatment [42].

Activation of VEGFR-2 via PI3K and its downstream serine protein kinase, Akt, stimulates eNOS, leading to the production of NO. Thus, inhibition of VEGF signaling might lead to a decrease in NO bioavailability, resulting in vasoconstriction and a rise in BP [42]. In addition, decreased NO bioavailability disturbs the balance between the vasodilator NO and the vasoconstrictor endothelin-1 (ET-1), favoring ET-1 production and thereby inducing further vasoconstriction and an additional rise in BP [42, 43]. Indeed, plasma ET-1 concentrations were increased in subjects treated with sunitinib [44, 45].

Genetic polymorphisms that are associated with BP regulation may be involved in the differential occurrence of hypertension in different patients (Chap. 32). Pharmacogenetic studies have previously demonstrated that SNPs in genes encoding for metabolizing enzymes, efflux transporters, and drug targets are associated with sunitinib-induced toxicities in patients with cancer [46]. Importantly, polymorphisms in *VEGF-A* and *VEGFR-2* and in the downstream mediators *eNOS* and *ET*-1 may be important factors in BP changes [42].

The predictive value of SNPs and haplotypes (combinations of alleles of SNPs) in *VEGF-A*, *VEGFR-2*, *eNOS*, and *ET-1* was recently evaluated regarding sunitinib-induced hypertension. SNPs in *VEGF-A* and *eNOS* were shown to independently predict rise in BP and/or development of severe hypertension in sunitinib-treated patients (Table 33.1) [42].

33.5 Polymorphisms in the *VEGF-A* Gene and Hypertension

VEGF causes vasodilation and stimulates endogenous NO formation [47–49]. Therefore, it is reasonable to suggest that VEGF affects arterial BP regulation [50].

Plasma nitrite and nitrate (NOx, products of NO oxidation) levels are circulating markers which may reflect endogenous NO formation. Lower VEGF and NOx levels are described in hypertensive patients than in healthy subjects, and these biomarkers correlate positively in healthy subjects, but not in hypertensives [51]. Indeed, NO is a major physiologic vasodilator [52], and impaired NO bioavailability apparently contributes to clinical hypertension [53]. Therefore, it is possible that SNPs in the *VEGF* gene contribute to cardiovascular disease susceptibility, in particular to hypertension [50].

We studied whether SNPs in the *VEGF* gene (C-2578A, G-1154A, and G-634C) and their haplotypes affect the susceptibility to hypertension and assessed plasma NOx levels to study whether these *VEGF* SNPs affect NO formation in hypertensive and normotensive subjects [50]. We found that the “C-A-G” haplotype was more

common in normotensive than in hypertensive subjects, and the same haplotype was more common in subjects with higher than with lower NOx levels (Table 33.1). Therefore, *VEGF* haplotypes may affect hypertension susceptibility, and the haplotype associated with normotension was more common in subjects with increased NO formation, which supports that impaired NO bioavailability contributes to hypertension [50].

Interestingly, the same "C-A-G" haplotype was recently found marginally associated with the group of normotensive subjects when compared to a different group of hypertensive patients [54] (Table 33.1).

33.6 Polymorphisms in the *VEGF-A* Gene and Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy, including gestational hypertension (GH) and preeclampsia (PE), complicate 3–10 % of pregnancies and are major contributors to maternal mortality [55]. PE is characterized by hypertension and proteinuria after 20 weeks of gestation and is associated with maternal and fetal complications [56]. Moreover, women with a history of PE are at increased risk of future cardiovascular disease [57, 58].

The mechanisms responsible for PE are not fully elucidated, but reduced placental perfusion is postulated as an initiating mechanism, which leads to widespread dysfunction of the maternal vascular endothelium and hypertension [59, 60]. One major hypothesis is based on abnormal cytotrophoblast differentiation leading to hypoperfusion of placenta and then hypoxia and release of some soluble factors to the maternal circulation, thereby causing systemic endothelial dysfunction [61, 62].

VEGF is induced by hypoxia as it initiates vasculogenesis in the placenta in coordination with other angiogenic factors [63]. PE is associated with modified cytotrophoblast expression of VEGF family ligands and receptors, and increased expression of sFlt-1, which captures VEGF and prevents its interaction with ligands and downregulates its biological effects [19, 47, 64, 65].

Since abnormalities in VEGF functions are possibly associated with PE, we studied whether SNPs in the *VEGF* gene (C-2578A, G-1154A, and G-634C) and their haplotypes affect the susceptibility to GH and PE [66]. We found that the haplotype "C-G-C" was more common in healthy pregnant than in PE (Table 33.1). Interestingly, this haplotype was associated with higher *VEGF* gene expression [67, 68], suggesting a protective effect for this haplotype against the development of PE [66].

33.7 Antiangiogenic Factors and NO Bioavailability in Preeclampsia

Normal pregnancy is accompanied by increased blood volume and vasodilation, which involves increased NO formation, thus decreasing peripheral vascular resistance [69]. Conversely, deficient NO formation has been implicated in PE [70, 71].

Abnormal cytotrophoblast differentiation leads to hypoperfusion of placenta and then hypoxia and release of soluble factors, including the antiangiogenic factors sFlt-1 and soluble endoglin (sEng) produced in the placenta, which gain access to the maternal circulation and are involved in the pathogenesis of PE [72, 73]. The circulating sFlt-1 captures VEGF and downregulates its biological effects, such as angiogenesis [74] and stimulation of NO synthesis by endothelial cells [47, 75]. Concentrations of sEng are increased in PE. sEng is highly expressed in vascular endothelial cells and may inhibit transforming growth factor (TGF)-β1 signaling in the vasculature [76, 77]. Interestingly, endoglin enhances Smad2 protein levels potentiating TGF-β signaling and leading to an increased eNOS expression in endothelial cells [78].

Since both sFlt-1 and sEng interfere with eNOS activity, we assessed the correlations between these antiangiogenic factors and plasma and whole blood nitrite levels (circulating markers of NO formation) in GH and PE [20]. Nitrite levels are lower in GH and PE patients than in healthy pregnant (both $P<0.05$). As expected, we found higher circulating sFlt-1 and sEng levels in PE than in GH or healthy pregnant (both $P<0.05$) [20]. Therefore, NO formation is inversely related to sFlt-1 and sEng levels in PE [20], which suggests a possible inhibitory effect caused by these antiangiogenic factors produced in the placenta on the endogenous formation of NO in patients with PE. It is possible that therapeutic approaches focusing on upregulating NO bioavailability may be useful targets in patients with gestational disorders of pregnancy [20].

33.8 Antihypertensive Therapy and NO Bioavailability in Preeclampsia

Antihypertensive therapy for PE includes methyldopa, nifedipine, hydralazine, and labetalol, which allow the prolongation of gestation, thereby decreasing fetal and maternal adverse outcomes [79] (Chap. 61). Several calcium channel blockers, including nifedipine, may improve endothelial function and restore NO bioavailability [80, 81]. In addition, hydralazine enhanced cyclic guanosine 3′, 5′ monophosphate levels in PE, thus suggesting that hydralazine produces its effects by activating NO synthesis [82]. Although there is no evidence that methyldopa produces antihypertensive effects by mechanisms involving NO production, it is possible that some drugs used to treat hypertensive disorders of pregnancy produce their effects by enhancing NO bioavailability, thus counteracting the impaired NO formation that has been reported in these hypertensive conditions [19, 20] (Chap. 39).

However, according to the responsiveness criteria presented by our group, 42 % of preeclamptic women do not respond to antihypertensive therapy, and this subgroup of pregnant women is associated with the worst clinical outcomes [83]. These findings suggest the need for the development of new therapies, which may be guided by pharmacogenomic approaches [84]. In addition, they suggest that the use of biomarkers may benefit a subgroup of pregnant women through a more individualized treatment [85].

Pathophysiological mechanisms previously recognized in PE may be further explored in an attempt to identify potential therapeutic targets, and the NO system is a notable example. Endothelial dysfunction is associated with the hypertension and proteinuria in PE, and NO plays an important role in regulating endothelial function [85]. Reduced expression of eNOS consequently results in reduced NO bioavailability, which plays a significant role in the endothelial dysfunction associated with PE [20]. We have shown that haplotypes of the *eNOS* gene are associated with PE [86, 87] and that *eNOS* haplotypes affect the responsiveness to antihypertensive therapy in PE [83]. However, both *eNOS* and other candidate genes have not been totally accepted as causal for PE [85].

These findings highlight the importance of considering the interaction among different candidate genes [84, 85, 88]. We studied the interactions among SNPs in the *eNOS*, *MMP-9* (matrix metalloproteinase-9), and *VEGF* genes in PE and found specific combinations of *MMP-9* and *VEGF* genotypes which may affect susceptibility to PE [89]. We hypothesized that the VEGF effects on angiogenesis and vascular homeostasis may be compromised not only to VEGF binding to the sFlt-1 but also to the degradation of the VEGFR-2 extracellular domain by MMP-9 in PE. Both mechanisms may involve diminished NO bioavailability as a result of impaired eNOS phosphorylation by Akt. Additional studies are required to confirm the hypothesis regarding the molecular mechanisms underlying these interactions [89].

33.9 Concluding Remarks

In this chapter, we covered the principles regarding the VEGFs as the principal regulators of vascular biology and angiogenesis and hypertension as a cardiovascular adverse effect of angiogenesis inhibitors interfering with VEGF signaling used to treat cancer. The mechanism for VEGF inhibitors-induced hypertension focuses on the role of VEGF-A in NO regulation, a potent vasodilator that plays a critical role in blood pressure control. Since VEGF stimulates vasodilation and NO, VEGF may affect blood pressure regulation. Interestingly, a haplotype in the *VEGF* gene is present more frequently in normotensive than in hypertensive subjects, and it is also found in subjects with higher plasma nitrite/nitrate levels (circulating markers of NO formation). This supports that impaired NO bioavailability contributes to clinical hypertension.

Preeclampsia is characterized by hypertension and proteinuria, and NO formation is inversely related to the antiangiogenic factors soluble VEGF receptor-1 (sFlt-1) and soluble endoglin levels in patients with PE. Antihypertensive therapy may produce their effects by enhancing NO bioavailability, thus counteracting the impaired NO formation reported in PE. Further interaction studies among candidate genes coupled with functional studies focused on clarifying the underlying molecular mechanisms may help to identify novel biomarkers of PE. In addition, further studies with focus on the mechanisms linking VEGF and NO bioavailability may reveal potential specific targets for gestational hypertension and PE antihypertensive therapy.

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Chapter 34
Role of Gi Proteins in Hypertension

Yuan Li and Madhu B. Anand-Srivastava

Abstract Guanine nucleotide regulatory proteins (G proteins) regulate a variety of physiological functions such as platelet functions, including platelet aggregation, secretion, and clot formation, and cardiovascular functions, including arterial tone and reactivity through the activation of various signal transduction systems including adenylyl cyclase/cAMP and phospholipase C (PLC)/phosphatidylinositol turnover. Several abnormalities in adenylyl cyclase/cAMP, PLC/PKC, and G proteins have been shown to be responsible for the altered cardiac performance and vascular functions observed in cardiovascular disease states. The enhanced or unaltered levels of inhibitory G proteins (Giα-2 and Giα-3) and mRNA have been reported in different models of hypertension, whereas Gsα levels were shown to be unaltered. These changes in G proteins were associated with functional modulation. The enhanced levels of Giα proteins precede the development of blood pressure, and the attenuation of the development of high blood pressure by inactivation of Giα proteins by intraperitoneal injection of pertussis toxin to prehypertensive spontaneously hypertensive rats suggests that overexpression of Gi proteins may be one of the contributing factors in the pathogenesis of hypertension. The augmented levels of Giα proteins and associated adenylyl cyclase inhibition in hypertension were attributed to the increased circulating levels of vasoactive peptides. In addition, enhanced oxidative stress induced by endogenous vasoactive peptides in hypertension through the transactivation of growth factor receptors and MAP kinase signaling might contribute to the enhanced expression of Giα proteins and hypertensive disease pathology.

Keywords G proteins • Adenylyl cyclase • Vasoactive peptides • Growth factor receptors • Oxidative stress • MAP kinase • Hypertension • Endothelin • Angiotensin II • L-NAME

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34.1 Introduction

Guanine nucleotide regulatory proteins (G proteins) are a family of guanosine triphosphate (GTP)-binding proteins that play a key regulatory role as transducers in a variety of signal transduction systems. G proteins are heterotrimeric proteins composed of three distinct subunits: α, β, and γ subunits [1]. The α-subunits bind and hydrolyse GTP and confer specificity in receptor and effector interactions [1]. The GDP-bound form of α binds tightly to βγ and is inactive, whereas the GTP-bound form of α dissociates from βγ and serves as a regulator of effector proteins. All α-subunits possess intrinsic GTPase activity and hydrolyse the terminal phosphate of bound GTP to yield bound GDP and free inorganic phosphate (Pi). Upon hormone binding and receptor activation, the hormone-receptor complex interacts with the heterotrimeric protein to promote a conformational change and dissociation of bound GDP from the guanine nucleotide binding site. GDP is released and replaced by GTP. Binding of GTP to α subunit induces a conformational change and promotes the dissociation of hormone receptor and the holo G protein into α and βγ subunits. Both α-GDP and βγ subunits can interact with effectors. This activation cycle is terminated by intrinsic GTPase activity of α-subunit. The GDP-bound form of α-subunit has high affinity for βγ and then reassociates with the βγ dimer to form the heterotrimer in the basal resting state. The family of G protein α-subunits can be subclassified according to functional or structural relationship. More than 20 mammalian Gα gene products and several alternatively spliced isoforms have been identified. These can be divided into four major subfamilies according to amino acid homology and are represented by Gsα, Giα, Gqα/α11, and α12/α13. The G proteins Gsα and Giα are implicated in the regulation of adenylyl cyclase/cAMP signal transduction system (Chap. 5).

The hormone-sensitive adenylyl cyclase system is composed of three components: the receptor, the catalytic subunit, and G proteins, stimulatory (Gs) and inhibitory (Gi). Molecular cloning has revealed four different forms of Gsα having molecular weights of 45, 47, and 52 kD, resulting from the different splicing of one gene [2–4]. Gsα is positively coupled to adenylyl cyclase and mediates the stimulatory responses of hormones on adenylyl cyclase [5, 6]. The Gs-mediated activation of adenylyl cyclase results in enhanced formation of cAMP from ATP. The cAMP, thus formed, activates cAMP-dependent protein kinase A that induces the phosphorylation of contractile filaments, sarcolemmal and sarcoplasmic proteins, and regulates intracellular calcium homeostasis [7]. In addition, Gsα activation was also shown to open the Ca^{2+} channels directly by cAMP-independent mechanism [8]. In contrast, Giα protein is associated with adenylyl cyclase inhibition [5, 6]. Three distinct forms of Giα, namely, Giα-1, Giα-2, and Giα3, have been cloned and encoded by three distinct genes [9–11]. All three forms of Giα (Giα-1–3) have been implicated in adenylyl cyclase inhibition [12] and activation of atrial Ach-K^+ channels [13].

Both the Gα and Gβγ dimer mediate G protein signaling. Five different β subunits of 35–36 kDa and 12 γ subunits of 8–10 kDa have been identified by molecular cloning. The βγ dimer is tightly associated with GDP-bound chain and facilitates

interaction of G protein with a receptor molecule. The effectors regulated by Gβγ include K^+ channels, phospholipase C-β, and adenylyl cyclase [14–16]. Like the α-subunit, the γ-subunit is subject to a cascade of posttranscriptional modification including isoprenylation and myristoylation that contributes to βγ membrane association and the interaction of the subunits [17].

G protein α-subunits also possess specific residues that can be covalently modified by bacterial toxins. Cholera toxin catalyzes the transfer of ADP-ribose moiety of NAD to a specific arginine residue in certain α-subunits, whereas pertussis toxin ADP-ribosylates those α-subunits that contain a specific cysteine residue close to the carboxy terminus. Modification of α-subunit by cholera toxin persistently activates Gsα proteins by inhibiting their GTPase activity, whereas pertussis toxin inactivates Giα proteins and thereby results in the uncoupling of the receptor from the effector. G protein α-subunits are regulated by covalent modifications by fatty acids myristate and palmitate. These lipid modifications serve to anchor the subunits to the membrane and increase their interaction with other proteins and also increase the affinity of α subunit for βγ. In this regard, the myristoylation of Giα is required for adenylyl cyclase inhibition in cell-free assay [18].

34.2 G Proteins and Membrane Signaling in Cardiovascular Disease

A number of cardiovascular disease states that eventually result in chronic heart failure are associated with alterations in cardiac performance. Several neurohormonal factors such as catecholamines, angiotensin II, endothelin-1, and alterations in signal transduction mechanisms including adenylyl cyclase and phospholipase C (PLC) play an important role in the alterations of cardiac performance.

34.3 G Proteins and Membrane Signaling in Hypertension

Alterations in G protein levels and functions such as altered adenylyl cyclase responsiveness to various agonists have been demonstrated in cardiovascular and non-cardiovascular tissues from genetic as well as experimental hypertensive rats [19–25].

An overexpression of Giα-2 and Giα-3 proteins as well as their genes was shown in hearts and aortas from spontaneously hypertensive rats (SHRs), deoxycorticosterone acetate (DOCA)-salt hypertensive rats, N-[Omega]-nitro-L-arginine methylester (L-NAME) HRs, and 1 kidney 1 clip (1K1C) HRs [19–21, 23, 25–30]. On the other hand, Gsα protein and its gene were not altered in SHRs, 1K1C, and L-NAME HRs and were decreased in DOCA-salt HRs [20, 21, 23, 24, 27–30]. In addition, the levels of Goα in the heart were also not altered [24]. However, several studies have shown a decreased expression of Giα proteins in different tissues from different

models of HRs including Milan hypertensive rats (MHS) [22, 31–33]. Platelets from SHRs [19] and hypertensive patients [34] exhibited a decreased expression of Giα-2 and Giα-3 protein as compared to Wistar Kyoto (WKY) rats and normotensive control subjects, respectively, whereas the levels of Gsα protein were not altered. On the other hand, McLellan et al. [35] were unable to show any changes in the levels of Gsα, Giα-2, and Gβ in platelets from hypertensive patients as compared to normotensive subjects, whereas Gs-mediated stimulation of adenylyl cyclase by PGE1 was enhanced in hypertensive patients as compared to normotensive subjects. Furthermore, lymphocytes from SHRs [36] and hypertensive patients [37] showed a decreased responsiveness of adenylyl cyclase to stimulatory hormones, which may be attributed to the alterations in Gs and Gi proteins. The potentiation of stimulatory responses of several hormones on adenylyl cyclase has also been demonstrated in platelets and splenocytic membranes from SHRs [38].

Alterations in Gi protein levels have been shown to be reflected in altered responsiveness of adenylyl cyclase to stimulatory and inhibitory hormones in SHRs and experimental models of hypertensive rats [19, 24, 29, 30, 39]. For example, increased expression of Giα proteins was reflected in increased inhibition of adenylyl cyclase by inhibitory hormones and diminished stimulation of adenylyl cyclase by stimulatory hormones, resulting in decreased levels of cAMP [19, 24, 29, 30, 39]. The reduction in the hormone receptor binding sites may be one of the possible mechanisms responsible for such an impaired response of hormones [40–42]. However, the decreased stimulation of adenylyl cyclase by dopamine D-1 receptors in the kidney tubules from SHRs was shown to be attributed to the defective receptor-G protein coupling and not to the changes in the receptor number [43].

On the other hand, decreased expression of Giα proteins in platelets from SHR and hypertensive patients was correlated with decreased adenylyl cyclase inhibition by inhibitory hormones including atrial natriuretic peptide (ANP) and Ang II and augmented stimulations exerted by stimulatory hormones including PGE1, N-ethylcarboxamide adenosine (NECA), and forskolin, resulting in enhanced levels of cAMP [19, 34]. In addition, antihypertensive drug therapy (a combination of β-blocker, Ca^{2+} channel blocker, ACE inhibitor, etc.) to hypertensive patients partially restored the decreased levels of Giα-2 and the enhanced stimulation of adenylyl cyclase by NECA and PGE1 in platelets toward normotensive subjects [34]. These results suggest that the altered responsiveness of platelet adenylyl cyclase to hormones in hypertension and the normalization of the response with antihypertensive drug therapy could partially be due to the ability of the antihypertensive drugs to modulate Giα protein expression. These effects on platelet function may underlie the beneficial effects of antihypertensive agents in some of the complications of hypertension.

Furthermore, the increased levels of Giα were shown to be associated with hypertension and not with hypertrophy, due to the fact that the heart and aorta from L-NAME-induced hypertensive rats, which do not have cardiac hypertrophy, exhibited enhanced levels of Giα-2 and Giα-3 proteins as well as mRNA, whereas the levels of Gsα protein were unaltered [27, 28]. The increased levels of Giα-2 and Giα-3 proteins and their mRNA in the heart and aorta precede the development of blood pressure in SHRs [44] and in DOCA-salt hypertensive rats [45] and suggest

that the enhanced levels of Giα proteins which result in the decreased levels of cAMP may be one of the contributing factors in the pathogenesis of hypertension. This was further supported by the studies showing that the inactivation of Giα protein in prehypertensive rats (2-week-old SHR) by single injection of pertussis toxin (PT) (1.5 μg/100 g body weight) prevented the development of high blood pressure which was associated with PT-induced decreased levels of Giα proteins [46]. Furthermore, Triggle et al. [47] have also shown that treatment of the SHRs (adult) with PT lowered the blood pressure.

34.4 Role of Endogenous Vasoactive Peptides and Growth Factor Receptor Transactivation in the Enhanced Expression of Giα Proteins in Hypertension

The enhanced levels of vasoactive peptides such as angiotensin II (Ang II), endothelin (ET-1), and arginine vasopressin (AVP) as well as growth factors reported in various models of hypertension [48–56] may be responsible for the enhanced expression of Giα proteins in hypertension. In this regard, a role of Ang II in enhanced expression of Giα protein in SHR and 1K1C HR was demonstrated in the studies showing that captopril treatment of the SHR and 1K1C HR decreased the blood pressure and restored the enhanced levels of Giα protein to control levels [29, 57]. Similarly, the increased blood pressure and enhanced expression of Giα proteins in L-NAME HRs were shown to be restored to control levels by losartan [58], suggesting the implication of Ang II in increased levels of Giα proteins and increased blood pressure in L-NAME HRs. These treatments were also shown to restore the diminished stimulation of adenylyl cyclase by stimulatory hormones and enhanced inhibition by inhibitory hormones observed in SHRs, 1K1C, and L-NAME HRs [29, 57, 58]. In addition, infusion of Ang II in rats increased blood pressure accompanied by enhanced levels of Giα proteins [59]. Nitrendipine and fosinopril treatments have also shown similar effects on Gi proteins and functions in hearts from SHRs [60] and further support the implication of Ang II in enhanced levels of Giα protein in SHR.

Furthermore, VSMC from SHR were also shown to exhibit an enhanced expression of Giα proteins which was attributed to the enhanced levels of endogenous Ang II ant AT_1 receptor because the treatment of VSMC from SHR with captopril as well as losartan attenuated the enhanced expression of Giα-2 and Giα-3 proteins to control levels [61, 62]. This was further supported by the fact that the silencing of AT_1 receptor by siRNA attenuated the enhanced expression of Giα proteins in VSMC from SHR [61]. In addition, a role of endogenous endothelin-1 that is increased in hypertension in enhanced expression of Giα proteins in VSMC from SHR was also reported in a study showing that inhibitors of endothelin ET_A and ET_B receptors, BQ123 and BQ788, respectively, restored the enhanced expression of Giα proteins in VSMC from SHR to WKY rat levels [63]. Growth factor receptors have also been shown to contribute to the enhanced expression of Giα proteins in VSMC from SHR, because the inhibitors of growth factor receptors attenuated the augmented expression of Giα proteins to control levels [63].

The activation of AT_1 receptor by Ang II and ET_A/ET_B by ET-1 has also been reported to enhance the activation of growth factor receptors, such as the platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), and the insulin-like growth factor 1 receptor (IGF-1R), in a variety of cell types [64–66], the phenomenon known as transactivation [64] (Chap. 36). We showed that the enhanced phosphorylation of EGFR in VSMC from SHR was attenuated by captopril, losartan, BQ123, and BQ788 to control levels [67], suggesting the transactivation of EGFR by endogenous Ang II and ET-1 in VSMC from SHR. In addition, we showed that the increased levels of endogenous Ang II and ET-1 contributed to the enhanced expression of Giα proteins in VSMC from SHR through the transactivation of growth factor receptor and MAP kinase signaling (Fig. 34.1) [61, 63].

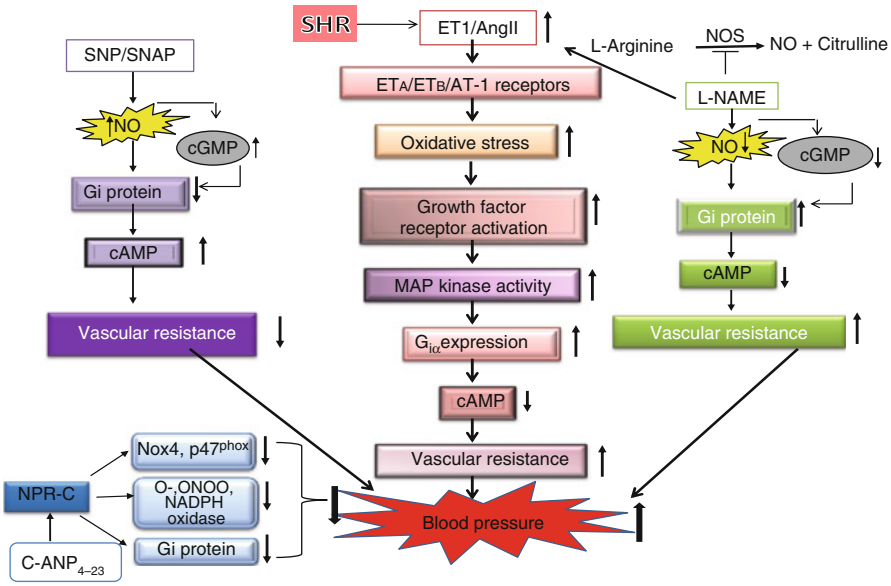

Fig. 34.1 Possible mechanisms involving angiotensin II (*Ang II*), endothelin (*ET*), oxidative stress, and nitric oxide in enhanced expression of Giα protein in hypertension. Giα protein expression is enhanced in genetic (*SHR*) and experimental hypertension including L-NAME-induced hypertension. Inhibition of nitric oxide synthase (*NOS*) by L-NAME activates renin-angiotensin system, decreases the level of NO, and results in increased expression of Giα proteins. ET-1/Ang II increases oxidative stress which through growth factor receptor activation, increases MAP kinase activity, resulting in enhanced expression of Giα proteins leading to hypertension. On the other hand, increased level of NO, generated by NO donors (*SNP*/*SNAP*) and cGMP, decreases the expression of Giα proteins in VSMC which may be an additional mechanism through which NO decreases BP in L-NAME-induced hypertension. In addition, $C\text{-}ANP_{4–23}$ through the activation of NPR-C inhibits the enhanced nitroxidative stress and Giα protein expression, resulting in the attenuation of the development of high BP in SHRs (Adapted from Li and Anand-Srivastava (2014)). *SNP* sodium nitroprusside, *SNAP* S-nitroso-N-acetyl-DL-penicillamine, *SHR* spontaneously hypertensive rats, *L-NAME* Nω-nitro-L-arginine methyl ester hydrochloride, *NPR-C* natriuretic peptide receptor-C, *C-ANP$_{4–23}$* [des(Gln^{18}, Ser^{19}, Glu^{20}, Leu^{21}, Gly^{22})ANP$_{4–23}$-NH2], *NO* nitric oxide, *NOS* nitric oxide synthase, *$ONOO^-$* peroxynitrite

The implication of Giα proteins in the regulation of blood pressure was further demonstrated in our studies showing that nitric oxide (NO) donors S-nitroso-N-acetyl-DL-penicillamine (SNAP) and sodium nitroprusside (SNP) that have been reported to decrease blood pressure [68] also attenuated the expression of Giα proteins and associated functions in VSMC [69]. Additionally, cGMP, a second messenger of NO action, also decreased the levels of Giα proteins and functions in VSMC [70]. These results indicate that the decreased levels of NO in SHR and in L-NAME HRs are responsible for the enhanced expression of Giα proteins. Thus, NO-induced decreased levels of Giα proteins may represent an additional mechanism through which NO decreases blood pressure (Fig. 34.1). Furthermore, C-ANP$_{4–23}$, which specifically interacts with natriuretic peptide receptor-C, has been reported to attenuate the enhanced expression of Giα proteins in A10 VSMC and VSMC from SHR [71, 72]. We showed recently that intraperitoneal injection of C-ANP$_{4–23}$ to prehypertensive SHR attenuated the increased blood pressure through the inhibition of enhanced expression of Giα proteins and enhanced nitroxidative stress [73].

34.5 Role of Oxidative Stress Induced by Endogenous Vasoactive Peptides in the Enhanced Expression of Giα Protein in Hypertension

Increased reactive oxygen species (ROS) cause oxidative stress and contribute to the pathophysiology of cardiovascular diseases such as hypertension and atherosclerosis [74, 75]. The implication of Ang II and ET-1 in increased generation of ROS through the activation of NAPDH oxidase has been reported in different models of hypertensive rats including DOCA-salt HRs [76, 77]. This is evidenced in studies where ET_A receptor antagonist BQ123 attenuated ET-1-induced enhanced production of superoxide anion ($\bullet O_2^-$) in VSMC from hypertensive rats [78] and AT_1 receptor antagonist losartan inhibited the enhanced production of O_2^- anion in VSMC from SHR [62]. In the study of Sedeek et al. [79], ET-1 induced a significant and dose-dependent augmentation of O_2^- in VSMC from ET-1-induced hypertensive rats. In our studies, AT_1, as ET_A and ET_B receptors, has been implicated in enhanced oxidative stress exhibited by VSMC from SHR as evidenced by attenuation of increased production of O_2^- and increased activity of NADPH oxidase by losartan, BQ123 and BQ788 [67]. A role of enhanced oxidative stress in Ang II-induced enhanced levels of Giα proteins has also been reported [80]. In SHR, treatment with antioxidants such as diphenyleneiodonium (DPI) and N-acetyl cysteine (NAC) restored the enhanced levels of Giα proteins, implicating oxidative stress as the causative factor in the enhanced expression of Giα protein in SHR [62]. A similar antagonism to Ang II-induced increased Giα proteins and superoxide anion (O_2^-) by antioxidants in A10 VSMC was reported by us [80]. It is further strengthened by our recent findings that H_2O_2, an oxidant that induces oxidative stress, enhanced the expression of Giα proteins in aortic VSMC [81].

34.6 Role of Map Kinase Cascade in the Enhanced Expression of Giα Proteins in Hypertension

Mitogen-activated protein (MAP) kinase is a serine/threonine-specific kinase that plays an important role in cellular differentiation, growth, and apoptosis and in the regulation of various transcription factors and gene expression [82]. Several studies have demonstrated the implication of Ang II and ET-1 in the modulation of ERK1/2 and physiological responses in different cell types including A10 VSMC [83], cardiomyocytes [84], and fibroblasts [85]. The implication of ERK1/2 in the enhanced expression of Giα-2 and Giα-3 protein in VSMC from SHR has also been reported [62]. Furthermore, the role of endogenous Ang II in enhanced phosphorylation of ERK1/2 and enhanced expression of Giα proteins in VSMC from SHR was shown by the fact that the treatment of VSMC from SHR with captopril and losartan attenuated the hyperphosphorylation of ERK1/2 and enhanced expression of Giα proteins [61]. Furthermore, Iwasaki and collaborators [86] have shown that the ET_A receptor-induced transactivation of EGFR results in the activation of ERK1/2 in aortic VSMC. We have also shown the implication of both ET_A and ET_B receptors in ET-1-induced enhanced ERK1/2 phosphorylation in A10 VSMC and aortic VSMC from SHR, because ET_A and ET_B receptor antagonists, BQ123 and BQ788, respectively, attenuated the ET-1-induced enhanced phosphorylation of ERK1/2 [63, 67]. In addition, we also demonstrated that ET-1-induced increased phosphorylation of ERK1/2 was attributed to transactivation of EGFR, because AG1478, an inhibitor of EGFR, inhibited the ET-1-evoked increased ERK1/2 phosphorylation [63, 67] (Chap. 31). In addition, the enhanced phosphorylation of ERK1/2 in SHR was restored to WKY levels with the treatments of antioxidants [67] and inhibitor of EGFR [63, 67] which suggest that the enhanced oxidative stress and EGFR through MAP kinase signaling may contribute to the enhanced expression of Giα protein in SHR. Taken together, it is suggested that the enhanced levels of endogenous vasoactive peptides, through the transactivation of EGFR, increase the phosphorylation of ERK1/2 in VSMC from SHR, which contributes to the enhanced expression of Giα proteins in SHR (Fig. 34.1).

34.7 Concluding Remarks

Vasoactive peptides including Ang II and ET-1 modulate the expression of Giα proteins that regulate cardiovascular functions, including vascular tone and reactivity and cell proliferation. The levels of Giα proteins and mRNA are increased in the heart and aorta from genetic and experimentally induced hypertensive rats, whereas the levels of Gsα are unaltered in genetic and decreased in experimentally induced hypertensive rats with established cardiac hypertrophy. The increased levels of Giα proteins might contribute to the pathogenesis of hypertension because the enhanced expression of Giα proteins and mRNA precede the development of blood pressure

while inactivation of Giα proteins by PT treatment in prehypertensive SHR prevented the development of high blood pressure. The concentrations of vasoactive peptides, including Ang II and ET-1, and growth factors and ROS are increased in hypertension. The increased levels of endogenous Ang II and ET-1 increase oxidative stress which through the transactivation of growth factor receptors and MAP kinase signaling contribute to the enhanced expression of Giα proteins implicated in the pathogenesis of hypertension. On the other hand, natriuretic peptide C-$ANP_{4–23}$ attenuates the high blood pressure in SHR through the inhibition of enhanced expression of Giα proteins and nitroxidative stress.

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Chapter 35
Sympathetic and Renin–Angiotensin Activity in the Pathophysiology of Hypertension

Adrian Covic and Liviu Segall

Abstract The implication of the sympathetic nervous system (SNS) in the pathogenesis of essential hypertension has been suggested a long time ago, considering the major role played by this system in blood pressure (BP) regulation. Studies based on both global (e.g., plasma norepinephrine) and regional (norepinephrine spillover and microneurography) assessments of sympathetic activity have demonstrated that neurogenic mechanisms may be involved in up to 50 % of all cases of essential hypertension. In addition, renal sympathetic denervation has been shown to induce significant and persistent decreases in BP. Moreover, there is evidence that sympathetic hyperactivity may contribute directly to target-organ damage, including cardiac hypertrophy, vascular remodeling, and renal dysfunction. The specific causes of sympathetic activation in essential hypertension are not entirely known, but genetic factors, high dietary salt intake, as well as several metabolic and neurohumoral abnormalities have been involved. In patients with obesity- and metabolic syndrome-associated hypertension, SNS overactivity may result from many factors, including hyperinsulinemia, hyperleptinemia, hypoadiponectinemia, hypoghrelinemia, and RAAS activation.

The renin–angiotensin system (RAS) is another key regulator of BP and fluid homeostasis. Ang II induces BP elevation by vasoconstriction of renal and systemic arterioles, stimulation of renal tubular sodium reabsorption, and release of aldosterone from the adrenal glands. Moreover, both Ang II (via AT_1 receptors) and aldosterone exert proinflammatory, profibrotic, and prooxidant effects on the cardiovascular system, contributing to myocardial hypertrophy and fibrosis, vascular remodeling and calcification, cerebrovascular damage, and renal glomerular and tubulointerstitial injury. In contrast, other components of the RAS, including mainly the AT_2 receptors and the ACE2/Ang-(1–7)/Mas axis, counteract most of the negative cardiovascular effects of the Ang II/AT_1/aldosterone system and might play a compensatory role in hypertension.

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Keywords Blood pressure • Hypertension • Sympathetic nervous system • Renin–angiotensin system • Target-organ damage • Angiotensin II • Aldosterone • Insulin resistance • Salt intake • Genetic factors • Ang-(1–7)/Mas axis • Aldosterone

35.1 Introduction

The implication of the sympathetic nervous system (SNS) and the renin–angiotensin system (RAS) in the pathogenesis of arterial hypertension has been assumed for a long time, since the earliest discoveries regarding the vasopressor effects of these systems.

Studies performed in the nineteenth century by physiologists such as Stelling, Bernard, Waller, and Brown-Sequard showed that stimulation of sympathetic nerves induces tachycardia, vasoconstriction, decreased urinary flow rate, and blood pressure (BP) elevation [1]. Pheochromocytoma, a catecholamine-secreting tumor of the adrenal gland, initially described by Frankel in 1886, was the first known cause of curable hypertension [2]. In the 1920s, surgical sympathectomy was introduced in the treatment of severe hypertension, with remarkable BP-lowering results and survival benefits. Partial or total adrenalectomies, sometimes in combination with sympathectomy, were also performed in selected hypertensive patients, in the 1950s [2]. Such procedures were subsequently abandoned, because of substantial operative risks and side effects; however, they led to the development of "chemical sympathectomy," using ganglionic blockers – the first truly efficient antihypertensive drug class [1]. Other sympatholytic drugs quickly followed, including reserpine, guanethidine, α-methyldopa, and β-blockers, which demonstrated clear therapeutic benefits, thus confirming the implication of the SNS in hypertension. In the late 1930s and 1940s, based on experimental studies, Selye speculated that "stress"-induced release of adrenal hormones might play a role in high BP. In 1949, Page elaborated the "mosaic theory" of hypertension, in which neural factors were included as important contributors [2].

The story of the renin–angiotensin system (RAS) begins in 1898, when Tigerstedt and Bergman discovered that the injection of a crude extract of rabbit kidneys into other rabbits raised the BP. They named the pressor substance in the kidney extract "renin." In 1932, Goldblatt et al. showed that unilateral renal artery clamping produced hypertension in dogs, which could be reversed either by removal of the clamp or by unilateral nephrectomy. It was later determined that this hypertension was caused by renin release from the ischemic kidney [2]. The identification of angiotensin, as the effector, BP-increasing substance, and of angiotensinogen, as the renin substrate, soon followed, leading to the concept of "RAS" [3]. In 1972, Brunner et al. observed that hypertensive patients have variable levels of plasma renin activity, reflecting the existence of two main pathophysiological mechanisms of hypertension: volume-dependent (low plasma renin) and renin-dependent (high plasma renin). They further suggested that patients in the first group should preferably be treated with diuretics or calcium channel blockers,

while those in the second group should rather receive RAS inhibitors [2]. In the following decades, a huge array of RAS antagonists were developed, especially ACE inhibitors and angiotensin II receptor blockers, which demonstrated significant benefits in many clinical trials and are widely used today in the treatment of hypertension (Chap. 36).

This chapter will focus on the most recent experimental and clinical evidence for the implication of SNS and the RAS in the pathophysiology of essential hypertension. We will review the current knowledge concerning the role of these two systems in BP regulation; the causes and mechanisms of their overactivation in hypertension; their complex interactions with each other, as well as with other neural and endocrine systems involved in the pathogenesis of hypertension; and their implication in hypertensive target-organ damage. We will refer only briefly to SNS- and RAS-inhibiting drugs, which are extensively discussed in Chaps. 36 and 39 of this book.

35.2 The Role of the Sympathetic Nervous System (SNS) in BP Regulation

Blood pressure (BP) is a function of vascular resistance and cardiac output. Cardiac output depends on three factors: end-diastolic volume, myocardial contractility, and heart rate. Myocardial contractility and heart rate are regulated by both the sympathetic and parasympathetic systems. End-diastolic volume is determined by venous pressure, which is related to blood volume and venous smooth muscle tone, both of which are under sympathetic control [4]. At kidney level, sympathetic stimulation causes vasoconstriction, renin secretion, and sodium and water reabsorption [5].

The primary cardiovascular role of the SNS is the short-term regulation of BP, via the arterial baroreflex. Vessel wall stretchings caused by acute elevations in BP are sensed by baroreceptors in the carotid sinus and the aortic arch [6]. Afferent signals from these baroreceptors are sent to the nucleus of the solitary tract (nucleus tractus solitarius, NTS) and subsequently to the caudal ventrolateral medulla (CVLM) and the rostral ventrolateral medulla (RVLM). The RVLM provides efferent output to the preganglionic neurons in the spinal cord, which control sympathetic outflow to the heart and blood vessels. Vasomotor sympathetic tone is also influenced by the paraventricular nucleus of the hypothalamus (PVN), via direct connections with the NTS, RVLM, and spinal cord (see Fig. 35.1) [7]. The increase in afferent input induces a reflex decrease in sympathetic discharge, which in turn decreases vasoconstrictor tone, myocardial contractility, and heart rate, whereas during an acute decrease in BP, the opposite occurs and the SNS enhances vasoconstriction, stroke volume, and heart rate [6]. The arterial baroreflex responds to the normal small variations in BP associated with the respiratory cycle and with changes in posture. Arterial baroreceptors work in conjunction with cardiopulmonary baroreceptors, which are located in the walls of the atria and the ventricles and react to changes in blood volume [6].

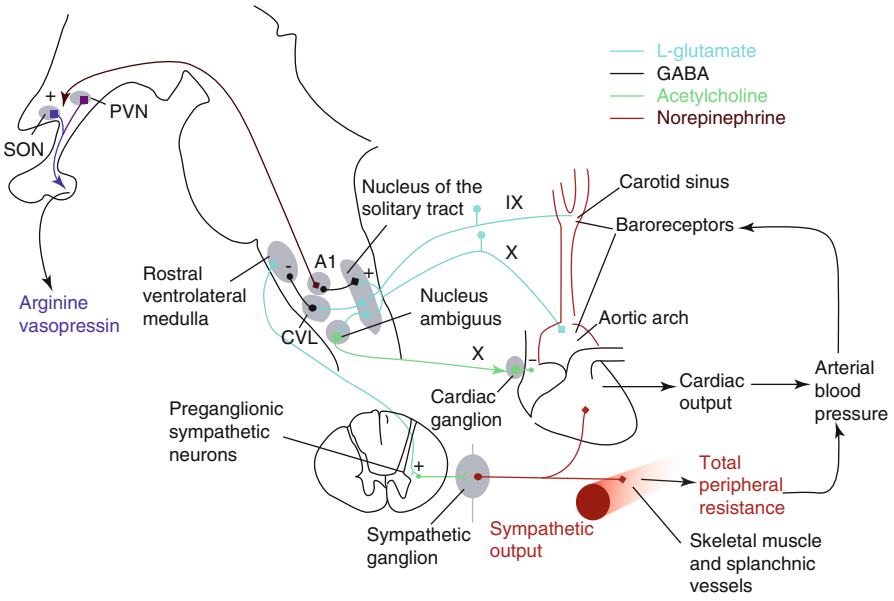

Fig. 35.1 Baroreflex circuit. The arterial baroreceptors are mechanoreceptors located in the carotid sinuses (innervated by the glossopharyngeal nerve, IX) and aortic arch (innervated by the vagus nerve, X) that respond to stretch elicited by increase in arterial pressure. Primary baroreceptor afferents provide monosynaptic excitatory input to the nucleus of the solitary tract (NTS). Barosensitive NTS neurons initiate a sympathoinhibitory pathway that involves a projection from the NTS to interneurons in the caudal ventrolateral medulla (*CVL*) that send an inhibitory projection to sympathoexcitatory neurons located in the rostral ventrolateral medulla. The baroreflex-cardioinhibitory pathway involves a direct input from the NTS to a group of vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguus (NA). These neurons project to the cardiac ganglion neurons that elicit bradycardia. The baroreflex, via the NTS, also inhibits secretion of arginine vasopressin by magnocellular neurons of the supraoptic (*SON*) and paraventricular (*PVN*) nuclei of the hypothalamus, in part by inhibiting noradrenergic cells of the A1 group (Reproduced with permission from Benarroch [7])

More recently, the implication of the SNS in the long-term regulation of BP has also been recognized [8]. A crucial role in this regard seems to be played by the lamina terminalis of the third ventricle of the hypothalamus. This structure is able to sense plasma concentrations of several hormones involved in the regulation of BP and volume, such as angiotensin II (Ang II). The information is integrated and transmitted to the PVH, which sends excitatory stimuli to the sympathetic neurons in the RVLM [7].

35.3 Evidence of Increased SNS Activity in Patients with Essential Hypertension

Early evidence for the role of SNS in the pathogenesis of essential hypertension came from observations in hypertensive individuals exhibiting signs of hyperkinetic circulation and/or high levels of plasma norepinephrine (NE) or urinary adrenergic metabolites [9].

Substantial progress in the understanding of mechanisms of neural hypertension has been made after the introduction of sophisticated techniques for measuring organ-specific sympathetic activity, such as regional NE spillover and microneurography. The regional NE spillover measurement provides information about the activity of sympathetic nerves in organs such as the heart and the kidney. The procedure requires infusion of labeled NE and blood sampling from the coronary sinus (for cardiac NE spillover) or the renal vein (for renal NE spillover) [6]. Microneurography involves the percutaneous insertion of a high-impedance microelectrode, enabling the recording of sympathetic nerve discharges to skin and skeletal muscle vasculature. In humans, the most common measurement is muscle sympathetic neural activity (MSNA), performed at the peroneal nerve [6].

Interestingly, in healthy young persons of both sexes, no relation was found between MSNA and BP. In young men this is explained by the fact that the level of resting MSNA is inversely correlated with cardiac output and vascular reactivity (i.e., higher MSNA is balanced by lower cardiac output and diminished vascular responsiveness to NE). In young women these relationships are absent, but other compensatory mechanisms (including the vasodilator effect of estrogens) may be involved [8]. In contrast, in people older than 40 years, resting levels of MSNA are strongly correlated with resting BP, suggesting that the balance between MSNA and cardiovascular functions is no longer preserved in older persons. In addition, MSNA increases with age and this may further contribute to the increase in the risk of hypertension associated with aging [6].

Studies using both global and regional assessments of SNS activity have shown that sympathetic hyperactivity can be detected in many patients with essential hypertension, including borderline, mild-to-moderate, and severe hypertension, in young, middle-age, and elderly patients, in isolated systolic hypertension and combined systolic-diastolic hypertension, as well as in white-coat and masked hypertension [9]. It is currently estimated that a neurogenic pathogenesis is involved in up to 50 % of all cases of essential hypertension [10]; this estimate is based on both the proportion of untreated patients with essential hypertension who have evidence of sympathetic hyperactivity and the number in whom significant BP lowering is achieved with sympatholytic drugs [11].

Interestingly, it has been observed that the adrenergic overdrive in hypertension parallels the increase in BP, suggesting a cause-effect relationship. In addition, for a similar level of BP, MSNA appears to be more elevated in patients with refractory hypertension than in those who respond well to antihypertensive drug therapy [12].

Important evidence for the involvement of SNS in the pathogenesis of hypertension has been provided by studies with sympatholytic drugs including β-blockers and central α2 receptor agonists (like clonidine and moxonidine), which have long been confirmed as effective antihypertensive therapies (Chap. 39). Furthermore, sympathetic denervation procedures (particularly, renal denervation) have also demonstrated high efficacy in decreasing both sympathetic activity and BP in patients with essential hypertension. Surgical procedures, such as total thoracic sympathectomy, splanchnicectomy, and celiac ganglionectomy, were used several decades ago in the treatment of hypertension, especially in resistant cases, and have resulted in significant lowering of BP, target-organ protection, and increased survival in many patients; however, these surgical methods have been abandoned, because of their invasiveness and high rate of adverse events and mortality [13]. Instead, renal sympathetic denervation has gained

increasing popularity in the past 15 years for the treatment of resistant hypertension, due to its proven efficacy and tolerability (Chap. 42). Renal denervation is a percutaneous, minimally invasive procedure, which consists of delivering radiofrequency energy to the renal artery wall from within the vascular lumen. This results in a thermal injury to the renal sympathetic nerves that lie within and next to the renal artery wall [5]. Data collected in different animal models of experimental hypertension (including spontaneously hypertensive rats, stroke-prone rats, Dahl rats, DOCA-salt-induced hypertension, Goldblatt rats, and Ang II- or overfeeding-induced hypertensive rabbits and dogs) have convincingly documented that renal denervation may prevent the development or slow down the progression of hypertension [13]. In hypertensive humans, renal denervation markedly decreases whole-body NE spillover, renal NE spillover, and MSNA [14]. More importantly, clinical trials including the Symplicity Hypertension (HTN)-1 (with extended follow-up) [15] and the Symplicity HTN-2 studies [16] have demonstrated that after renal denervation systolic BP decreases by 20–30 mmHg on average, and this reduction in BP is long lasting, persisting for more than 3 years of follow-up [11]. In addition, other studies have shown that renal denervation significantly decreases left ventricular hypertrophy, improves systolic and diastolic functions, and reduces arterial stiffness, the incidence of proteinuria, and insulin resistance [17]. However, the very recent Symplicity HTN-3 trial, in which 535 patients were randomized single blind to denervation group versus sham-procedure group, did not show a significant reduction of 24-h ambulatory systolic BP [18].

35.4 SNS Hyperactivity and Target-Organ Damage

Sympathetic activation was shown to be more pronounced in hypertensive patients with target-organ damage than in those with uncomplicated hypertension. Thus, sympathetic nerve activity is higher in the presence of renal impairment and appears to increase as renal function worsens. Sympathetic drive is also higher in patients with hypertension complicated with left ventricular hypertrophy, diastolic dysfunction, heart failure, and ventricular arrhythmias [12] (Chap. 5).

The role of the SNS in the development of cardiac hypertrophy has been demonstrated by numerous studies in both animals and humans. In virtually all experimental models, the increase in ventricular wall thickness is associated with increased sympathetic cardiac drive. Chronic systemic infusion of NE induces ventricular hypertrophy, whereas both α-blockade and sympathectomy can reduce the fibrosis associated with myocardial hypertrophy [19].

A few experimental and human studies have shown that vascular remodeling and renal damage in hypertension may also be mediated by the SNS. For example, NE and epinephrine stimulate proliferation of vascular smooth muscle cells (VSMCs) in cultures. In rabbits, carotid artery wall thickness is reduced after local denervation, while in rats, carotid artery distensibility increases after chemical sympathectomy. In humans, sympathetic activity is correlated with BP variability, which is an independent cardiovascular risk factor [12].

35.5 Causes and Mechanisms of SNS Hyperactivity in Hypertension

The specific causes of the increased sympathetic activity in essential hypertension are only partially known. Genetic influences, high salt intake, as well as several metabolic and neurohumoral abnormalities appear to be involved.

35.5.1 Genetic Factors

Spontaneously hypertensive rats exhibit an increased renal SNS activity even before the onset of hypertension [20].

In humans, baroreceptor dysfunction [14] and abnormal increases in plasma NE and whole-body NE spillover have been demonstrated in normotensive individuals with a family history of hypertension [12]. In microneurography studies including normotensive controls, both the number and amplitude of muscular sympathetic bursts were shown to be higher in individuals with a family history of hypertension [14], as well as in those with white-coat [21] and masked hypertension [22]. During mental stress, SNS activity and BP increase in normotensive offspring of patients with essential hypertension, but not in those with normotensive parents [10].

Genetic polymorphisms concerning several genes have been found to be associated with a high prevalence of SNS overactivity and hypertension, including the genes of neuropeptide Y receptor, renalase (amine oxidase that specifically degrades circulating catecholamines), and catestatin (a product of adrenergic neurotransmitter chromogranin A) [23]. Also see Chap. 32.

35.5.2 High Salt Intake

In salt-sensitive hypertensive rats, salt loading increases renal sympathetic activity, which, in turn, may contribute to BP elevation [24]. In deoxycorticosterone acetate (DOCA)-treated rats, salt loading-induced sympathetic stimulation indirectly activates the thiazide-sensitive Na^+/Cl^- cotransporter (NCC), whereas renal sympathetic denervation leads to the normalization of both NCC activity and BP. The infusion of NE in mice also upregulates NCC, leading to salt-induced hypertension, while treatment with β-blocker propranolol reverses these changes [25]. On a high-salt diet, hypertensive patients with salt-sensitive hypertension have higher plasma NE levels than salt-resistant individuals [25]. Hypertensive humans and animals also develop slightly higher Na^+ concentrations in plasma and cerebrospinal fluid after exposure to high-salt diet. It has been suggested that these high Na^+ concentrations activate osmoreceptors in the hypothalamic lamina terminalis, which subsequently induces SNS activation. These osmoreceptors are not downregulated by

prolonged osmolality changes and thus are able to maintain chronic sympathetic stimulation [10]. Surprisingly, however, in patients with established hypertension, dietary salt restriction can actually lead to an augmentation rather than a decrease of sympathetic activity, as measured by microneurography [12].

35.5.3 Baroreceptor and Chemoreceptor Dysfunctions

In essential hypertension, the function of arterial baroreceptors is altered, exhibiting a decrease in the vagal drive to the heart. In contrast, the sympathetic baroreflex modulation appears to be preserved, although it is reset to a higher level [13]. However, an increased sympathetic drive may result from a reduction in the inhibitory influence of cardiac stretch receptors, in the presence of left ventricular hypertrophy and diastolic dysfunction [12]. Another mechanism that can lead to sympathetic hyperactivation is the impairment of arterial chemoreceptors. Studies based on microneurography have found an exaggerated hypoxia-triggered sympathetic response in patients with hypertension, particularly in those with sleep apnea [12], while deactivation of chemoreceptors with hyperoxia resulted in reductions of MSNA [26].

35.5.4 Obesity and the Metabolic Syndrome

Several studies have shown that chronic SNS activation is particularly increased in patients with obesity- and metabolic syndrome-related hypertension [11]. Central (visceral) obesity is associated with a higher sympathetic activity than subcutaneous obesity [27]. Although there has been a debate as to whether sympathetic activation is a cause or a consequence of obesity, most studies support the view that obesity leads to sympathetic activation [17], which is presumably a compensatory mechanism, aiming to increase energy expenditure [28].

In rabbits, body weight, BP, heart rate, and renal sympathetic nerve activity (RSNA) increased after 1 week of high-fat diet feeding [29]. Similarly, high-fat diets in rats produced an increase in body fat mass, associated with an increase in lumbar sympathetic nerve activity, which became significant by day 12 [30]. Obese dogs receiving a high-fat diet developed sodium retention and hypertension, whereas renal denervation prevented both, indicating that renal nerves have a critical role in obesity-related hypertension [31].

In human obesity, sympathetic overdrive is detectable before hypertension occurs. High levels of circulating catecholamines, MSNA, and kidney NE spillover have been observed in normotensive obese individuals [27]. In one study, MSNA was found to be approximately 40 % higher in obese than in lean normotensive subjects [31]. When obesity and hypertension are both present in the same patient, the degree of sympathetic activation is much greater than in those with either

condition separately [27]. On the other hand, weight loss during hypocaloric diet significantly reduces MSNA and whole-body NE spillover rate in obese subjects [32]. In patients with metabolic syndrome, dietary weight loss decreases sympathetic nerve firing and improves hemodynamic and metabolic parameters [33].

However, the activation of the SNS in obesity is not homogeneous. In fact, SNS outflow to the skeletal muscle vasculature and the kidneys is elevated, whereas activation to the heart is reduced, and activation to the skin and splanchnic regions remains unchanged [34]. It is thought that renal sympathetic nerves mediate most, if not all, of the chronic effects of SNS activation on BP in obesity [27]. Several potential factors have been proposed to contribute to increased SNS activity in obesity, including hyperinsulinemia/insulin resistance, hyperleptinemia, hypoadiponectinemia, hypoghrelinemia, increased Ang II levels, obstructive sleep apnea, oxidative stress, inflammation, and baroreceptor dysfunction.

35.5.4.1 Insulin Resistance and Hyperinsulinemia

Insulin resistance is due to the failure of glucose transporter-4 (GLUT-4) to uptake blood glucose into peripheral tissues, especially skeletal muscle; consequently, blood glucose levels remain elevated and continue to trigger insulin release, leading to hyperinsulinemia [34].

In animal studies, intracerebral administration of insulin increases sympathetic outflow, by stimulating the arcuate nucleus, via the PVN [35]. Hyperinsulinemia induces sympathetic activation in normal individuals [31]. Insulin secretion following a meal or during a hyperinsulinemic–euglycemic clamp determines an increase in MSNA and enhances the arterial baroreflex gain of sympathetic activity [27].

However, other studies did not confirm the influence of hyperinsulinemia on sympathetic overactivity and hypertension. For example, the BP does not rise in dogs or in humans treated with insulin [36]. Although acute CNS injection of insulin in rodents may raise RSNA, chronic CNS infusion of insulin does not alter the BP or heart rate [37]. Patients with insulin-resistant metabolic syndrome show blunted sympathetic responses to increased plasma insulin following a glucose load [38]. Finally, patients with insulinoma, in whom fasting insulin levels are four- to fivefold higher than normal, do not exhibit increased SNS activity or elevated BP [39].

35.5.4.2 Hyperleptinemia

Leptin is a protein secreted by adipocytes, in direct relation with fat mass. Leptin acts on multiple CNS centers, especially in the hypothalamus, to inhibit appetite and increase thermogenesis. Thus, leptin's function is to maintain adipose tissue mass stability through a negative feedback mechanism [40].

Leptin also contributes to the regulation of BP, through its ability to stimulate SNS centers in the hypothalamic arcuate nucleus and the NTS [27]. Transgenic mice that overexpress leptin have elevated BP compared with normal controls

[41]. In rats, leptin administration was shown to increase sympathetic outflow to the kidneys, adrenal glands, and limbs. Chronic increases in systemic or CNS leptin concentrations induce BP elevation in rodents, which can be prevented by adrenergic receptor blockade [31]. Diet-induced obesity in mice is associated with hyperleptinemia and elevated SNS activity and BP [42]. In humans, plasma leptin concentration positively correlates with RSNA, as well as with the development of hypertension [43]. Several epidemiological studies have shown positive correlations between circulating leptin and BP levels, independent of obesity [31].

In obese animals and patients, although resistance to the anorexigenic action of leptin has been clearly documented, leptin's sympathetic effects are preserved [44]. Thus, despite failing to regulate food intake and body weight, leptin appears to have a significant role in the development of hypertension in obesity [42].

35.5.4.3 Hypoadiponectinemia

Adiponectin is a cytokine synthesized by adipose tissue, which regulates lipid and glucose metabolism. High levels of adiponectin improve insulin resistance, dyslipidemia, and atherosclerosis [31].

Adiponectin also reduces efferent sympathetic nerve traffic to the kidney and decreases BP in rodents. Higher circulating adiponectin levels are associated with lower BP in humans. On the other hand, metabolic syndrome and hypertension are associated with low adiponectin levels. Furthermore, subjects with hypoadiponectinemia exhibit cardiac sympathetic overactivity. Taken together, these findings suggest that low adiponectin may play a role in the pathogenesis of obesity-associated hypertension [31].

35.5.4.4 Hypoghrelinemia

Ghrelin is a peptide produced by the stomach, which rises during fasting and appears to play a key role in triggering hunger. In addition, acute ghrelin infusion into the CNS of rodents reduces SNS activity and counteracts the stimulatory effects of leptin. Ghrelin levels are reduced in obesity, perhaps as a compensation for excess energy intake [40]. Thus, it seems plausible that the low ghrelin concentrations observed in obesity could contribute to hypertension.

35.5.4.5 Angiotensin II

Increased Ang II levels in obesity have also been suggested to cause SNS activation. In two studies in rabbits, Ang II treatment produced a modest rise in BP but a marked increase in RSNA [45]. Ang II-induced oxidative stress in the RVLM was shown to induce sympathoexcitation in rats with obesity-related hypertension [28]. Hilzendeger et al. showed that the intracerebroventricular administration of losartan,

an Ang II receptor blocker, inhibited leptin-mediated increases in RSNA, suggesting that Ang II may also facilitate sympathetic activation by leptin [46]. Acute Ang II infusion in normotensive humans raises MSNA, while renin–angiotensin system inhibition reduces it [28]. In a study by Grassi et al., the blockade of Ang II for 3 months in patients with metabolic syndrome decreased MSNA by 21 % [47].

35.5.4.6 Obstructive Sleep Apnea

In patients with obstructive sleep apnea (OSA), MSNA is increased, even during the awake state. Patients with OSA are often obese, and MSNA is higher in obese persons with OSA than in those without OSA. Sympathetic activation associated with OSA is due to chemoreflex mechanisms stimulated by hypoxia and hypercapnia, as well as to altered baroreflex responsiveness. This sympathetic activation, along with other mechanisms, contributes to the increased risk of hypertension and cardiovascular disease seen in these patients [6]. OSA can be complicated by pulmonary hypertension, which has also been associated with increased MSNA [48]. Nevertheless, sympathetic hyperactivation in patients with OSA can be partially or completely reversed by long-term continuous positive airway pressure therapy [6].

35.6 The Renin–Angiotensin System in BP Regulation

The renin–angiotensin system (RAS) is a key regulator of BP and fluid homeostasis. Hyperactivation of the RAS plays a central role in the pathogenesis of several forms of secondary hypertension, such as renin-secreting tumors, renal artery stenosis, and renal microvascular diseases. In addition, there is evidence that RAS is involved in essential hypertension, as well as in vascular, cardiac, and renal damage associated with hypertension and other disorders [49].

The RAS cascade begins with the synthesis of renin by the juxtaglomerular (JG) cells in the kidney. The release of renin into the circulation depends on four mechanisms: (1) a renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pressure, (2) changes in the delivery of NaCl to the macula densa cells of the distal tubule (which lie close to the JG cells and, together, form the "JG apparatus"), (3) sympathetic nerve stimulation via β-1 adrenergic receptors, and (4) negative feedback by a direct action of angiotensin II (Ang II) on the JG cells. Renin secretion is stimulated by a decrease in perfusion pressure or in NaCl distal tubule delivery and by an increase in sympathetic activity [49].

Renin controls the initial, rate-limiting step of the RAS by cleaving the N-terminal portion of angiotensinogen, a high-molecular-weight globulin, mainly secreted by the liver, to form the biologically inactive decapeptide Ang I or Ang-(1–10). Ang I is further hydrolyzed by the angiotensin-converting enzyme (ACE), which removes the C-terminal dipeptide to form the octapeptide Ang II [Ang-(1–8)], the active effector of the RAS (Chap. 36). ACE is a membrane-bound carboxypeptidase,

located on various cell types, including vascular endothelial cells (ECs), brush border epithelial cells, and neuroepithelial cells [49].

Ang II acts on many tissues and organs, including blood vessels, kidney, heart, and brain, through binding and activation of receptors, which belong to the large family of G protein-coupled (GPCR) or 7 transmembrane (7TM) spanning receptors. At least four angiotensin receptor subtypes have been described (AT_1R to AT_4R) [49].

A summary of the RAS, including the Ang peptide family and physiological effects mediated via ATR subtypes, is presented in Fig. 35.2 [50].

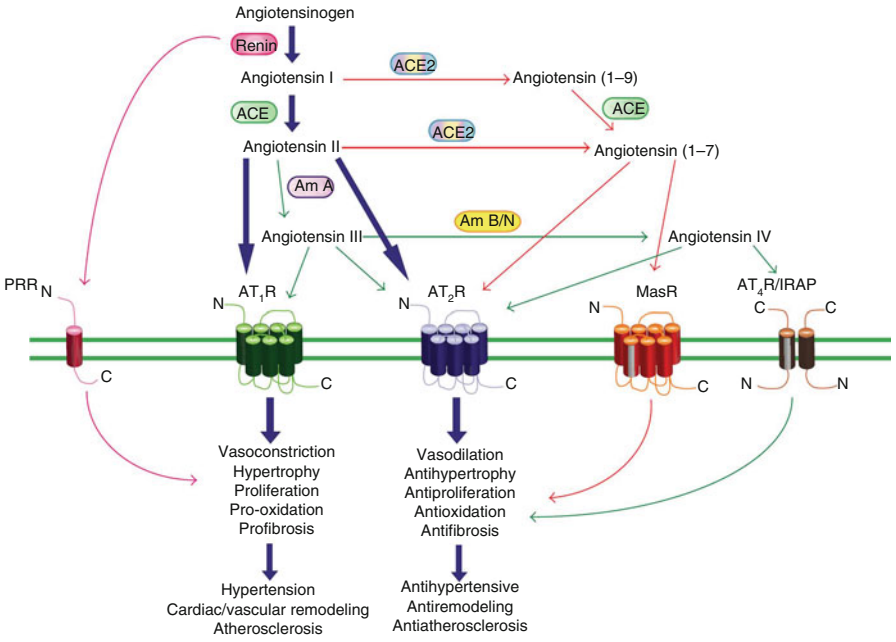

Fig. 35.2 Summary of the RAS incorporating the Ang peptide family and physiological effects mediated via ATR subtypes. Under the classical RAS schema, Ang II is produced, via renin and ACE, to act with equal affinity on two ATR subtypes, AT_1R and AT_2R (*large arrows*). However, it is now appreciated that a number of breakdown products of Ang II, namely, Ang (1–7), Ang III, and Ang IV, exert their own unique effects that are distinct (and often opposite) to those of Ang II. Such effects are often mediated via newly recognized receptors such as MasR for Ang (1–7) and AT_4R (also known as IRAP) for Ang IV or additionally via AT_2R stimulation. ACE2 is also a new pathway for the formation of Ang (1–7). Newly identified Ang receptor-binding proteins associated with different ATR subtypes may also modify ATR activation. Thus, overstimulation of AT_1R (and PRR) by Ang II, which can contribute to a plethora of cardiovascular disease processes, may be counter-regulated by a number of non-AT_1R mechanisms. Most notably, AT_2R stimulation usually causes opposing effects to AT_1R, as indicated. It is also likely that the MasR exerts a similar counter-regulatory role, whereas the evidence is more preliminary and speculative for AT_4R/IRAP. In terms of mediators, Ang II itself stimulates AT_2R, whereas the shorter Ang peptides stimulate their cognate receptors and possibly also AT_2R. (*Am A* aminopeptidase A, *Am B/N* aminopeptidase B/N, *IRAP* insulin-regulated aminopeptidase, *PRR* prorenin receptor) (Reproduced from Elton et al. [50] (an open access article))

35.6.1 AT_1R-Mediated Effects of Ang II

The main physiological function of Ang II is to maintain BP and volume homeostasis. This is achieved by several mechanisms, including vasoconstriction of renal and systemic arterioles, stimulation of renal tubular sodium reabsorption, and release of aldosterone from the adrenal glands. All these effects are mediated by AT_1 receptors (AT_1R) [51]. In states of hypotension and volume depletion, Ang II acts as a rapid and potent vasoconstrictor, by activation of phospholipase C (PLC) pathway in vascular smooth muscle cells (VSMCs) [52].

In the kidney, the activation of apical Na^+/H^+ exchange, basolateral Na^+/HCO_3^- cotransport, and basolateral Na^+/K^+-ATPase and apical H^+-ATPase are implicated in Ang II-induced sodium and bicarbonate reabsorption in the proximal tubule, whereas Na^+/H^+ exchange and H^+-ATPase contribute to reabsorption of sodium and bicarbonate in distal tubules [53]. Hypertensive patients display an enhanced antinatriuretic response to exogenously administered Ang II [54].

Ang II has been shown to induce NE discharge at the neurovascular junction, in the kidneys, adrenal glands, and CNS [55]. In the brain, Ang II activates the SNS by promoting oxidative stress and the release of an endogenous digitalis-like factor (EDLF) [56], whereas RAS inhibitors can suppress sympathetic hyperactivity [55]. Ang II also stimulates thirst, salt appetite, and vasopressin secretion, by binding to AT_1R in the subfornical organ, the median preoptic nucleus, the PVN, and the supraoptic nucleus [57].

Moreover, Ang II is presently recognized not merely as a BP regulator but as a pleiotropic hormone, which contributes to the development and progression of vascular, cardiac, and renal damage associated with hypertension and other diseases. These deleterious effects are mainly mediated by AT_1R, via several intracellular signaling systems, including G protein-dependent [like protein kinase C (PKC), ERK1/2, Raf, tyrosine kinases, nuclear factor κB (NFκB), and reactive oxygen species (ROS)] and independent (such as β-arrestin-mediated MAPK activation and Src-JAK/STAT) pathways. The AT_1R-mediated activation of NADPH oxidases (NOX) releases ROS, resulting in the activation of proinflammatory transcription factors and stimulation of small G proteins such as Ras, Rac, and RhoA [58].

Proinflammatory, profibrotic, and prooxidant effects of Ang II on the cardiovascular system have been demonstrated in numerous animal and human studies [59]. For example, it has been shown that Ang II induces increased expression of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF- α) in the heart [60], arteries [61, 62], and peripheral monocytes [63]. Ang II also upregulates chemokines, like monocyte chemoattractant protein-1 (MCP-1) [61, 62], and adhesion molecules, including vascular cell adhesion molecule 1 (VCAM-1) [62] and intercellular adhesion molecule-1 (ICAM-1) [64], thereby inducing activation and infiltration of monocytes and other leukocytes into the heart and vessel wall [61, 64]. Furthermore, Ang II contributes to oxidative stress, by stimulating NOX, which produce superoxide and hydrogen peroxide, and by increasing the production of mitochondrial ROS [65]. Ang II also facilitates vascular calcification, by reducing the expression of matrix Gla protein (MGP), an inhibitor of calcification, in VSMC

[66]. All of these effects are mediated by AT_1R and can be prevented by administration of AT_1R antagonists [61, 62, 64].

In animal models of hypertension, elevated cardiac Ang II enhances cardiac myocyte apoptosis, macrophage infiltration, and expression of NOX2 and transforming growth factor-β1 (TGF-β1), thus contributing to left ventricular hypertrophy and fibrosis [67]. The inflammatory and profibrotic effects of Ang II seem to be regulated by cytosolic adaptor caspase recruitment domain 9 (CARD9) [68] and by C-reactive protein [69]. Interestingly, studies of Crowley et al. in a mouse kidney cross-transplantation model have shown that Ang II infusion is capable to induce cardiac hypertrophy only in the presence of renal AT_1R; when AT_1R are deleted from the kidney, the residual repertoire of systemic, extrarenal AT_1R is not sufficient to induce hypertension or cardiac hypertrophy. This suggests that Ang II causes cardiac hypertrophy not by direct effects on cardiac AT_1R but by increasing the BP through activation of renal AT_1R [70].

In the kidney, besides vasoconstriction and sodium reabsorption, Ang II induces inflammation, renal cell growth, mitogenesis, apoptosis, migration, and differentiation [71]. Infusion of Ang II in mice results in increased NOX activity, increased expression of proinflammatory cytokines and fibrosis-associated genes (such as α-smooth muscle actin, TGF-β, procollagen type I-α1), and increased levels of collagen I, with histological evidence of tubulointerstitial fibrosis [72]. In animal models of glomerular disease, Ang II induces oxidative stress, expression of adhesion molecules, macrophage infiltration, and exacerbation of proteinuria [73]. These effects were also shown to be mediated by AT_1R and prevented by AT_1R blockade.

In the cerebral circulation, Ang II has been involved in ROS generation, alterations of vasomotor function, impaired neurovascular coupling, inflammation, and vascular remodeling [74]. Ang II infusion in rodents increases ROS production by cerebral arteries [75], via activation of AT_1R and NOX2 [76]. Ang II also induces constriction of cerebral arteries, mediated by AT_1R on VSMC and EC [77], and impairs endothelium-dependent vasodilation by reducing the bioavailability of NO and potentially by interfering with other endothelium-dependent mechanisms [77]. Ang II-induced hypertension is associated with impairment of neurovascular coupling (i.e., regulation of local cerebral blood flow in response to changes in metabolic demands that result from increased brain activity) [75]. Furthermore, Ang II causes remodeling and hypertrophy of cerebral arterioles, possibly mediated by NOX2 [78]. In spontaneously hypertensive rats, AT_1R blockade reduces the expression of ICAM1 and macrophage infiltration in the brain, suggesting a key role for Ang II in cerebral inflammation [79]. Increased leukocyte and platelet adhesion has been observed during Ang II-induced hypertension, dependent on AT_1R on these cells [80]. On the other hand, several studies in hypertensive patients have demonstrated that treatment with ACE inhibitors and, especially, with AT_1R blockers is capable to improve total cerebral blood flow [74].

35.6.2 The Role of Aldosterone in Hypertension

The implication of elevated aldosterone levels in hypertension has been recognized long ago, in the setting of primary hyperaldosteronism, initially described by Conn in 1955 [81].

Aldosterone is secreted by the zona glomerulosa of the adrenal cortex under the influence of Ang II (via AT_1R), serum potassium, and adrenocorticotropic hormone (ACTH). In the kidney, aldosterone binds to the mineralocorticoid receptors (MRs) in the epithelial cells of the distal convoluted tubules and collecting ducts. By upregulating the basolateral Na^+/K^+ exchange pump, the epithelial sodium channels (ENaCs), and the outer medullary renal K channels, aldosterone promotes sodium and water reabsorption and secretion of K into the tubular lumen. These effects are mediated by both genomic and nongenomic (rapid) pathways [81]. In addition, it has been recently shown that aldosterone can directly induce vasoconstriction, via MR on VSMC [82]. Aldosterone can also activate the SNS by central mechanisms [83], thus further contributing to the increase of BP.

Besides its antinatriuretic and vasopressor effects, aldosterone is involved in vascular and target-organ damage, by promoting oxidative stress, inflammation, and fibrosis of the heart, vasculature, and kidneys, through both MR-dependent and MR-independent pathways [81]. Aldosterone induces the formation of ROS through several mechanisms: (1) stimulation of NOX activity in macrophages, VSMC, EC, cardiomyocytes, podocytes, and mesangial cells, (2) decrease of glucose-6-phosphate dehydrogenase in vascular cells, and (3) stimulation of mitochondrial production of ROS. Oxidative stress in the vasculature induces endothelial dysfunction and VSMC proliferation and migration [82].

Direct activation of MR in VSMC and EC has been shown to promote inflammatory gene expression [82]. In mineralocorticoid-induced hypertension models, MR activation has been associated with perivascular inflammatory cell infiltration; increased expression of proinflammatory factors including ICAM1, MCP-1, and cytokines in cardiac tissue [84]; and increased expression of osteopontin, MCP-1, IL-6, and IL-1β in the kidney [85]. MR activation in human EC promotes expression of adhesion molecules ICAM1 and VCAM1, resulting in enhanced leukocyte adhesion to human coronary EC [86]. MR antagonism reduces the vascular inflammation and ameliorates cardiac and renal injury, even without changes in BP, supporting that MR activation participates in vascular inflammation and damage through a BP-independent, direct vascular process [87]. In clinical studies, infusion of aldosterone or Ang II into healthy subjects increases circulating IL-6 concentrations, and the Ang II effect is blocked by spironolactone, suggesting an MR-dependent mechanism [88]. Treatment with spironolactone has also been shown to reduce MCP-1 and plasminogen activator inhibitor (PAI-1) levels in subjects with type 2 diabetes and hypertension, respectively [89].

Aldosterone also stimulates the expression of profibrotic molecules, such as transforming growth factor-β1 (TGF-β1), PAI-1, endothelin 1 (ET-1), placental

growth factor (PGF), connective tissue growth factor (CTGF), osteopontin, and galectin-3 [89]. In cultured VSMC, aldosterone stimulates collagen and fibronectin synthesis [90]. In vivo, chronic administration of aldosterone causes interstitial and perivascular fibrosis in the heart, fibrosis and stiffness of the aorta, and glomerulosclerosis and interstitial fibrosis in the kidney [89]. Patients with primary aldosteronism were found to have significantly increased vascular medial thickness and narrowed vessel lumens, compared to patients with similar degrees of essential hypertension and other forms of secondary hypertension [82]. In the Framingham Offspring Study, the aldosterone/renin ratio was positively correlated with left ventricular hypertrophy and with the development of arterial stiffness [91].

The proinflammatory and profibrotic effects of aldosterone are prevented by MR antagonism in most models [89]. For example, spironolactone inhibits the expression of PGF and CTGF in human aorta, while eplerenone attenuates collagen accumulation in pig coronary arteries after angioplasty and decreases aortic stiffness. Luther et al. showed that genetic aldosterone deficiency can prevent cardiac hypertrophy, aortic remodeling, and albuminuria induced by Ang II administration in mice; furthermore, they found that MR antagonism has additional renal benefits in mice with aldosterone deficiency [92]. This suggests not only that aldosterone mediates a part of Ang II-induced cardiac, renal, and vascular injury but also that Ang II can mediate MR-dependent effects in vivo in the absence of aldosterone.

35.6.3 The AT_2R-Mediated Effects of Ang II

AT_2Rs are mainly expressed in the kidney, heart, vasculature, and adrenal cortex, and their actions are generally opposed to those of AT_1R. The intracellular signaling of AT_2R involves the inhibition of MAP kinases ERK-1 and ERK-2, whereas extracellular signaling is mainly mediated by the bradykinin–NO–cGMP pathway [93].

AT_2R stimulation has vasodilatory effects, both in small resistance arteries and in large capacitance vessels [93]. In addition, AT_2R activation by Ang III (but not by Ang II) inhibits renal sodium reabsorption, mainly in the proximal tubule but also in the thick ascending limb of Henle's loop [94].

Furthermore, AT_2R seems to have protective effects against vascular, cardiac, and renal damage associated with hypertension [95]. Indirect evidence for a favorable role of AT_2R in vascular remodeling is provided by studies in AT_2R-deficient mice, which develop more prominent remodeling of the aorta, coronary, and femoral arteries in response to high BP [96]. On the other hand, in hypertensive rats, AT_2R stimulation decreases arterial fibrosis and stiffness [97], as well as myocardial fibrosis [98]. Hypertensive AT_2R-deficient mice were found to have more severe glomerular and interstitial inflammation, higher albuminuria, worse renal function, and increased mortality, compared with wild-type mice with similar BP levels [99]. Treatment with an AT_2R agonist in rats with renovascular hypertension reduced the renal expression of TNFα, TGFβ1, and IL-6 and inflammatory cell infiltration [100]. In spontaneously hypertensive stroke-prone rats, the same treatment

prevented renal inflammation and fibrosis, delayed the occurrence of brain damage, and prolonged survival, without influencing the BP [101].

It has been shown that the beneficial effects of AT_1R antagonists, including vasodilation, natriuresis, and prevention of vascular remodeling, are due in part to AT_2R activation, in addition to AT_1R blockade [93, 95]. Considering all these data, it is reasonable to believe that AT_2R agonists could emerge in the future as a new class of antihypertensive drugs. However, the observation that AT_2R stimulation lowers the BP only in the presence of AT_1R blockade indicates that the vasopressor activity of AT_1R is dominant over the vasodilatory effect of AT_2R in vivo, and therefore, AT_2R agonists may not be suitable for monotherapy but rather as second-line agents, in addition to AT_1R antagonists [95].

35.7 Other Pathways of RAS

35.7.1 Tissue RAS and Alternative Pathways of Ang II Biosynthesis

RAS functions both as a circulating system and as a tissue paracrine/autocrine system. It has been suggested that hyperactivation of tissue RAS may contribute to the pathogenesis of cardiovascular and renal damage even in the absence of any abnormality in the circulating RAS.

Local or tissue Ang II biosynthesis may be initiated by renin and/or angiotensinogen taken up from the circulation; however, independent Ang II-generating systems also exist in the heart, blood vessels, kidney, brain, adrenal glands, adipose tissue, and other organs. These systems include serine proteases, like tonins, cathepsin G, and chymase. In humans, non-ACE pathways are responsible for about 40 % of Ang II generation in the kidney, whereas over 80 % of Ang II formation in the heart and more than 60 % of that in arteries are chymase dependent [49, 53]. The activation of these alternative pathways could contribute to the so-called "ACE escape" phenomenon, which may occur during treatment with ACE inhibitors and result in resistance to this treatment [102].

35.7.2 Ang II-Derived Peptides: Ang III, Ang IV, Ang A, and Angioprotectin

Ang III and Ang IV are formed by the sequential removal of amino acids from the N-terminus of Ang II by the action of aminopeptidases, particularly in the brain and kidneys. Ang III [Ang-(2–8)] is a heptapeptide and Ang IV [Ang-(3–8)] is a hexapeptide. Ang III binds to renal AT_1R and AT_2R to induce either natriuretic or antinatriuretic effects, depending on the dose and the type of receptor. When administrated

into the CNS, Ang III stimulates vasopressin release and thirst and increases the BP. Ang IV stimulates the AT_1 and AT_4 receptors. The Ang IV stimulation of AT_1R increases the BP and induces renal vasoconstriction, similarly to Ang II. The roles of AT_4R, which has been identified as the insulin-regulated aminopeptidase (IRAP), are largely unclear, but it might be involved in cognitive function and memory [103].

Ang A is an octapeptide generated from Ang II by decarboxylation of its N-terminal aspartate residue. Compared to Ang II, Ang A has similar affinity for both AT_1R and AT_2R and induces similar increase in BP and renal vasoconstriction via AT_1R [104]. Angioprotectin is also an octapeptide, generated enzymatically from Ang II in endothelial cells. Angioprotectin antagonizes the vasoconstrictor actions of Ang II by stimulating the Mas receptor, for which it has a stronger affinity than Ang-(1–7) [105].

35.7.3 The ACE2/Ang-(1–7)/Mas Pathway

Like ACE, ACE2 is a membrane-bound carboxypeptidase that can be found in many tissues, including the blood vessels, heart, kidney, liver, and brain. The most important role of ACE2 is to degrade Ang II (and, to a much lesser extent, Ang I) to the heptapeptide Ang-(1–7), which has been shown to have vasodilatory, natriuretic, and antifibrotic properties. Recently, the Ang-(1–7) ligand, the Mas receptor, has been characterized. It is now accepted that the ACE2/Ang-(1–7)/Mas pathway is able to counteract most of the deleterious actions of the ACE/Ang II/AT_1R axis [106].

In spontaneously hypertensive rats, the expression of renal and cardiac ACE2 is significantly lower than in normotensive rats [107], which suggests that ACE2 deficiency may be involved in genetic hypertension. Dysregulation of renal and cardiac activity of ACE2 has also been reported in experimental models of secondary hypertension, such as endocrine hypertension [deoxycorticosterone (DOCA)-salt, Ang II infusion], renal failure (subtotal nephrectomy), and renal artery stenosis (Goldblatt hypertension) [106].

Several studies in rodents suggest that ACE2 may play a role in central regulation of BP. For example, ACE2 gene deletion was associated with impaired baroreflex sensitivity and autonomic function [108], while in various hypertensive models, ACE2 expression was found to be reduced in some brain regions involved in cardiovascular function control [109]. In mice, genetic ACE2 deficiency was associated with only a small increase in BP but with higher susceptibility to Ang II-induced hypertension [110]. Cardiac ACE2 gene transfer or overexpression reduced BP and attenuated cardiac hypertrophy and fibrosis in hypertensive but not in normotensive rats [111]. These findings suggest that ACE2 may play a compensatory role in hypertension but not in normal physiology. Treatment with recombinant human ACE2 (rhACE2) was shown to blunt the increase in BP and to prevent cardiac remodeling induced by Ang II infusion in rodents [112]. A few clinical studies have found higher plasma ACE2 levels in hypertensive patients, but this association has not been confirmed by others. Large clinical studies are required to clarify the potential role of ACE2 in hypertension [106].

The ACE2/Ang-(1–7)/Mas activation induces the release of vasodilatory mediators, including prostaglandins and NO [103], and enhances the effect of bradykinin in rats [113]. As a result, Ang-(1–7) elicits vasodilation in several vascular beds and provokes the decrease of BP in normal and hypertensive rats. However, contradictory effects of Ang-(1–7) have been reported by studies on human vessels [113]. The diuretic/natriuretic effects of Ang-(1–7) are due to renal vasodilation, as well as to reduction of sodium reabsorption, by inhibition of Na^+/K^+-ATPase in the proximal renal tubule [103].

Ang-(1–7) and Mas can prevent cardiac remodeling in hypertension. Treatment of cardiac fibroblasts with Ang-(1–7) inhibits Ang II-induced collagen synthesis. Chronic administration of Ang-(1–7) and other Mas agonists significantly reduces left ventricular hypertrophy and fibrosis in hypertensive rats, whereas Mas deletion is associated with myocardial collagen deposition and dysfunction. Furthermore, Ang-(1–7) can induce coronary vasodilation, prevent ischemia–reperfusion arrhythmias, and increase cardiac output. These favorable cardiac effects seem to be mediated by several mechanisms, including release of prostacyclin and/or NO, potentiation of bradykinin, and decrease of Ang II levels in the heart [113].

The renal effects of ACE2/Ang-(1–7)/Mas are unclear. In mice, genetic deletion of Mas increases glomerular TGF-β expression and fibronectin and collagen deposition [113]. Chronic inhibition of ACE2 worsens glomerular injury and albuminuria in diabetic mice [114], while administration of recombinant ACE2 diminishes Ang II-induced renal fibrosis [72]. In contrast, another study found that Ang-(1–7) infusion leads to NF-κB activation and inflammation via Mas [115]. Ang-(1–7) can also bind to AT_1R, competing with Ang II for these receptors. Thus, Ang-(1–7) antagonizes the Ang II-induced activation of PKC and ERK1/2 in VSMC [113].

Very recently, a new derivative of Ang-(1–7), alamandine, and its receptor, the Mas-related G-coupled receptor type D (MrgD), have been identified. Alamandine is generated by catalysis of Ang A via ACE2 or directly from Ang-(1–7), and its actions seem to be cardioprotective, comparable to those of Ang-(1–7) [116].

35.8 Heterogeneity of the ACE Gene

In 1990, a polymorphism of the ACE gene was described, based on the insertion (I) or deletion (D) of a 287-base pair element in intron 16. Subjects with D alleles have a higher ACE activity [117] and an increased risk of left ventricular hypertrophy [118], myocardial infarction [119], overweight/obesity [120], and end-stage renal disease [121].

Some studies have also shown an association between the D allele and hypertension. For example, in a Chinese population, the DD and ID genotypes were associated with a significantly higher risk of hypertension than the II genotype (with adjusted OR of 1.94 and 1.72, respectively) [122]. Another study in a group of obese children and adolescents found that the DD and ID genotypes were associated with a higher prevalence of hypertension in boys but not in girls, compared to the II

genotype [123]. The D allele of the ACE gene was also associated with higher BP in pregnant women [124]. However, other studies have failed to confirm a significant relation between ACE I/D polymorphism and the risk of hypertension (Chaps. 32 and 36).

35.9 Concluding Remarks

There is currently sufficient evidence, resulting from both experimental and clinical studies, to support a significant role for the SNS and the RAS in the pathophysiology of arterial hypertension. Sympathetic overactivity can be detected in many patients with hypertension; however, it is particularly prominent in those with severe and resistant hypertension, with target-organ damage, and with obesity or metabolic syndrome. The causes of the sympathetic activation include genetic, dietetic, and neurohumoral factors. In obese individuals, endocrine abnormalities such as high levels of insulin and leptin and low levels of adiponectin and ghrelin might contribute to SNS activation. The sympathetic overdrive is capable not only to induce and/or maintain the increase in BP, but it can directly cause vascular and cardiac damage. However, many questions still remain unanswered. For example, how can we determine the place of sympathetic hyperactivity among other pathophysiological factors in a given hypertensive individual and, thus, identify patients which are most likely to respond to sympathetic inhibition therapies (e.g., sympatholytic drugs or renal denervation)? What is the exact role of various genetic, lifestyle, endocrine, and metabolic factors in sympathetic activation, and how can these factors be targeted by specific therapies? Does SNS hyperactivity increase the risk of cardiovascular events and mortality in hypertensive patients? Future research should also focus on finding other possible causes of sympathetic activation in hypertension and designing more simple and accurate methods of assessing sympathetic activity.

The RAS also plays an important role in hypertension, by promoting vasoconstriction of renal and systemic arterioles, stimulation of renal tubular sodium reabsorption, and release of aldosterone from the adrenal glands. Moreover, both Ang II (via AT_1R) and aldosterone are not merely vasopressors but pleiotropic hormones, which are capable to induce inflammatory, proliferative, profibrotic, and oxidative effects in the cardiovascular system, thus contributing to atherosclerosis and hypertensive target-organ damage. The concept of RAS has considerably expanded in recent years to include newly discovered enzymes, peptides, and receptors. Of these, the AT_2 receptor of Ang II and the ACE2/Ang-(1–7)/Mas axis have been the most studied. These pathways might counteract the classical ACE/Ang II/AT_1/aldosterone axis, providing natriuretic, vasodilator, and cardiovascular protective effects. Thus, it is hypothesized that reduced expression and/or activity of these counter-regulatory systems might contribute to the development and aggravation of hypertension and its complications. Furthermore, components of the RAS have been identified in several organs and tissues, which might play important roles in target-organ damage, independently of systemic RAS activity. Future studies

should focus on developing drugs that stimulate the AT_2 receptors and the ACE2/Ang-(1–7)/angioprotectin/Mas axis, which might provide new therapeutic options for hypertensive patients. The clinical relevance of other RAS components (e.g., the prorenin receptor, Ang III, Ang IV, angioprotectin, and alamandine) and of local (tissue) RAS also needs to be clarified by further research.

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Chapter 36
Drugs Targeting RAAS in the Treatment of Hypertension and Other Cardiovascular Diseases

Pitchai Balakumar and Gowraganahalli Jagadeesh

Abstract Drugs with diversified structure and class target the RAAS cascade at various levels. Beginning with the inhibition of renin from the juxtaglomerular cells of the kidney, it extends to the blockade of formation and actions of its principal component, Ang II, and its effector, aldosterone and its synthesis. Although all of them are very efficacious in combating overactivation of RAAS, ACE inhibitors and ARBs stand out in the armamentarium of RAAS inhibitors. All of them are effective in lowering blood pressure but differ from each other in potency, pharmacokinetic properties and additional pharmacologic actions that are contributed by their unique functional groups. Therapeutic uses of RAAS blockers stem from the dynamics of the complex intertwined downstream signaling molecules that interact to contribute beyond blood pressure control. Thus, some of the ACE inhibitors and ARBs are also indicated in the treatment of heart failure, left ventricular dysfunction following myocardial infarction, and nephropathy in T2DM, reducing the risk of cardiovascular mortality, nonfatal myocardial infarction, and the risk of developing heart failure. Several studies have investigated the dual inhibition of the RAAS in hypertension and heart failure with an outcome of more adverse events without an increase in benefit. While considering Ang II and aldosterone escape processes during ACE inhibitors and ARBs therapies, RAAS at the base level can be halted using aldosterone receptor antagonists for the management of hypertension and heart failure. In

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this chapter, we review and discuss the pharmacologic interference with the functioning of the RAAS at different levels in the axis, a major therapeutic approach in the treatment of hypertension and other cardiovascular disease.

Keywords RAAS inhibitors • ACE inhibitors • ARBs • Renin inhibitor • AT_1 receptor • Aldosterone antagonists • Aldosterone synthase inhibitor • Angiotensin

36.1 Introduction

Hypertension is a multifaceted disease associated with cardiovascular, cerebral, and renovascular abnormalities. Its prevalence increases with advancing age as more than 75 % of those aged 70 years or above are hypertensive [1]. Large-scale clinical trials such as Framingham Heart Study [2] and Multiple Risk Factor Intervention Trial [3] have demonstrated the association between elevated blood pressure and increased risk of cardiovascular events. The Eighth Joint National Committee recommends a blood pressure of less than 140/90 mmHg in hypertensive persons younger than 60 years [4] so that risk for cardiovascular events is lower. Achieving the target value is very challenging given the insufficient diagnosis, less than effective treatment, and low patient compliance to therapy [5]. Various strategies are being followed to achieve the goal blood pressure. The treatment regimens often involve more than one class of drugs for novel targets with unique properties that could prove to be superior to the conventional therapy. Some drug classes and some individual drugs may have differences in effects on other important endpoints. This is probably because of the pharmacologic effects beyond blood pressure reduction [6]. One of the pharmacologic approaches targeting both the blood pressure control and related structural and functional improvements of the heart and blood vessels is to interrupt the renin-angiotensin-aldosterone axis, which may be considered a major scientific advancement in drug therapy of hypertension and its effects on health.

The principal and proximal substrate in the complex cascade of renin-angiotensin-aldosterone system (RAAS) is "angiotensinogen." It is the product of the first and most important gene, a member of the serpin gene located on chromosome 1, linked to essential hypertension [7]. The initial and rate-limiting step in the RAAS cascade is the formation of renin from its precursor prorenin. Renin cleaves angiotensinogen (AOG) to form angiotensin I (Ang I), which is subsequently converted by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II), the primary effector pleiotropic hormone of the RAAS. Ang II is also formed from Ang (1–12) by a non-ACE pathway in the human heart involving chymase. Ang I is converted into Ang (1–9) by angiotensin-converting enzyme 2 (ACE2), an enzyme homologous to ACE. In addition, ACE2 has an affinity for Ang II to form Ang (1–7), which is also formed from Ang (1–9) by ACE. Mediated through the Mas receptor (Mas R, a G protein-coupled receptor), Ang (1–7) has physiological functions that are opposite to that of Ang II [reviewed in 8]. The first component, ACE-Ang II-AT_1 R axis,

predominantly mediates vasoconstriction, proliferation, inflammation, and cardiac remodeling, and the second component, ACE2-Ang (1–7)-Mas R axis, might counterbalance the cardiovascular adverse effects of Ang II as Ang (1–7) has natriuretic, endothelial protective, cardioprotective, vasodilatory, and antiproliferative properties [8, 9]. Controversial findings, however, exist in the literature revealing a negative role of Ang (1–7) in the cardiovascular and renal system (Chap. 35).

The RAAS plays a fundamental role in maintaining the cardiovascular and renal physiology. However, overactivation of the RAAS results in an induction and progression of cardiovascular and renal disorders. Therapeutic blockade of the RAAS is more effective in high-renin hypertensive patients. Plasma renin activity (PRA) is highly predictive of future cardiovascular events in hypertensive patients, and around 20 % of hypertensive patients have high renin levels. The RAAS overactivation can be mitigated by renin inhibitors, angiotensin-converting enzyme (ACE) inhibitors, Ang II-AT_1 receptor blockers (ARBs), aldosterone receptor antagonists, and aldosterone synthase inhibitors. In this chapter, we review Ang II-AT_1 receptor signal transduction followed by drugs targeting the RAAS at various loci in the cascade in the treatment of hypertension and other cardiovascular disease.

36.2 Ang II-Induced AT_1 Receptor-Mediated Signal Transduction

Ang II acts on AT_1 and AT_2 receptors, both of which belong to the G protein-coupled receptor (GPCR) superfamily. AT_1 and AT_2 receptors may oppose the action of each other in response to Ang II binding [10]. The AT_1 receptor overactivation by Ang II causes direct vasoconstriction, enhancement of sympathetic outflow, and release of aldosterone, all of which adversely affect cardiovascular and renal function [reviewed in 8] (Fig. 36.1). On the other hand, activation of AT_2 receptors by Ang II induces vasorelaxation by increasing the production of nitric oxide and cGMP [11]. Activation of AT_2 receptors might not have direct beneficial actions on high blood pressure but might improve the function of the cardiovascular system by reducing vasoconstriction and fibrosis [reviewed in 8].

The AT_1 receptor activation transduces G protein-dependent and G protein-independent signals, which in turn activate multiple downstream signaling cascades, resulting in contraction, endothelial dysfunction, cell survival and migration, hypertrophy, fibrosis, and thrombosis. AT_1 receptors are coupled to Gαq/11 that stimulates the phospholipase C-protein kinase C (PLC-PKC) pathway. The AT_1 receptor-mediated activation of Gβγ subunits stimulates both PLC and PLD. The latter is an important inducer of Ang II-induced oxidative stress, playing a critical role in redox-sensitive growth in human VSMCs. The PLD activation via phosphatidic acid (PA) release activates NADPH oxidase in VSMCs. Ang II-PLD-NADPH oxidase and ROS cascades function as second messengers in long-term Ang II-associated cell growth. Ang II-induced AT_1 receptor interaction also activates

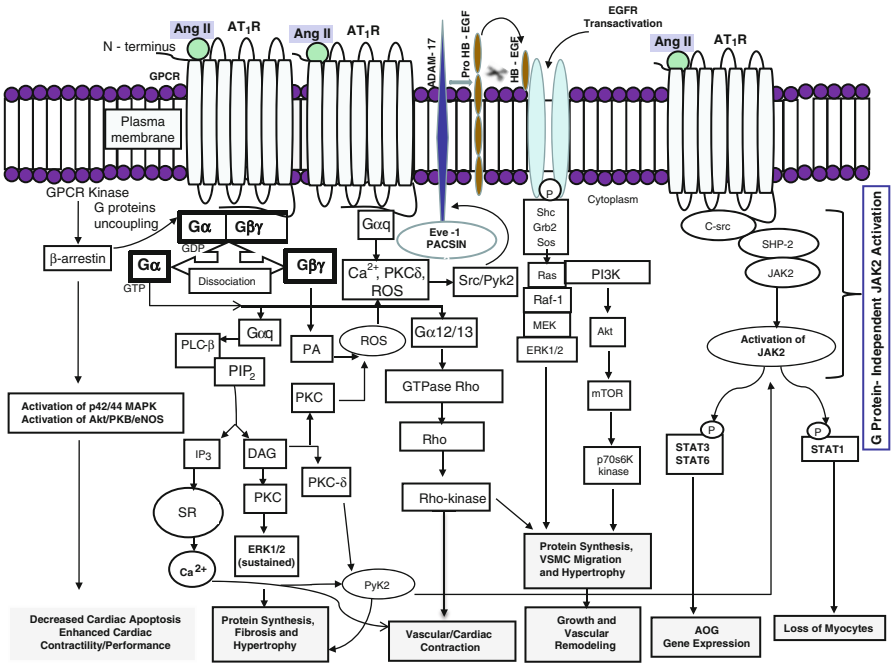

Fig. 36.1 Ang II-induced G protein-dependent and G protein-independent signal transduction. Ang II signaling through AT_1 receptors is coupled to Gαq, activating PLC-β. This leads to generation of IP_3 and DAG, resulting in vascular/cardiac contraction, protein synthesis, fibrosis, and hypertrophy. Ang II-AT_1R-Gαq signals causes activation of PKC, ERK1/2, tyrosine kinases (Src, Pyk2, Tyk2), and generation of reactive oxygen species, which might activate metalloprotease ADAM-17, cleaving proHB-EGF to HB-EGF, resulting in EGFR transactivation. This initiates a MAPK signaling, leading to protein synthesis, VSMC migration, hypertrophic growth, and vascular remodeling. AT_1 receptor-associated coupling to Gα12/13 activates Rho-kinase, resulting in vascular contraction and hypertrophy. The GPCR kinase-mediated receptor phosphorylation increases the receptor affinity for β-arrestin, leading to functional uncoupling of G protein signaling and also activation of cytoprotective/cardioprotective signals via p42/44 MAPK and Akt/PKB/eNOS. JAK/STAT signals can be activated by Ang II-AT_1R coupling by G protein-dependent and G protein-independent mechanisms. *ADAM17* A disintegrin and metalloprotease 17, *Ang II* angiotensin II, *Akt* protein kinase B, *AOG* angiotensinogen, AT_{1R} angiotensin-II AT1 receptor, *DAG* diacylglycerol, *EGFR* epidermal growth factor receptor, *eNOS* endothelial nitric oxide synthase, *ERK 1/2* p42/p44 mitogen-activated protein kinase or extracellular signal-regulated protein kinases 1 and 2, *GPCR kinase* G protein-coupled receptor kinase, *GPCRs* G protein-coupled receptors, *HB-EGF* heparin-binding endothelin growth factor, IP_3 inositol trisphosphate, *JAK* janus kinase, *PA* phosphatidic acid, *PIP2* phosphatidylinositol-4,5-bisphosphate, *PKC* protein kinase C, *PLC* phospholipase C, *ROS* reactive oxygen species, *SHP-2* Src homology phosphatase-2, *SR* sarcoendoplasmic reticulum, *STAT* signal transducer and activators of transcription, *VSMC* vascular smooth muscle cells

PLA2, resulting in the production of arachidonic acid, which is metabolized by lipoxygenases to leukotrienes. The latter also activates NADPH oxidases to generate ROS [reviewed in 8, 12, 13].

Ang II-induced activation of AT_1 receptors also stimulates G protein-independent signaling pathways such as β-arrestin and Src-JAK/STAT signals [reviewed in 8].

β-Arrestin would seem to be a target in developing drugs for treating cardiovascular disorders with an objective of selectively blocking the deleterious G protein-dependent pathways and simultaneously activating beneficial β-arrestin-mediated cardioprotective signaling. Currently, TRV120027, a unique drug that combines "blockade of AT_1 receptor" and "β-arrestin2 stimulating activity," is undergoing clinical trials for the treatment of acute decompensated heart failure [14]. Figure 36.1 summarizes Ang II-induced G protein-mediated signal transduction and growth factor receptor transactivation and G protein-independent signaling leading to MAPK signaling activation by the AT_1 receptor.

In the subsequent section, we describe the nature and blockade of the RAAS at different upstream and downstream points that has different effects on its components. This forms the basis for describing the various classes of RAAS inhibitors for the control of blood pressure and beyond, although it does not make one class superior to another.

36.3 Drugs Targeting the RAAS Pathway

Pharmacologic agents that interrupt the functioning of the RAAS prevent the actions of Ang II either by reducing its production or by preventing its binding to target receptors. Therefore, blocking of the RAAS at different points in the axis has different effects on its components. The relative contribution of these levels in the RAAS cascade toward blood pressure regulation and prevention of cardiovascular events is not precisely known, although a considerable number of drugs interrupting the functioning of RAAS are approved and marketed worldwide. As illustrated in Fig. 36.2, these drugs fall into seven categories. The first approach, not necessarily a preferred choice, is to block the action of enzyme renin, a rate-limiting step in the synthesis of Ang I from AOG. The first such drug was aliskiren, arrived in 2007. Inhibition of this step prevents the production of angiotensin peptides by the renin-ACE and non-ACE pathways. The second approach was first employed in the late 1970s with the introduction of the ACE inhibitor, captopril. The drugs in this category have constituted one of the major advances in the treatment of mild-to-moderate hypertension, heart failure, myocardial infarction, and diabetic nephropathy. Although ACE inhibitors are well tolerated, their actions have resulted in adverse effects such as dry cough, increased bronchial reactivity, and angioedema. As the role of the RAAS in the pathophysiology of cardiovascular disease was well explored, so was the realization of the importance of finding other methods for inhibiting the actions of Ang II. This was accomplished in the third approach with the introduction of non-peptide Ang II AT_1 receptor blocker (ARB), losartan, in 1995. This opened up new vistas in understanding the additional biological effects of Ang II. The AT_1 receptor stimulation results in suppression of renin release. This negative feedback is interrupted where there is reduced or non-availability of angiotensin II at the receptor site, which occurs during treatment with ACE inhibitors and ARBs and leads to an increase in plasma renin activity (PRA) and plasma renin concentration (PRC). Although treatment with renin inhibitors

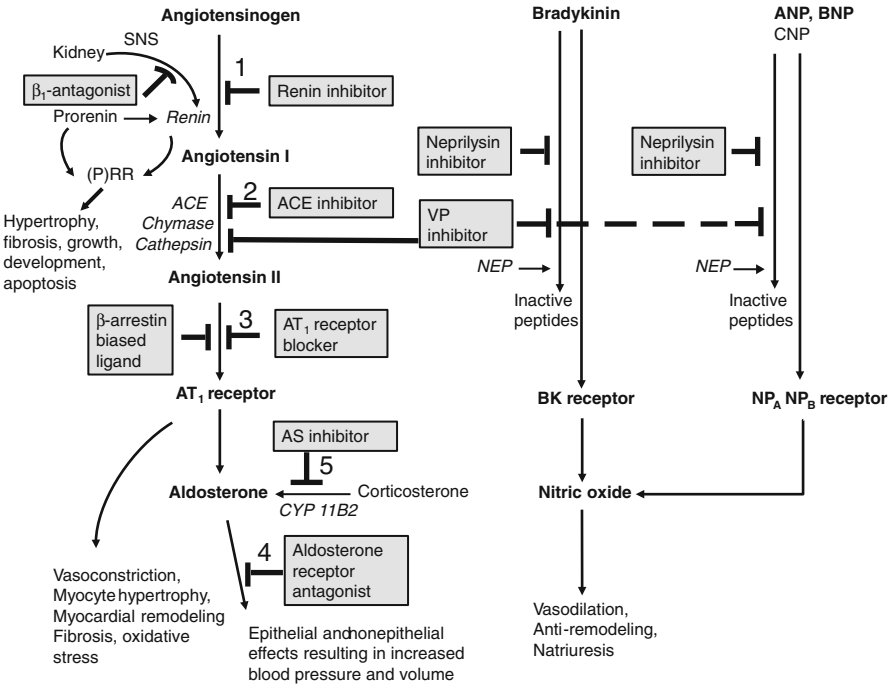

Fig. 36.2 Potential sites interrupting the functioning of RAAS are drug target for hypertension and other cardiovascular diseases. Renin converts AOG to Ang I, which further cleaved into Ang II by ACE. The cardiovascular effects of Ang II are mediated by AT_1 receptors. Pharmacologic agents that interrupt the functioning of RAAS prevent the actions of Ang II by either reducing its production or preventing its binding to the AT_1 receptor, thus targeting several sites in the axis involving several components. Besides the numbered potential five target sites interrupting the functioning of RAAS discussed in the text, other promising sites are also indicated in the flow diagram. β-Arrestin-biased ligand (e.g., TRV120027) combines "blockade of AT_1 receptor" and "β-arrestin2 stimulating activity." Additionally, simultaneous inhibition of AT_1 receptor and NEP (e.g., LCZ696) is more promising than the inhibition of ACE and NEP (e.g., omapatrilat). Note aldosterone synthase (CYP11B2) converts 11-deoxycorticosterone to corticosterone, to 18-hydroxycorticosterone, and finally to aldosterone. Ang (1–7), a vasodilator formed from Ang II by ACE2, is not shown in the figure

also interrupts the negative feedback loop, resulting in elevated PRC, renin inhibitors reduce PRA and consequently decrease the generation of both Ang I and Ang II. Further downstream in the RAAS pathway, effector of Ang II, and mediator of some of its unfavorable effects, aldosterone is considered a rational therapeutic target. Thus, the fourth class, aldosterone receptor antagonists (mineralocorticoid receptor antagonists, e.g., spironolactone), was introduced for the management of hypertension and heart failure. A new and fifth strategy opened up in recent years is to inhibit the formation of aldosterone itself using aldosterone synthase inhibitors. Investigational substances blocking the enzyme aldosterone synthase are in the pipelines of pharmaceutical drug development.

Current research is focused on the development of a new class of vasopeptidase inhibitors (e.g., omapatrilat) that have a novel action of simultaneously inhibiting ACE and neutral endopeptidase (NEP, neprilysin) and thus increasing the bioavailability of natriuretic peptides. Simultaneous inhibition of both ACE and NEP has the potential to oppose the activity of the RAAS and to potentiate the vasodilatory, natriuretic, and antiproliferative effects of natriuretic peptides. This sixth approach has not met with much success because of severe adverse effects relative to ACE inhibitors, and will not be discussed further.

The seventh approach is simultaneous inhibition of the AT_1 receptor and NEP. Neprilysin degrades several endogenous vasoactive peptides, including natriuretic peptides and bradykinin. Pharmacologic inhibition of neprilysin increases the levels of these vasopeptides, which could counteract the neurohormonal overactivation of Ang II and catecholamines and reduce systemic vascular resistance, sympathetic tone, vasoconstriction, sodium retention, cardiac fibrosis, ventricular hypertrophy, and maladaptive remodeling [15]. The combined inhibition of ACE and neprilysin was associated with serious angioedema. On the other hand, LCZ696, which constitutes a combination of neprilysin inhibitor sacubitril (AHU377, a prodrug that is converted to LBQ657) and an ARB (valsartan), was designed to minimize the risk of serious angioedema. A recent clinical study in chronic heart failure patients with a reduced ejection fraction compared LCZ696, an angiotensin receptor-neprilysin inhibitor (ARNI) with enalapril. In the study, LCZ696 was superior to enalapril in reducing the risks of death and hospitalization for heart failure [16]. In addition, LCZ696 was superior to enalapril in reducing the risk of death from any cause and reducing heart failure-associated symptoms and physical limitations. The LCZ696 group was noted to have higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group [16]. This study suggests that the combined inhibition of the AT_1R and neprilysin is superior to RAAS inhibition alone in patients with chronic heart failure. The drug is still under clinical investigation.

Drugs targeting RAAS are classified as follows (Fig. 36.2):

1. Renin inhibitor: Aliskiren
2. ACE inhibitors: Captopril, enalapril, lisinopril, ramipril, fosinopril, benazepril, quinapril, perindopril, moexipril, trandolapril, zofenopril, and imidapril
3. AT_1 receptor blockers: Losartan, valsartan, irbesartan, eprosartan, candesartan, telmisartan, olmesartan, azilsartan, and fimasartan
4. Mineralocorticoid or aldosterone receptor antagonists: Spironolactone and eplerenone
5. Aldosterone synthase inhibitors: FAD 286 and LCI699 (developmental stages)

In subsequent sections, we describe drugs in each of the above class with reference to landmark clinical trials and pharmacokinetic properties followed by therapeutic uses and adverse effects. Table 36.1 summarizes the key features of approved drugs in each class.

Table 36.1 Pharmacologic, PK, therapeutic, and adverse profile of RAAS inhibitors

Drugs by site of action	Pharmacology	PK properties	Indication	Potential adverse effects	Remarks
1. *Renin inhibition*					
Aliskiren	A direct renin inhibitor. It inhibits renin and successively prevents the generation of Ang I from AOG, thereby preventing the activation of the RAAS at the proximal step in the pathway	Rapidly absorbed and reaches maximum plasma concentration within 1–3 h. High-fat meal decreases its absorption. It is eliminated in maximum through the hepatobiliary route as an unchanged drug. BA 2.5 % [23]	Treatment of hypertension	Fatigue, headache, dizziness, diarrhea, nasopharyngitis, and back pain [24]. Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face and extremities	The use of aliskiren in combination with other RAASi is associated with an increased risk for hyperkalemia. Monitor serum K^+ periodically. Avoid coadministration with NSAIDs. Discontinue the drug when pregnancy is detected. Discontinue the drug when pregnancy is detected
2. *ACE inhibition*					
Captopril	All are specific competitive inhibitor of ACE. Inhibits the conversion of angiotensin I to angiotensin II and as a result increases PRA Drug-associated angioedema might occur possibly due to accumulation of bradykinin	Rapidly absorbed and reaches maximum plasma concentration within 1 h. Food decreases its absorption. BA ~75 %	Treatment of hypertension, CHF (in combination with diuretics, digitalis), LVD after m.i., nephropathy in patients with T1DM	Hypersensitivity reactions such as anaphylactic reactions and angioedema of the face, neck, head, and extremities; cough, hyperkalemia. Black patients have higher incidence of angioedema than nonblack. Other effects are hypotension, agranulocytosis and bone marrow depression, impaired renal function, jaundice, and elevated hepatic enzymes	Dual blockade with other class of RAAS inhibitors is associated with increased risks of hypotension, syncope, hyperkalemia, changes in renal function, and acute renal failure. Do not coadminister with aliskiren in patients with diabetes and in patients with renal impairment. Avoid coadministration with NSAIDs including selective COX-2 inhibitors, which may result in deterioration of renal function/ acute renal failure. The effects are usually reversible. Such coadministration may attenuate antihypertensive effect of ACE inhibitors
Enalapril		A prodrug bioactivated to enalaprilat. Rapidly absorbed, reaches maximum plasma concentration within 1 h. Food has no effect on absorption. BA ~60 %	Treatment of hypertension, symptomatic HF (in combination with diuretics, digitalis), asymptomatic LVD		

Lisinopril	Many ACE inhibitors are prodrugs. Most of them are cleared primarily by the kidney, while the impaired renal function could considerably decrease their plasma clearance. Initial dosages of all ACE inhibitors might be needed to be reduced in patients with high plasma levels of renin (HF patients and salt-depleted patients) [135]	Long acting, slow absorption, does not undergo metabolism and is excreted unchanged in the urine. Food has no effect on absorption. BA ~25 % (reduced to 16 % in CHF)	Treatment of hypertension, HF (as adjunctive therapy), acute m.i, to improve survival, diabetic nephropathy in patients with T1DM		
Ramipril		A prodrug hepatically cleaved to active metabolite ramiprilat. Rapidly absorbed, reaches maximum plasma concentration within 1 h. The extent of absorption (50–60 %) is not affected by the presence of food	Treatment of hypertension, cardiovascular event risk reduction, HF following m.i.		
Fosinopril		A prodrug with phosphinic acid binding site undergoes hepatic and gut esterification to an active drug, fosinoprilat. Slowly absorbed, reaches maximum plasma concentration, approximately 3 h. Food decreases its absorption. The BA of parent drug is ~36 % and that of metabolite is 75 %	Treatment of hypertension and in the management of HF as adjunctive therapy (added to diuretics, digitalis)		

(continued)

Table 36.1 (continued)

Drugs by site of action	Pharmacology	PK properties	Indication	Potential adverse effects	Remarks
Benazepril		A prodrug hepatically cleaved to active drug, benazeprilat. Rapidly absorbed, reaches maximum plasma concentration within 1 h. The extent of absorption is 37 % and. Food has no effect on absorption	Treatment of hypertension		
Quinapril		A prodrug quickly deesterified to its major active metabolite quinaprilat. Rapidly absorbed, reaches a maximum plasma concentration within 1 h. High-fat meal decreases the rate of absorption. BA ~60 %	Treatment of hypertension, management of HF as adjunctive therapy (added to diuretics, digitalis)		
Perindopril		A prodrug hydrolyzed by hepatic esterases to an active drug perindoprilat. Rapidly absorbed, reaches maximum plasma concentration within 1 h Food decreases its absorption. The BA of parent drug is 75 % and that of metabolite is 25–30 %	Treatment of hypertension, patients with stable coronary artery disease to reduce the risk of cardiovascular mortality or nonfatal m.i.		
Moexipril		A prodrug deesterified to its major active metabolite moexiprilat. Rapidly absorbed, reaches maximum plasma concentration in 1.5 h. Food decreases the rate of absorption. BA ~13 %	Treatment of hypertension		

Trandolapril		A prodrug hepatically cleaved to active metabolite trandolaprilat. Rapidly absorbed, reaches maximum plasma concentration within 1 h. Food slows absorption. BA 10 % (parent) and 70 % (metabolite)	Treatment of hypertension, HF post m.i. (in combination with diuretics, digitalis), LVD after m.i.		
3. *AT1 receptor antagonism*					
Losartan	ARBs are competitive antagonists that selectively inhibit the binding of Ang II to AT_1 receptors. The blockade is surmountable or insurmountable (see text for details)	It is converted in part to an active metabolite EXP 3174. Rapidly absorbed, reaches maximum plasma concentration within 1 h. Food decreases its absorption. BA ~33 %	Treatment of hypertension, to reduce the risk of stroke in patients with hypertensive and left ventricular hypertrophy (may not be applicable to Black patients) and nephropathy in T2DM with elevated serum creatinine and proteinuria	Chest pain, hypotension, hyperkalemia, hyponatremia, hypoglycemia, diarrhea, gastritis, anemia, backache, rhabdomyolysis sinusitis, and bronchitis. The incidence of cough is significantly lower than ACE inhibitor and placebo	A complete RAAS blockade is not beneficial and involves additional risks of side effects. ARBs may present an alternative to ACE inhibitors, and several trials demonstrated non-inferiority as compared to ACE inhibitors
Valsartan	Like ACE inhibitors, ARBs inhibit negative feedback inhibition and thereby increase PRA, PRC, and Ang II. ARBs make Ang II to be available significantly at the AT_2 receptor sites and activate them. However, the AT_2-mediated precise beneficial actions are obscure	Reaches maximum plasma concentration in 2–4 h. Food has no effect on absorption. BA ~25 %	Treatment of hypertension and NYHA class II–IV heart failure; to reduce CV mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following m.i. (may not be applicable to Black patients); treatment of nephropathy in T2DM	Severe, chronic diarrhea with substantial weight loss has been noted in patients taking olmesartan	Do not coadminister with aliskiren in patients with diabetes and in patients with renal impairment. Avoid coadministration with NSAIDs

(continued)

Table 36.1 (continued)

Drugs by site of action	Pharmacology	PK properties	Indication	Potential adverse effects	Remarks
Irbesartan		Rapidly absorbed, reaches maximum plasma concentration within 2 h. Food has no effect on absorption. BA 60–80 %	Treatment of hypertension and nephropathy in T2DM		ARBs also have teratogenic effect and must be avoided during pregnancy. Nursing mothers should choose to discontinue nursing or drug
Eprosartan		Rapidly absorbed, reaches maximum plasma concentration within 2 h. Food delays absorption. BA ~13 %	Treatment of hypertension		An increase in cancer risk was not found with ARBs
Candesartan cilexetil		Rapidly absorbed and bioactivated by ester hydrolysis in the gut. Reaches maximum plasma concentration in 3–4 h. Food does not affect the BA, which is ~15 %	Treatment of hypertension and HF (NYHA class II–IV) with left ventricular systolic dysfunction to reduce cardiovascular mortality and hospitalizations		
Telmisartan		Rapidly absorbed, reaches maximum plasma concentration in <1 h. Food has no effect. BA is dose dependent, 42–58 %	Treatment of hypertension and for the reduction of the risk of m.i., stroke, or death from cardiovascular causes		
Olmesartan medoxomil		Rapidly absorbed and bioactivated by ester hydrolysis in the gut. Reaches maximum plasma concentration in 1–2 h. Food does not affect the BA, which is ~26 %	Treatment of hypertension		

Azilsartan medoxomil		A prodrug rapidly absorbed and hydrolyzed in the gut. Reaches maximum plasma concentration in 1.5–3 h. Food does not affect the BA, which is ~60 %	Treatment of hypertension		
4. *Aldosterone receptor blockade, ARAs*					
Spironolactone	A competitive and nonselective ARA. Causes excretion of Na^+ and water while retains K^+	Rapidly and extensively metabolized. Reaches maximum plasma concentration 1–3 h. Food increases absorption. BA is ~73 %. Duration after a single dose lasts 16–24 h, and therapeutic effects may persist 2–3 days following discontinuation of therapy	Essential hypertension; primary hyperaldosteronism; edematous conditions, CHF cirrhosis of the liver accompanied by edema and/or ascites; nephrotic syndrome; hypokalemia, severe HF (NYHA class III–IV); to increase survival and to reduce the need for hospitalization	Dizziness, diarrhea, coughing, fatigue, and flu-like symptoms	Owing to "aldosterone escape phenomenon," the escaped aldosterone (during chronic ACE inhibitors/ARBs therapy) might cause cardiovascular abnormalities, justifying the use of ARAs. This class of drug might be better than ACE inhibitors/ARBs in the treatment of low-renin hypertension and reduction in proteinuria in CKD patients. Potassium supplement, potassium-sparing diuretics, RAAS inhibitors should not be given with these drugs. Avoid coadministration with NSAIDs. Eplerenone should not be used in T2DM with microalbuminuria. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus

(continued)

Table 36.1 (continued)

Drugs by site of action	Pharmacology	PK properties	Indication	Potential adverse effects	Remarks
Eplerenone	Selectively blocks the AR with insignificant effect at other steroid receptors. Increases PRA and aldosterone by inhibiting negative regulatory feedback of aldosterone on renin secretion	Peak plasma concentration is reached in 1.5 h. Absorption is not affected by food. BA 69 %. A short half-life and does not have any active metabolites [218]. Metabolized predominantly by CYP3A4	Hypertension, CHF following m.i. (to improve survival of stable patients with left ventricular systolic dysfunction and clinical evidence of CHF after an acute m.i.)	Both drugs can cause life-threatening hyperkalemia Spironolactone causes gynecomastia, breast tenderness, erectile dysfunction, dysmenorrhea, and amenorrhea. Eplerenone has up to a 500-fold lesser affinity for androgen/progestin receptors [207, 217; thus, it causes very less progestogenic and antiandrogenic adverse effects. Eplerenone use is associated with abdominal pain and diarrhea [226]	

Indication and most of the PK data and adverse effects are based on the prescribing information as approved by the US Food and Drug Administration [64]
Class effect: Plasma concentration of PRA increases in a dose-dependent manner after administration of RAAS inhibitors. All RAAS inhibitors should be discontinued as soon as possible when pregnancy is detected. These drugs reduce fetal renal function and increases fetal and neonatal morbidity and death. ACE inhibitors, ARBs, and direct renin inhibitor are used alone or in combination with diuretics and calcium channel blockers. The ACE inhibitors and ARBs have an effect on blood pressure that is less in Black patients than in non-Blacks. In addition, it should be noted that Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-Blacks
AOG angiotensinogen, *RAAS* renin-angiotensin-aldosterone system, *BA* bioavailability, *LVD* left ventricular dysfunction, *m.i.* myocardial infarction, *CKD* chronic kidney disease, *CHF* congestive heart failure, *T1DM* type 1 diabetes mellitus, *T2Dm* type 2 diabetes mellitus, *ACE* angiotensin-converting enzyme, *ARB* angiotensin AT_1 receptor blocker, *ARA* aldosterone receptor antagonist, *NSAID* nonsteroidal anti-inflammatory drug, *NYHA* New York Heart Association

36.3.1 Renin Inhibitors

Preprorenin is generated from renin mRNA in juxtaglomerular cells of the afferent arteriole in the kidney and is converted to prorenin. The precursor prorenin is cleaved into the active proteolytic enzyme renin. Active renin is then stored in and released from secretory granules in the kidney by exocytosis. It does so in response to a decrease in blood volume and blood pressure and increased sympathetic activity, the first step of the complex cascade of the RAAS. Prorenin is also synthesized at a high rate in a number of extrarenal tissues like the adrenal gland, collecting duct, retina, submandibular gland, placenta, ovary, and testis in several species. As the circulating levels of prorenin are much higher than those of renin, organs like the heart lacking renin expression might sequester and activate circulating prorenin [17]. Inactive prorenin is activated by irreversible proteolytic removal of the prosegment through the actions of kallikrein, convertase, trypsin, and cathepsin-B. The removal of the prosegment peptide from prorenin produces enzymatically active renin in the kidney. Also the inactive prorenin is activated by reversible nonproteolytic binding with the (pro)renin receptor (PRR) where the prosegment moves out of the catalytic site without getting detached from prorenin [reviewed in 18].

Both prorenin and renin bind to the PRR [19]. The circulating renin and prorenin bound PRR not only triggers the local generation of Ang II but also activates Ang II-independent signaling cascades. The PRR activation stimulates the phosphorylation of MAPKs, resulting in expression of profibrotic genes, generation of TGF-β1, plasminogen activator inhibitor-1, fibronectin, and collagen-1 synthesis, leading to end-organ damage [reviewed in 18]. Prorenin is no longer an inactive precursor of renin as its binding to the PRR dually activates tissue Ang II-dependent and -independent signal transduction leading to hypertension, cardiac fibrosis, glomerulosclerosis, and proteinuria. Blocking the PRR, the site strategically located at the proximal part of the RAAS cascade, should therefore lessen both the catalytic effect (Ang II generation) and noncatalytic signal transduction of renin and prorenin. At present, the logical target at a higher level in the cascade for RAAS inhibition is to block the action of the enzyme renin, a rate-limiting step in the synthesis of Ang I from AOG. This prevents the production of angiotensin peptides by renin-ACE and non-ACE pathways.

Research on renin inhibition started with antibodies and peptides even before the discovery of captopril. The first generation of renin inhibitors, peptides (e.g., pepstatin) or peptidomimetics (e.g., enalkiren, remikiren), demonstrated renin inhibitory activity and reduced blood pressure. However, they exhibited a short duration of action and low potency and had poor oral bioavailability (<2 %). The knowledge of the tridimensional structure of recombinant human renin opened the doors for structure-based design of renin inhibitors [20]. Using computational molecular modeling and crystallographic techniques, scientists synthesized a number of potent and selective non-peptidic low molecular weight renin inhibitors [21]. The lead candidate for further clinical development was aliskiren, which is the only direct renin inhibitor approved for the treatment of hypertension. Although aliskiren is well

tolerated and demonstrated non-inferiority to ACE inhibitors and ARBs for blood pressure reduction, it has a relatively low bioavailability (~2.5 %) and requires high doses to achieve a similar blood pressure reduction to that of ACE inhibitors and ARBS. This prompted the development of newer renin inhibitors with improved therapeutic profiles. Currently, a number of them are under different phases of clinical trials, the most prominent among them is VTP-27999 [22].

36.3.1.1 Aliskiren

This first-in-class selective renin inhibitor was approved in March 2007 by the US Food and Drug Administration (FDA) for the management of primary hypertension. Following oral administration, aliskiren is rapidly absorbed and reaches the maximum plasma concentration within 1–3 h, while its absolute bioavailability is a meager 2.5 %. A high-fat meal substantially decreases the absorption of aliskiren. Aliskiren is eliminated through the hepatobiliary route as unchanged drug and, to a lesser extent, through oxidative metabolism. About 0.6 % of the dose is recovered in the urine [23].

Aliskiren is indicated for the management of patients with mild-to-moderate hypertension who are intolerant to first-line antihypertensive therapies [24]. A recent meta-analysis from clinical studies suggested that the blood pressure control in hypertensive patients was better with aliskiren when combined with either amlodipine or hydrochlorothiazide than alone, with aliskiren and amlodipine combination being more effective than aliskiren and hydrochlorothiazide combination [25]. The Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial compared the effects of aliskiren and losartan, alone and in combination, on left ventricular mass index in hypertensive subjects with left ventricular hypertrophy [26]. For a similar blood pressure reduction, aliskiren was as effective as losartan in promoting left ventricular mass regression. Additionally, the reduction in left ventricular mass index in the combination group was not significantly different from that of losartan alone [26]. The Aliskiren Observation of Heart Failure Treatment (ALOFT) study in patients with New York Heart Association (NYHA) class II–IV heart failure suggested that addition of aliskiren to an ACE inhibitor (or ARB) and beta-blocker appeared to be well tolerated and had favorable neurohumoral effects [27]. The Aliskiren in Evaluation of Proteinuria I Diabetes (AVOID) trial in patients with diabetes, hypertension, and diabetic nephropathy suggested that aliskiren might have renoprotective effects independent of its blood pressure-lowering effect [28]. Likewise, the combination of aliskiren and irbesartan was more antiproteinuric than monotherapy in type 2 diabetic patients with albuminuria [28]. The ASPIRE (Aliskiren Study in Post-MI Patients to Reduce Remodeling) trial that included patients ~2 and 8 weeks following acute myocardial infarction with the left ventricular ejection fraction (LVEF) ≤45 % compared the administration of increasing doses of aliskiren with a placebo in patients receiving standard treatment with an ACE inhibitor or an ARB. Aliskiren was no more effective than was placebo at reducing the cardiovascular endpoints. Adding aliskiren to the standard therapy, including an inhibitor of

the RAAS, in high-risk post-myocardial infarction patients did not result in further attenuation of left ventricular remodeling. On the other hand, aliskiren in this group of patients statistically significantly *increased* the risk of renal failure, hypotension, and hyperkalemia [29]. The marked increase in risk overshadowed a nonsignificant trend toward a benefit associated with cardiovascular endpoints. Additionally, the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study in patients of type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both showed that the addition of aliskiren to an ACE inhibitor or an ARB is harmful as demonstrated by higher risk of renal impairment, stroke, hypotension, and hyperkalemia [30]. The trial was terminated early. The combined RAAS blockade strategy therefore may not be beneficial in hypertensive patients with metabolic disorders.

36.3.1.2 Therapeutic Use

Aliskiren is indicated for the management of primary hypertension to lower blood pressure, which could reduce the risk of fatal and nonfatal cardiovascular events like stroke and myocardial infarction.

36.3.1.3 Adverse Effects

The commonly reported adverse effects of aliskiren are fatigue, headache, dizziness, diarrhea, nasopharyngitis, and back pain [24] (see Table 36.1 for details).

36.3.2 ACE Inhibitors

ACE (dipeptidyl carboxypeptidase, also termed kininase II) is a nonspecific enzyme that cleaves dipeptide units from substrates with diverse amino acid sequences, especially Ang I and bradykinin. ACE inhibitors are structurally heterogeneous. They differ in the specific groups that bind to ACE, and this influences their pharmacokinetics. A study on the comparative binding affinity of some ACE inhibitors for the two binding sites of human endothelial ACE revealed that ACE inhibitors generally had higher affinity for bradykinin than for Ang I binding sites, suggesting that these agents are primarily, inhibitors of bradykinin degradation, and secondarily, inhibitors of Ang II production [31]. Among those tested, perindoprilat had the highest selectivity for bradykinin versus Ang I binding sites, while enalaprilat had the lowest, indicating that there are differences in the action of ACE inhibitors toward their substrates [31]. This could lead to differences in their efficacy in the treatment of cardiovascular disease.

Different drugs of this class exhibit different hydrophilic and lipophilic properties resulting in different ability to penetrate into tissues. Currently more than 12

ACE inhibitors are in use worldwide. They fall into three classes based on their chemical structures:

1. Sulfhydryl-containing agents: captopril and zofenopril
2. Carboxylate-containing agents: enalapril, ramipril, quinapril, perindopril, lisinopril, benazepril, imidapril, trandolapril, and moexipril
3. Phosphonate-containing agent: fosinopril

Zofenopril and imidapril are not available in the USA.

Although all ACE inhibitors are approved for the treatment of hypertension, all are not equally effective for all indications. Quantitative differences exist among ACE inhibition. Some of ACE inhibitors are lipophilic (e.g., fosinopril >>>quinapril = enalapril > captopril = ramipril = perindopril) that might influence enzyme-binding capabilities with tissue ACE [32]. This can theoretically provide greater penetration into the atherosclerotic plaque. However, this unique lipophilicity has not been shown to predict clinical outcomes [33]. A case-control study has shown that the risk of nonfatal myocardial infarction (MI) did *not* correlate with the degree of ACE inhibitor lipophilicity (tissue affinity) [33, 34]. However, in a randomized study involving patients who had an MI [35], high-tissue penetrating quinapril was shown to be significantly more effective than was comparatively low-tissue penetrating enalapril in reducing the concentration of C-reactive protein. One retrospective study demonstrated differential survival benefits in the first year after acute MI in patients 65 years of age or older to the specific ACE inhibitor prescribed, while ramipril was associated with lower mortality than were most other ACE inhibitors like enalapril, fosinopril, captopril, quinapril, and lisinopril [32]. This study suggested that ACE inhibitors do not benefit acute MI patients similarly. The differential efficacy among specific ACE inhibitors appears to extend to coronary artery disease (CAD) patients without a history of MI, as reported for ramipril in the HOPE study and for perindopril in the EUROPA study. On the other hand, trandolapril in the PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition) trial with stable CAD demonstrated no reduction in the primary composite endpoint of CV death and MI. The findings from these trials suggest that a "class effect" may not exist among ACE inhibitors for the treatment of stable CAD [36].

36.3.2.1 Mechanism of Action

Structurally, ACE is a zinc metalloprotease with two active catalytic sites: NH2 and COOH sites. ACE inhibitors bind to the active site of ACE and interfere with the ability of the enzyme to bind and cleave its substrates. As a result, the cleavage of Ang I to Ang II is inhibited. This results in reduced availability of Ang II at the receptor sites. Bradykinin, another substrate for ACE and naturally occurring vasodilator, is also prevented from its degradation by ACE inhibitors. Consequently, bradykinin binds to endothelial bradykinin B2 receptors resulting in nitric oxide-mediated vasodilation and associated effects. ACE inhibitors increase PRA and PRC by interfering with the negative feedback loop. This process results in increased

formation of Ang I, which may be converted by neutral endopeptidase (NEP) to Ang (1–7), a vasodilator. However, it is not clear to what extent Ang (1–7) can contribute to alleviating clinical hypertension during ACE inhibitor therapy. ACE inhibitors decrease systemic vascular resistance without increasing heart rate [37]. Most ACE inhibitors are cleared principally by the kidney, so impaired renal function could significantly lessen the plasma clearance of these agents. The dose of ACE inhibitors should therefore be reduced in patients with impaired renal function.

36.3.2.2 Heterogeneity of the ACE Gene May Influence the Effectiveness of ACE Inhibitors

The variations in response to ACE inhibitors might be associated with ACE insertion/deletion (I/D) polymorphism [38]. The ACE gene polymorphism is based on the presence or absence of a 287-bp element on intron 16 on chromosome 17 [38]. The level of circulating ACE enzymes depends on the I/D polymorphism [39]. These differences in plasma ACE activity associated with the ACE genotype might modify the efficacy of ACE inhibitors. Patients with a deletion genotype at the intron 16 of the ACE gene exhibited higher activity of plasmatic ACE compared to patients with the insertion genotype [40]. Hass et al. [40], in patients with biopsy-proven proteinuric glomerular diseases and the DD ($n = 10$) and ID/II ($n = 26$) genotype, studied the hemodynamic and antiproteinuric effect of a 6-month therapy using enalapril. Neither blood pressure nor proteinuria changed significantly in patients with the DD genotype in spite of slightly higher dose of enalapril. In contrast, both were significantly reduced in the II/ID group after 10 weeks and 6 months of enalapril therapy. Creatinine clearance was noted to be decreased steadily in DD patients. On the other hand, in II/ID patients, creatinine clearance was noted to be reduced significantly after 10 weeks of enalapril therapy, and then it increased again, while the value at 6 months was again similar to that of DD patients [40]. This study concluded that ACE genotype could influence the antihypertensive and antiproteinuric effect of enalapril in patients with proteinuric glomerular disease [40]. Of note, Kohno et al. [41] suggested that hypertensive patients with the DD genotype when treated with ACE inhibitors were less likely to have regression of left ventricular hypertrophy than were patients with other ACE genotypes [41]. In this study, 18 patients of II genotype for the ACE gene, 19 patients of ID genotype, and 17 patients of DD genotype were tested. Baseline serum ACE activity was significantly greater in the DD group than in the II or ID genotype groups. Despite similar blood pressure reductions, after 2 years, mean regression in posterior wall thickness was significantly less in the DD group than in the ID and II genotype groups [41]. In a randomized placebo-controlled trial of perindopril in normotensive, normoalbuminuric patients with type 1 diabetes mellitus, the nephroprotective effect of ACE inhibition was not associated with the ACE genotype (II, ID, DD) [42]. In a study of 479 patients with systolic dysfunction (LVEF 0.25 ± 0.08) who were genotyped for the ACE-D/I polymorphism [43] and followed to the endpoint of death or cardiac transplantation, 227 patients

received ACE inhibitors at "low doses" (≤50 % of target dose), 201 patients received "high (standard) dose," and 51 patients received ARBs. The ACE-D allele was noted to be associated with an increased risk of events while this effect was primarily in the low-dose group (1-year percent event-free survival: II/ID/DD = 86/77/71, 2-year = 79/66/59, $p = 0.032$). In the standard-dose group, the impact was noted to be markedly diminished (1-year: II/ID/DD = 91/81/80, 2-year: 77/70/71, $p = 0.64$). The impact of beta-blockers and high-dose ACE inhibitors was noted to be greatest in patients of ACE DD genotype and was less apparent with II and ID genotypes [43], suggesting that determination of ACE genotype might help target therapy for heart failure. Evidence also highlights that ACE gene DD polymorphism is associated with poorer survival and an increase in left ventricular mass in idiopathic heart failure patients, suggesting a possible pathophysiologic pathway between ACE gene polymorphism, ACE activity, myocardial hypertrophy, and survival [44]. Taken together, ACE gene polymorphism might play a key role in a marked interindividual difference in the efficacy of ACE inhibitors. However, further studies are needed for a confirmation (Chap. 35).

36.3.2.3 Captopril

It was the first-in-class short-acting ACE inhibitor approved in 1981. After oral administration, captopril is absorbed rapidly with a bioavailability of around 75 %. It is eliminated in urine, 40–50 % as captopril and the rest as captopril disulfide dimers and captopril-cysteine disulfide. Ingestion of food decreases its absorption and bioavailability [45]. The Survival and Ventricular Enlargement (SAVE) trial examined the effect of captopril in patients within 3–16 days after myocardial infarction, with ejection fraction ≤40 % and without overt heart failure or symptoms of myocardial ischemia [46]. In patients with asymptomatic LV dysfunction after MI, long-term treatment with captopril improved survival and reduced morbidity and mortality due to cardiovascular events, and these benefits were seen in patients who received thrombolytic therapy, aspirin, or β-blockers as well as those who did not [46]. The Captopril Prevention Project (CAPP) evaluated the effects of an ACE inhibitor-based therapeutic regimen on cardiovascular events in hypertensive diabetic patients. In the study, captopril was superior to a diuretic/beta-blocker in preventing cardiovascular events in hypertensive diabetic patients, particularly in those with metabolic decompensation [47]. In addition, a captopril-based antihypertensive treatment regimen was reported to be associated with a lower risk of diabetes mellitus development when compared with conventional therapy based on diuretics and/or beta-blockers [48]. Captopril is also shown to reduce progression of diabetic nephropathy. The European Microalbuminuria Captopril Study in nonhypertensive patients with insulin-dependent diabetes mellitus and persistent microalbuminuria revealed that captopril therapy significantly impeded the progression to clinical proteinuria and prevented the increase in albumin excretion rate [49]. Likewise, the North American Microalbuminuria Study in normotensive subjects with insulin-dependent diabetes mellitus reported that 24 months of therapy with

captopril was well tolerated, and, compared to placebo, it reduced significantly the progression of microalbuminuria to clinical proteinuria and also the albumin excretion [50]. The Captopril in Heart Insufficient Patients Study (CHIPS) in patients with mild-to-moderate heart failure indicated that a high dose of captopril as compared to a low dose improved the long-term clinical outcome without significantly increased toxicity [51]. In the study of Kazerani et al. [52], sublingual captopril was reported effective, easily applicable, and safe treatment for the management of hypertensive urgency for 120 min for those patients who did not receive a multidrug antihypertensive regimen. A recent study showed a similar effect of sublingual and oral captopril in hypertensive crisis [53]. However, the taste of the sublingual drugs might be unpleasant.

36.3.2.4 Enalapril

Enalapril is a relatively inactive prodrug with good oral absorption (60–70 %). It is hydrolyzed by esterases in the liver to form enalaprilat, which is a potent ACE inhibitor [54]. Most of the drug undergoes renal elimination as either intact enalapril or enalaprilat. Since enalaprilat as such is not absorbed orally, it is available for intravenous administration. Chronic hypertension considerably increases cardiovascular disease risk in patients with diabetes mellitus. The Appropriate Blood Pressure Control in Diabetes (ABCD) trial in type 2 diabetic hypertensive patients over a 5-year follow-up period demonstrated an advantage of enalapril over nisoldipine (a long-acting calcium channel antagonist) in reducing the incidence of cardiovascular events [55]. Nisoldipine was noted to be associated with a higher incidence of fatal and nonfatal myocardial infarctions than was enalapril in patients with type 2 diabetes mellitus and hypertension [56]. In the studies of Jong et al. [57], treatment with enalapril for 3–4 years in patients with left ventricular systolic dysfunction led to a sustained improvement in survival beyond the original trial period. In patients with heart failure, both enalapril and fosinopril have similar short-term effects on event-free survival, ejection fraction, functional capacity, and quality of life [58]. In patients on hydrochlorothiazide with uncontrolled blood pressure, enalapril was more effective than amiloride in lowering blood pressure [59]. In patients with mild-to-moderate hypertension, a fixed-dose combination of enalapril and nitrendipine was well tolerated and effectively lowered blood pressure, with lower incidence of edema than with calcium channel blocker monotherapy [60, 61]. The Studies Of Left Ventricular Dysfunction (SOLVD) trial in patients with congestive heart failure reported that diabetes mellitus was associated with an increased risk of renal impairment, but this risk was reduced in the enalapril group compared with the placebo group [62]. In a recent clinical study in stable, older patients with compensated heart failure and preserved ejection fraction and controlled blood pressure, enalapril treatment for 12 months failed to improve exercise capacity or aortic distensibility, suggesting that ACE inhibition might not substantially improve key long-term clinical outcomes in this group of patients [63].

36.3.2.5 Lisinopril

On oral administration, lisinopril is absorbed slowly and incompletely and, thus, is a long-acting ACE inhibitor. Food has no significant effect on the absorption of lisinopril. The extent of absorption is approximately 25 %. However, its bioavailability is reduced to about 16 % in patients with stable NYHA class II–IV CHF [see 64, US FDA labeling for lisinopril]. It does not undergo metabolism, and it is excreted intact in the urine [65]. Impaired renal function decreases the elimination of lisinopril. In patients with mild-to-moderate essential hypertension, lisinopril is well tolerated and effectively reduces the blood pressure [66]. In type 1 and type 2 diabetic hypertensive patients and early or overt nephropathy, lisinopril lowers blood pressure and preserves renal function without adversely affecting glycemic control or lipid profiles [67, 68]. The EUrodiab Controlled trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) trial supported an additional place for lisinopril in managing normotensive patients with type 1 diabetes mellitus and microalbuminuria [67]. Furthermore, it was noted that hypoglycemia occurred at a similar frequency in both lisinopril and placebo groups, while patients on lisinopril had significantly lower HbA_{1c} at baseline than those on placebo [67, 69]. The Italian Microalbuminuria Study in normotensive insulin-dependent diabetes mellitus patients with microalbuminuria showed that lisinopril was effective in delaying the occurrence of macroalbuminuria [70]. Lisinopril appeared powerful in slowing the course of nephropathy [70]. The Blood Pressure Reduction and Tolerability of Valsartan in Comparison with Lisinopril (PREVAIL) study in patients with mild-to-severe hypertension reported that both lisinopril and valsartan were highly effective in controlling blood pressure, while valsartan was noted to be associated with a substantially reduced risk for cough [71]. The fixed combination of lisinopril and hydrochlorothiazide in patients with essential hypertension was efficacious in treating essential hypertension and showed a regression of left ventricular hypertrophy [72, 73]. A recent study (DETECT trial) investigated the effects of carvedilol, lisinopril, and their combination for 9 months on vascular and cardiac health in patients with borderline blood pressure. In this study, all treatment groups produced a sustained and well-tolerated functional improvement but not a structural improvement [74].

36.3.2.6 Ramipril

Ramipril is transformed by hepatic esterases into ramiprilat. After oral administration, ramipril is rapidly absorbed, which is reduced in the presence of food. The glucuronides of ramipril and ramiprilat undergo renal excretion. The Acute Infarction Ramipril Efficacy (AIRE) trial in patients with clinical evidence of either transient or ongoing heart failure reported that oral administration of ramipril, initiated between the second and ninth day after myocardial infarction, substantially reduced premature death from all causes, and this benefit was

apparent as early as 30 days and was consistent across a range of subgroups [75]. The Ramipril Efficacy In Nephropathy (REIN) study in patients with chronic nephropathies and high proteinuria reported that ramipril safely reduced the rate of decline of the glomerular filtration rate and halved the risk of end-stage renal failure [76]. The REIN follow-up study in patients with chronic nephropathy and high risk of rapid progression to end-stage renal failure showed that ramipril reversed the tendency of glomerular filtration rate to decline with time [76]. In addition, patients previously treated with antihypertensive drugs other than ACE inhibitors benefited from shifting to ramipril [76]. The effects of ramipril on coronary events in high-risk persons were evaluated in the Heart Outcomes Prevention Evaluation (HOPE) trial. The study reported that in high-risk cohort, ramipril reduced the risk of myocardial infarction, worsening and new angina, and the occurrence of coronary revascularizations [77]. In addition, ramipril reduced the risk of fatal and nonfatal serious arrhythmic events in high-risk patients without clinical heart failure or overt left ventricular systolic dysfunction [78]. A recent clinical study showed that ramipril improved walking distance in patients with claudication possibly through reduction of arterial stiffness [79]. Likewise, among patients with intermittent claudication, 24-week treatment with ramipril significantly increased pain-free and maximum treadmill walking times relative to those taking placebo [80].

36.3.2.7 Fosinopril

Fosinopril is a phosphate-containing prodrug transformed by hepatic esterases into fosinoprilat. This metabolite is more potent than captopril but less potent than enalaprilat. After oral administration, fosinopril is absorbed slowly and incompletely and averages 36 % of an oral dose. Both fosinoprilat and the glucuronide conjugate of fosinoprilat are excreted in urine and bile [81]. The Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET), which compared the effects of fosinopril and amlodipine on serum lipids and glucose control in patients with type 2 diabetic patients with hypertension, showed both treatments were equally effective in lowering blood pressure. There were no significant differences in lipid profile and glucose control between the two groups. However, patients receiving fosinopril had a significantly lower risk of combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine alone [82]. Fogari et al. [83] compared the long-term effect of the combination of amlodipine and fosinopril versus monotherapy on urinary albumin excretion in hypertensive diabetic patients. In this study, combination therapy was more effective in reducing blood pressure than either drug alone at any time of the study without affecting glucose homeostasis. Although all three treatments, amlodipine, fosinopril, or their combination, caused a significant decrease in urinary albumin excretion during the 48-month study period, the combination had a greater effect on reducing albuminuria than either drug did alone [83].

36.3.2.8 Benazepril

Benazepril is a prodrug and is converted by hepatic esterases into benazeprilat, which is a potent inhibitor of ACE. Food slightly delays the absorption of benazepril, but may not affect its ultimate bioavailability. Severe hepatic impairment could slow the conversion of benazepril to benazeprilat, but may not affect the overall bioavailability of benazeprilat. Benazepril is mostly metabolized to benazeprilat and benazepril-glucuronide conjugates [84, 85]. The Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial in patients with hypertension who were at high risk for cardiovascular events reported that the combination of benazepril and amlodipine was superior to the combination of benazepril and hydrochlorothiazide in reducing cardiovascular events [86]. It was further reported that initial antihypertensive treatment with the combination of benazepril and amlodipine should be considered in preference to the combination of benazepril and hydrochlorothiazide since it slowed the progression of nephropathy to a greater extent [87]. Likewise, a recent clinical trial reports the non-inferiority of the combination of amlodipine and benazepril, as compared to the combination of valsartan and hydrochlorothiazide, in lowering blood pressure [88]. Moreover, this combination exerted beneficial effects on renal function, glucose control, and HDL-C and triglyceride levels when compared with the combination of valsartan and hydrochlorothiazide [88].

36.3.2.9 Quinapril

Quinapril is a prodrug transformed by hepatic esterases into quinaprilat, a long-acting ACE inhibitor [89]. After oral administration, quinapril is rapidly absorbed. The metabolite quinaprilat is excreted in urine and feces. Diminished liver function could reduce the transformation of quinapril to quinaprilat. In patients with hypertension, the efficacy of quinapril was similar to that of other ACE inhibitors and showed a lower incidence of adverse events or withdrawals for adverse events relative to those associated with captopril or enalapril [90]. The TREND (Trial on Reversing ENdothelial Dysfunction) study in normotensive patients with coronary artery disease showed that ACE inhibition with quinapril improved endothelial dysfunction [91]. Interestingly, quinapril substantially increased the production of total nitric oxide relative to enalapril following acute myocardial infarction [92].

Comparative trial of quinapril versus captopril in patients with mild-to-moderate congestive heart failure suggested that treatment with 20 mg quinapril once a day was as effective as 100 mg captopril twice a day [93]. The results of this study are generally consistent with those of Acanfora et al. [94] who showed quinapril was as effective as captopril in reducing signs and symptoms of congestive heart failure patients (New York Heart Association [NYHA] class II to III) and improving left ventricular function and exercise capacity. In the study of Zi et al. [95], quinapril did not show beneficial effects on exercise tolerance and quality of life in elderly heart failure patients with preserved systolic function. The Sadko-CHF study in patients

with mild-to-moderate congestive heart failure showed no significant benefit with triple combination (quinapril, valsartan, and bisoprolol) over the combination of quinapril and bisoprolol or bisoprolol and valsartan in the functional status, quality of life, and parameters of left ventricular remodeling [96]. Furthermore, the combination of quinapril and bisoprolol was more effective on 24-h heart rate variability parameters, sympathoadrenal activity, and renal function than the combination of bisoprolol and valsartan or triple combination [96]. In this study, the triple combination might have a negative effect on neurohormonal profile such as excessive activation of Ang II and epinephrine. Thus, the investigators did not recommend the triple combination therapy for stable mild-to-moderate congestive heart failure patients [96]. A recent study in patients with arterial hypertension and functional class I–II chronic heart failure with preserved left ventricular ejection fraction demonstrated the advantages of quinapril monotherapy over metoprolol therapy [97]. Quinapril treatment has also been shown to improve insulin resistance and low-grade inflammatory state in hypertensive patients [98].

36.3.2.10 Perindopril

It is a non-sulfhydryl ester prodrug transformed by hepatic esterases to its active diacid metabolite perindoprilat. It is a long-acting ACE inhibitor. The major part of the active metabolite is cleared by the kidneys, while the other major metabolite of perindopril is an inactive glucuronide. Aging is associated with increased serum perindoprilat concentration, which is possibly caused by a combination of enhanced conversion to the active metabolite and diminished renal clearance [99]. Perindopril was reported to normalize blood pressure in a large majority of hypertensive diabetic patients. In patients at risk of developing diabetic nephropathy, perindopril induced a marked and sustained reduction of microalbuminuria [100]. In the study of Hui et al. [101], perindopril induced a significant regression of left ventricular hypertrophy associated with improvement in left ventricular diastolic performance. Furthermore, perindopril was more effective than was metoprolol in reversing left ventricular hypertrophy [101]. In the EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease (EUROPA) study in patients with stable coronary heart disease and no apparent heart failure, perindopril significantly improved the cardiovascular outcome. Additionally, the investigators recommend considering treatment with perindopril, on top of other preventive medications, in all patients with coronary heart disease [102]. Similar results were reported in the PERSUADE study of Daly et al. [103], in which perindopril tended to reduce major cardiovascular events in diabetic patients with coronary artery disease. According to Ferrari et al. [104], the direct vascular protective property of perindopril might be a reason for its beneficial action in preventing cardiac events in stable coronary artery disease patients. The ASCOT-BPLA trial showed that the free combination of amlodipine and perindopril effectively controlled blood pressure and was superior to the combination of beta-blocker/diuretic in reducing total mortality and cardiovascular outcomes [105]. The SafeTy & efficacy analysis of

coveRsyl amlodipine in uncOntrolled and Newly diaGnosed hypertension (STRONG) study concluded that the fixed combination of perindopril and amlodipine was an effective and well-tolerated antihypertensive treatment [105]. Results from a recent clinical study reveal that the addition of a fixed-dose combination of perindopril and amlodipine to blood pressure regimen is efficient in terms of blood pressure control for 62.3 % of those patients with not-at-goal hypertension [106]. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial showed that routine administration of a fixed-dose combination of perindopril and indapamide to patients with type 2 diabetes mellitus was well tolerated and reduced the risks of major vascular events [107]. The trial also showed that the systematic use of a fixed-dose combination of perindopril and indapamide afforded substantial protection against cardiovascular mortality and myocardial infarction and also renoprotection by reducing the development of micro- and macroalbuminuria [108].

36.3.2.11 Moexipril

Moexipril is a prodrug hydrolyzed after oral administration to its active metabolite moexiprilat [109]. Its bioavailability is markedly reduced in the presence of food and thus should be taken in a fasting state. Patients with moderate-to-severe hypertension inadequately controlled with hydrochlorothiazide benefitted from the addition of moexipril [110]. A statistically greater reduction in left ventricle mass was observed when moexipril was added to a diuretic than to a calcium channel blocker or a beta-blocker [111]. In hypertensive patients, moexipril monotherapy reversed left ventricular hypertrophy [112]. The MOexipril and REgression of left ventricle hypertrophy in combination therapy (MORE) trial reported a greater effect on blood pressure reduction with a combination of moexipril and diuretic than the combination of an ACE inhibitor and a beta-blocker or an ACE inhibitor and a calcium channel blocker [111].

36.3.2.12 Trandolapril

After oral administration, trandolapril is bioavailable as trandolapril (less extent) and trandolaprilat (more extent). The metabolite is about eight times more potent than is the parent compound in inhibiting ACE activity. Trandolaprilat and its inactive metabolites like glucuronides of trandolapril and deesterified products are recovered in the urine and feces. The plasma clearance of trandolaprilat is diminished by renal and hepatic insufficiency [see 113 for FDA labeling]. In the Danish TRACE study (Trandolapril Cardiac Evaluation) in patients with left ventricular dysfunction soon after myocardial infarction, trandolapril markedly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure [114]. A titration-based, escalating-dose regimen of trandolapril

was suggested to be effective and well tolerated in the management of subjects who were antihypertensive treatment naive or whose disease was uncontrolled on a diuretic or calcium channel blocker [115]. The fixed-dose combination of trandolapril and verapamil SR in patients with hypertension including those with type 2 diabetes mellitus was more effective than monotherapy [116]. The International Verapamil-Trandolapril Study (INVEST) trial in hypertensive coronary artery disease patients reported that the verapamil-trandolapril-based strategy was as clinically effective as was the atenolol-hydrochlorothiazide-based strategy [117].

36.3.2.13 Therapeutic Uses of ACE Inhibitors

(i) Treatment with ACE inhibitors is beneficial for the management of patients with mild-to-moderate hypertension. Most of hypertensive patients require at least two antihypertensive drugs to achieve optimal blood pressure control, while the use of combination therapy as first-line treatment is highly recommended. Patients with mild-to-moderate hypertension can better be managed with a combination of an ACE inhibitor and a Ca^{2+} channel blocker or a β-adrenergic receptor blocker or a diuretic than alone.

(ii) ACE inhibitors may be more suitable for the management of blood pressure in hypertensive patients with diabetes mellitus because of improvement of endothelial function and reduction of cardiovascular events.

(iii) ACE inhibitors are a valuable class of drugs for the management of patients with systolic dysfunction because they prevent/delay the progression of heart failure (see Box 36.1) and decrease the incidence of myocardial infarction and hospitalization. Therapy with ACE inhibitors might reduce overall mortality given that the treatment begins during the peri-infarction period. In patients with high risk of cardiovascular events, treatment with ACE inhibitors results in a decrease in the rate of myocardial infarction (Chaps. 8 and 20).

(iv) Treatment with ACE inhibitors prevents/delays the progression of nephropathy in type 1 diabetic as well as nondiabetic patients by reducing glomerular capillary pressure and glomerular injury.

(v) Both American and European guidelines for the management of stable angina, acute coronary syndromes, or ST-elevation myocardial infarction provide a broad recommendation for the use of ACE inhibitors (or ARBs, if patients are intolerant to ACE inhibitors) in patients with coronary artery disease [55, 118–125] (Chap. 20).

A substantial number of hypertensive patients are not adequately controlled with ACE inhibitors (e.g., Afro-Americans show poor response because of low levels of renin). ACE inhibitors might be less effective in heart failure patients with high level of epinephrine [126]. For adequate blood pressure control in these patients, a combination with diuretics, beta-blockers, and/or calcium channel blocker is recommended.

Box 36.1: ACE Inhibitors in Heart Failure
In patients with heart failure, clinical trials demonstrated the survival benefits of ACE inhibitors (Chap. 8). However, ACE inhibitors are sometimes underutilized in these patients because of renal insufficiency or the rise in serum creatinine level. It is suggested that ACE inhibitor therapy might not be discontinued unless serum creatinine level rises above 30 % over baseline during the first 2 months after initiation of therapy or development of hyperkalemia (serum potassium level ≥5.6 mmol/L) [138].

36.3.2.14 Adverse Effects of ACE Inhibitors

ACE inhibitors are not associated with serious untoward reactions. Their use can cause reversible hypotension. Incidence of hyperkalemia (in hypertensive patients with renal insufficiency or under treatment with K^+-sparing diuretics) is reported in high percentage of patients taking ACE inhibitors. Head and neck angioedema (up to 0.7 % of patients) characterized by rapid swelling in the skin of the face, around the mouth, and the mucosa of the mouth and/or throat, as well as the tongue occurs usually within the first week of therapy or within the first few hours after the initial dose. Angioedema and dry cough (5–35 % patients), the class effects of ACE inhibitors, occur possibly because of ACE inhibition-associated accumulation of bradykinin. However, these might disappear on cessation of therapy with ACE inhibitors. They are more common among African-Americans/Afro-Caribbeans (life threatening in 20 % cases). Acute renal failure while on ACE inhibitor therapy is not uncommon. ACE inhibitor-induced hepatotoxicity is rare with an incidence less than 0.1 %. Most hepatotoxicity is mild and transient. Enalapril, fosinopril, lisinopril, and ramipril have been linked to overt hepatotoxicity. As a class effect, ACE inhibitors can cause a fetal risk if taken during pregnancy. Fetal and neonatal morbidity and death have occurred from the use of these drugs during the term of pregnancy [37, 127–135]. All classes of drugs inhibiting RAAS carry a boxed warning on the label to discontinue when pregnancy is detected (see Box 36.2). Arrhythmias including both ventricular and atrial tachycardia, atrial fibrillation, premature ventricular contractions, and bradycardia may occur with drugs like lisinopril [136]. Other adverse effects of ACE inhibitors are skin rash usually consisting of a pruritic maculopapular eruption (less frequently); dysgeusia as characterized by an alteration in or loss of taste, which might often be associated with the use of captopril (the sulfhydryl drug); neutropenia (rarely but predominantly occurs in hypertensive patients with collagen-vascular or renal parenchymal disease) [135]; and sudden and potentially life-threatening anaphylactoid reaction (e.g., with lisinopril) in some patients undergoing dialysis [137].

Box 36.2: Prescribing Information: Boxed Warning from the US FDA
WARNING: FETAL TOXICITY

See full prescribing information for complete boxed warning.

When pregnancy is detected, discontinue [DRUG] as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.

36.3.3 Ang II-AT_1 Receptor Blockers (ARBs)

Although the prevention of Ang II generation by ACE inhibition is of potential therapeutic benefit, ACE inhibitors may permit an Ang II escape phenomenon. ACE inhibitor-mediated disrupted negative feedback mechanism increases the levels of renin and subsequently of Ang I. In such a situation, non-ACE enzymes such as chymase can convert Ang I to Ang II, resulting in Ang II escape [139]. Therefore, compared to ACE inhibition, selective AT_1 receptor blockade might have distinct advantages, like the absence of angiotensin II escape and unopposed AT_2 receptor-mediated effects of Ang II, predominantly vasodilation. In addition, the unwanted side effects of ACE inhibitors, such as dry cough and angioedema, are fewer with ARBs.

The primary goal of antihypertensive therapy is reduction in mortality. A meta-analysis of several trials has shown that the use of ACE inhibitors is associated with a 10 % reduction in all-cause mortality. On the other hand, ARBs had a neutral effect on mortality [140]. The lack of superiority in beneficial effects of ARBs (losartan and valsartan) over ACE inhibitors has been attributed to not using a high enough dose of ARBs. In clinical trials where *lower* doses of ARBs were used, a survival benefit was not found. An insufficient dose of an ARB used in ELITE II, OPTIMAAL, and VALIANT trials might be the reason for an observed lack of beneficial effect. A significant survival benefit in high-risk patients was observed when relatively larger doses of ARBs were used as in LIFE and RENAAL trials [36].

The discovery of drugs targeting AT_1 receptors dates back to saralasin, a peptidergic ARB. Because of its short duration of action, partial agonist activity, and low bioavailability, its use was limited to parenteral administration. The breakthrough came with the introduction of losartan, the first orally active non-peptide ARB in 1995, which is about 10,000 times more selective for the AT_1 receptor than for the AT_2 site. Non-peptide ARBs lack partial agonist activity and are highly specific for antagonizing AT_1 receptors linked to the CVS. Structurally, these drugs are classified into three categories, biphenyl imidazole (losartan, valsartan, candesartan, irbesartan, azilsartan, fimasartan), biphenyl carboxylic acid (telmisartan), and imidazole acrylic acid (eprosartan). Fimasartan is available in South Korea [141].

36.3.3.1 Mechanism of Action

All ARBs inhibit Ang II-induced AT_1 receptor-mediated vascular contraction, pressor responses, vasopressin release, aldosterone secretion, adrenal catecholamines release and increase in sympathetic tone, and cellular hypertrophy. ARBs are competitive antagonists and possess a high degree of selectivity for the AT_1 receptor. The blockade for most of the antagonists except losartan and eprosartan is insurmountable; that is, the maximal response to Ang II cannot be restored in the presence of an ARB. They bind tightly and dissociate slowly, causing the functional loss of occupied receptors. A small difference in the structure and variation in functional groups induces different receptor conformations that result in differences in binding affinity. Thus, losartan has the lowest affinity, whereas irbesartan has the highest affinity among ARBs [reviewed in 142]. Small differences in the molecular structure of each ARB have demonstrated unique molecular effects in experimental studies. Thus, some benefits conferred by ARBs beyond blood pressure control may not be class effects but rather molecular effects as shown in some experimental studies [143]. Some of these effects may account for differences in clinical outcome as shown in Table 36.1 under the column "indication."

36.3.3.2 Losartan

It is the first non-peptide reversible competitive inhibitor approved by the US FDA in 1995. After oral administration, losartan is converted in part to a pharmacologically active 5-carboxylic acid metabolite, EXP 3174, which is 10–40 times more potent than is losartan for the AT_1 receptor site. The oral bioavailability of losartan is around 33 %. The plasma clearance of losartan and EXP 3174 is affected by hepatic insufficiency [144]. In the Losartan Intervention For Endpoint reduction in hypertension study (LIFE), losartan was better tolerated, and it prevented cardiovascular morbidity and death better than did atenolol for a similar reduction in blood pressure. Losartan was thus suggested to confer these benefits other than through reduction in blood pressure [145]. In addition, the results from the RENAAL (Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan) study in patients with type 2 diabetes mellitus indicated the beneficial actions of losartan in reducing renal outcomes, while the antiproteinuric effect of losartan could be a major component of its specific renoprotective effect [146, 147]. Losartan markedly reduced the risk of cardiorenal outcomes and was well tolerated [146]. Increased levels of serum uric acid are considered an independent risk marker for cardiovascular complications. A post hoc analysis of the RENAAL and IDNT trials in patients with type 2 diabetes mellitus and nephropathy demonstrated losartan but not irbesartan significantly lowered serum uric acid relative to placebo, while the degree of reduction in serum uric acid could explain a part of the cardiovascular protective effects of losartan [148]. The Evaluation of Losartan in the Elderly (ELITE) study in elderly heart failure patients showed losartan was associated with lower mortality than captopril, and losartan

was generally better tolerated than was captopril [149]. The ELITE II trial in patients with symptomatic heart failure compared the effect of losartan with captopril in terms of prevention of mortality, and found no significant differences in all-cause mortality or sudden death or resuscitated arrests between the two treatment groups while significantly fewer patients in the losartan group discontinued study drug because of adverse effects [150]. A recent analysis suggested that in patients with symptomatic heart failure and systolic dysfunction or with preserved ejection fraction, ARBs as compared to placebo or ACE inhibitors did not reduce total mortality or morbidity. Moreover, adding an ARB in combination with an ACE inhibitor did not reduce total mortality or total hospital admission but increased withdrawals for adverse effects when compared with ACE inhibitor alone [151]. A recent clinical study in the management of hypertension refractory to losartan monotherapy suggested that a combination losartan and hydrochlorothiazide was more efficacious than was the combination of losartan and amlodipine in decreasing systolic blood pressure [152].

36.3.3.3 Valsartan

The bioavailability of valsartan is around 25 %. Food markedly decreases the oral absorption of valsartan. It is cleared by the liver, while the plasma clearance is affected by hepatic insufficiency [144]. The Valsartan in Acute Myocardial Infarction Trial (VALIANT) established the non-inferiority of valsartan as compared with captopril in patients at high risk for cardiovascular events after myocardial infarction. However, combining valsartan with captopril increased the rate of adverse events without improving survival [153]. In the Valsartan Heart Failure Trial (Val-HeFT), valsartan significantly reduced the combined endpoint of mortality and morbidity and improved clinical signs and symptoms, when added to prescribed therapy [154]. However, the post hoc observation of an adverse effect on mortality and morbidity in the subgroup receiving valsartan and a beta-blocker raised concern about the safety of this specific combination [154]. Based on Val-HeFT, valsartan was approved for the treatment of heart failure in patients who are unable to tolerate ACE inhibitors [144]. Additionally, valsartan is approved for treatment in patients with ST-segment elevation myocardial infarction (see Table 36.1). In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, the primary outcomes of cardiac morbidity and mortality did not differ between valsartan and amlodipine, although reduction in systolic and diastolic blood pressure was noted to be significantly more pronounced with amlodipine. In addition, myocardial infarction was significantly lower in the amlodipine-based regimen, while cardiac failure was nonsignificantly lower in the valsartan-based regimen [155]. Additionally, in patients with mild-to-moderate hypertension, a fixed-dose combination of amlodipine and valsartan was generally well tolerated with significantly greater reductions in blood pressure from baseline, as compared with the amlodipine or valsartan group. Intriguingly, the incidence of peripheral edema was significantly lower in the combination group than in the amlodipine

group [156, 157]. The MicroAlbuminuria Reduction With VALsartan (MARVAL) study in type 2 diabetic patients with microalbuminuria reported that valsartan lowered urine albumin excretion more effectively than did amlodipine despite attaining the same level of blood pressure and the same degree of blood pressure reduction. Also, the antiproteinuric effect of valsartan was independent of blood pressure lowering [158].

The Nateglinide and Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial group studied the effect of valsartan and nateglinide on the incidence of diabetes and cardiovascular events in patients with impaired glucose tolerance and cardiovascular disease or risk factors. Among these patients, the use of valsartan for 5 years, along with lifestyle modification, resulted in a relative reduction of 14 % in the incidence of diabetes mellitus, but did not reduce the rate of cardiovascular events [159]. On the other hand, these patients assigned to nateglinide for 5 years did not show reduction in the incidence of diabetes mellitus or cardiovascular outcomes [160].

36.3.3.4 Irbesartan

The bioavailability of irbesartan is 60–80 %. It is metabolized in part to glucuronide conjugate. Both irbesartan and its glucuronide conjugate are cleared by renal elimination (less extent) and biliary excretion (greater extent). Renal or mild-to-moderate hepatic insufficiency might not affect the plasma clearance of irbesartan [144]. The Swedish irbesartan left ventricular hypertrophy investigation versus atenolol (SILVHIA) study in hypertensive men and women with left ventricular hypertrophy showed that irbesartan reduced left ventricular mass more than was observed with atenolol. This suggests the beneficial action of irbesartan extends beyond lowering blood pressure to the regulation of left ventricular mass and geometry [161]. Additionally, the SILVHIA study showed that irbesartan reduced common carotid artery intima-media thickness, suggesting that Ang II could mediate structural vascular changes, beyond the effects of blood pressure control [162]. Another benefit of irbesartan therapy was a marked slowing of the progression of nephropathy in patients with established type 2 diabetic nephropathy [163]. The Irbesartan Diabetic Nephropathy Trial (IDNT) in patients with established type 2 diabetic nephropathy and chronic kidney disease demonstrated that irbesartan significantly slowed the rate of decline in mean changes in estimated glomerular filtration rate relative to amlodipine and placebo [164]. Interestingly, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) substudy in patients with type 2 diabetes and microalbuminuria reported that irbesartan treatment reduced biomarkers of inflammatory activity in patients with type 2 diabetes and microalbuminuria [165]. A recent study investigated long-term effects of irbesartan and amlodipine treatment in hypertensive patients on plasma aldosterone concentration and left atrial volume [166]. The blood pressure reduction was similar between the two treatment groups; however, a decrease in left atrial volume was larger in the irbesartan group than in the amlodipine group. Irbesartan was suggested possibly to facilitate reversed

remodeling of left atrium through a decrease in plasma aldosterone concentration [166]. In addition, the combination of irbesartan and hydrochlorothiazide was suggested to control effectively the blood pressure in patients with moderate-to-severe hypertension, with an acceptable safety profile [167].

36.3.3.5 Eprosartan

The bioavailability of eprosartan mesylate is around 13 %. It is metabolized in part to glucuronide conjugate. Both eprosartan and its glucuronide conjugate are cleared by renal and biliary elimination. The plasma clearance is affected by renal and hepatic insufficiency [144]. Clinical studies have indicated a relationship between hypertension and cognitive function. Antihypertensive therapy targeting renin-angiotensin system has been suggested to be associated with preserving cognitive function [168]. The Observational Study on Cognitive function And SBP Reduction (OSCAR) trial in patients with essential hypertension supported the hypothesis that antihypertensive therapy with eprosartan might be associated with preservation or improvement of cognitive function [169]. The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study in high-risk hypertensive stroke patients was designed to determine whether eprosartan was as effective as nitrendipine, in terms of prevention of mortality and cardiovascular events [170]. The study showed that eprosartan significantly lowered the combined primary endpoint of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events relative to nitrendipine [170, 171]. Eprosartan has a low potential for serious adverse events and is not associated with clinically significant drug interactions [172].

36.3.3.6 Candesartan Cilexetil

It is an inactive prodrug that is completely hydrolyzed to candesartan, the active form during gastrointestinal absorption. The bioavailability of candesartan is 15 %. Plasma clearance of candesartan occurs by renal (less extent) and biliary (more extent) excretion. Renal insufficiency affects plasma clearance of the drug [144]. The Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM) trial in patients with chronic heart failure showed that candesartan was well tolerated and markedly reduced cardiovascular deaths and hospital admissions for heart failure [173]. In the CHARM-Added trial in patients with chronic heart failure and reduced left ventricular systolic function, add-on candesartan to ACE inhibitor and other treatments lowered the rate of primary endpoint (cardiovascular death or hospitalization for heart failure) [174]. The combination of candesartan and hydrochlorothiazide was effective in patients with hypertension, and this combination was significantly more efficacious than either agent alone [175]. In Japanese patients with mild-to-moderate essential hypertension, the combination of candesartan cilexetil and amlodipine besylate was superior to

monotherapy in lowering blood pressure and was well tolerated [176], providing a potential drug combination choice to improve the rate of blood pressure control [177]. A recent clinical study also suggests that the combination of amlodipine and candesartan is beneficial in reducing major adverse cardiovascular events in hypertensive patients with coronary artery disease [178].

36.3.3.7 Telmisartan

The bioavailability of telmisartan is 42–58 %. It is cleared from the circulation by biliary secretion of intact drug. The clearance is affected by hepatic insufficiency [144]. Telmisartan 1-O-acylglucuronide is the principal metabolite of telmisartan [179]. Telmisartan is unique among ARBs in its pharmacologic and pharmacokinetic properties. It binds the receptor through a unique "delta-lock" structure that supports strong binding affinity and marked lowering of blood pressure. It has additional peroxisome proliferator-activated receptor gamma (PPARγ) partial agonistic action [180]. The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study in patients with type 2 diabetes, mild-to-moderate hypertension, and albuminuria showed that telmisartan conferred similar renoprotection to that of enalapril and was associated with a low incidence of mortality [181]. The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study in normotensive Japanese patients with type 2 diabetes mellitus suggested telmisartan was safe and well tolerated and prevented the progression of microalbuminuria, and, in some cases, it caused remission of albuminuria [182]. The inVestigate the efficacy of telmIsartan versus Valsartan in hypertensive type 2 DIabetic patients with overt nephropathy (VIVALDI) trial in patients with type 2 diabetes mellitus, hypertension, and overt nephropathy showed similar renoprotection by telmisartan and valsartan [183]. In addition, the A comparison of telMisartan versus losArtan in hypertensive type 2 DiabEtic patients with Overt nephropathy (AMADEO) study established the superiority of telmisartan relative to losartan in hypertensive patients with diabetic nephropathy for reducing proteinuria, despite a similar reduction in blood pressure [184]. These studies suggest the renoprotective effects of telmisartan. In patients with vascular disease or high-risk diabetes mellitus without heart failure, ACE inhibitors can reduce mortality and morbidity from cardiovascular causes. In this connection, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) study showed that telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema, while their combination was associated with more adverse events without an increase in benefit [119]. In people at high vascular risk, the effects of telmisartan were similar to ramipril, in terms of major renal outcomes. Although additive effects were seen when telmisartan and ramipril were combined for a greater reduction in proteinuria than with either drug alone, overall it worsened major renal outcomes [185]. This suggests an ARB should not be used in combination with an ACE inhibitor.

36.3.3.8 Olmesartan Medoxomil

It is an inactive prodrug that is completely hydrolyzed to olmesartan, the active form during gastrointestinal absorption. The bioavailability of olmesartan is around 26 %. Plasma clearance of olmesartan occurs by renal elimination and biliary excretion [144]. In older people, olmesartan might represent an effective alternative to ACE inhibitors among first-line drug therapies for hypertension [186]. In elderly patients with mild-to-moderate essential hypertension, olmesartan medoxomil provided an effective, prolonged, and well-tolerated blood pressure control, representing a useful option among first-line drug treatments of hypertension in these patients [187]. A recent clinical study demonstrated that the combination of olmesartan and amlodipine was superior to the combination of perindopril and amlodipine in reducing central systolic blood pressure and other efficacy measures, including a significantly higher rate of blood pressure normalization [188].

36.3.3.9 Azilsartan Medoxomil

It is an eighth ARB approved by the US FDA in February 2011. Azilsartan medoxomil is a prodrug, which is rapidly hydrolyzed to azilsartan (active metabolite) in the gastrointestinal tract during absorption. After oral administration, azilsartan medoxomil is not detectable in plasma. The oral bioavailability of azilsartan is about 60 %. Its elimination half-life is approximately 11 h [see 189 for FDA product labeling]. In the studies of Rakugi et al. [190], azilsartan demonstrated potent and 24-h sustained antihypertensive effect relative to candesartan with equivalent safety. In a multicenter, placebo-controlled trial, azilsartan medoxomil showed a greater blood pressure reduction than both olmesartan medoxomil and placebo with a side effect profile similar to that of placebo [191]. Also, azilsartan medoxomil was significantly more effective in lowering blood pressure than was valsartan in major trials of up to 24 weeks duration [192]. Azilsartan medoxomil was well tolerated and had low rates of discontinuation for adverse events, suggesting that patients are likely to persist with long-term treatment [192]. The combination of azilsartan medoxomil and chlorthalidone in hypertensive patients has demonstrated safety and efficacy in lowering blood pressure to a greater degree than was a combination of olmesartan medoxomil and hydrochlorothiazide or azilsartan medoxomil and hydrochlorothiazide [193].

36.3.3.10 Therapeutic Uses of ARBs

All ARBs are indicated for the treatment of hypertension, to lower blood pressure. They may be used either alone or in combination with a diuretic or other antihypertensive agents, but not with the drugs targeting RAAS (see Box 36.3). Irbesartan and losartan are also approved for the treatment of diabetic nephropathy. These drugs afford renoprotection in type 2 diabetes mellitus patients

independent of blood pressure lowering. ARBs might be an alternative option for heart failure patients who cannot tolerate or respond to ACE inhibitors. In this regard, valsartan and candesartan are indicated for the management of patients with heart failure who are intolerant of ACE inhibitors (Table 36.1) (Chaps. 8 and 20). Losartan might be effective for the treatment of portal hypertension in patients with cirrhosis although it has not been approved for that condition [36, 124, 125, 135, 194]. Although there is controversy regarding ARBs effect on MI, a systematic review of 25 clinical trials in 68,711 patients at MI risk showed that ARBs do not increase the risk of MI [36, 195].

Box 36.3: Dual Blockade of the RAAS

The combination of ARB and ACE inhibitor is controversial. The CHARM-Added trial in patients with chronic heart failure and reduced left ventricular ejection fraction reported that addition of candesartan to an ACE inhibitor and other treatment was superior to placebo and lead to a further clinically important reduction in relevant cardiovascular events [174]. Similar results were noted with the Valsartan Heart Failure Trial (Val-HeFT), which involved patients with heart failure of NYHA class II, III, or IV, when valsartan was added to existing therapy with ACE inhibitors. In this study, valsartan significantly reduced the combined endpoint of mortality and morbidity, when added to existing therapy [154].

The above two findings contrast with the following studies as well as recent practice guidelines for hypertension [4]. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT) study in patients who are at high risk for cardiovascular events after myocardial infarction, which established no inferiority of valsartan as compared with captopril, their combination increased the rate of adverse events without improving the survival [153]. Likewise, the ONTARGET study showed telmisartan to be clinically equivalent to ramipril in patients with vascular disease or high-risk diabetes; however, their combination was associated with more adverse events without any further cardiovascular risk reduction compared with telmisartan or ramipril monotherapy [119]. A recent meta-analysis suggested that while dual blockade of the renin-angiotensin system might have seemingly beneficial effects on certain surrogate endpoints, it failed to reduce mortality and was associated with an extreme risk of adverse events such as hypotension, hyperkalemia, and renal failure compared to monotherapy. Therefore, the risk-benefit ratio suggests against the use of dual therapy [4, 196]. Taken together, dual renin-angiotensin system blockade did not offer additional benefits in reducing overall mortality, cardiovascular mortality, or stroke [197], and there is a need for caution when using dual RAS blockade. The US FDA labeling for all RAAS inhibitors [64] warns against combination of two RAS inhibitors for obtaining any additional benefits (see also Table 36.1 and Chapt. 41).

36.3.3.11 Adverse Effects of ARBs

Like ACE inhibitors, ARBs also cause hyperkalemia and reduction in renal function in patients with renal artery stenosis. Hyperkalemia occurs with the use of ARBs in presence of renal insufficiency and the use of drugs that promote K^+ retention. Induction of dry cough is much less frequent with ARBs, while angioedema occurs very rarely. CNS effects include headache and dizziness, which have occurred less frequently. Like ACE inhibitors, ARBs have teratogenic potential and should not be given during pregnancy [119, 134, 135, 196]. See Box 36.2.

ARBs and Cancer Risk

The relationship between ARBs and cancer is controversial because of conflicting results with meta-analyses of randomized controlled trials and observational studies [198]. However, evidence supports that the use of ARBs does not increase the risk of cancer [199]. There was no significant increase in the overall or site-specific cancer risk from ARBs when compared to controls [200].

Other Adverse Effects

A recent study in middle-aged Americans with hypertension suggested that the use of ACE inhibitors or ARBs was associated with greater risk of appendicitis, exploring previously unrecognized non-cardiovascular side effect of these drugs [201]. The FDA-revised labeling warns that antihypertensive effects of RAAS inhibitors may be attenuated by nonsteroidal anti-inflammatory agents including selective cyclooxygenase inhibitors [see FDA product labeling 64]. Furthermore, in elderly patients or those with compromised renal function, coadministration may result in deterioration of renal function, including possible acute renal failure. However, these effects are reversible. Lithium toxicity (weakness, tremor, excessive thirst, confusion) has been reported during concomitant administration of lithium with ARBs. The FDA-revised labeling for olmesartan medoxomil indicates severe, chronic diarrhea with substantial weight loss as a result of a sprue-like enteropathy. Intestinal biopsies showed villous atrophy. This does not appear to be a class effect of ARBs.

36.3.4 Aldosterone Receptor Antagonists (ARA)

Aldosterone is the principal mineralocorticoid hormone and a neurohormonal mediator of the RAAS. Ang II increases the synthesis of aldosterone by upregulating the CYP11B2 gene, which encodes the enzyme aldosterone synthase, in the zona glomerulosa of adrenal cortex [202, 203]. It plays a central role in the regulation of blood pressure by primarily regulating electrolyte balance and body fluids through

its effects on the distal tubules and collecting ducts of kidneys by regulating Na^+ reabsorption and K^+ excretion. However, overproduction of aldosterone participates in the pathogenesis of cardiovascular and renal disorders by causing excessive salt-and-water retention, elevated blood pressure, left ventricular hypertrophy, cardiac fibrosis, coronary artery disease, stroke, and inflammation and necrosis of the kidney [204, 205]. Markedly high levels of aldosterone have been reported in patients with congestive heart failure [204].

Spironolactone and eplerenone are mineralocorticoid or aldosterone receptor antagonists (MRAs/ARAs) or K^+-sparing diuretics. ARAs are used in the treatment of hypertension with or without aldosteronism and in the volume-overload periods of various forms of heart failure and renal failure [206, 207]. The ARAs have shown clinical efficacy in randomized trials in patients with advanced symptomatic systolic heart failure, post-infarction heart failure with cardiac dysfunction, and systolic heart failure with mild symptoms [206]. Spironolactone is a commonly used add-on diuretic suggested to provide incremental benefit for salt-and-water excretion [207]. See also Chap. 38 on *Diuretics* for additional information.

36.3.4.1 Mechanism of Action

Aldosterone plays an important role in electrolyte homeostasis, regulating fluid and electrolyte balance by retaining Na^+ and water and excreting K^+ from kidneys. It does so by acting on MR present in the cytosol of epithelial cells on the distal and cortical collecting duct of the nephron. The receptors are also present in the mesangial cells and podocytes of the kidney, endothelial and vascular smooth muscle cells, cardiac tissues, adipocytes, monocytes, and brain. Aldosterone has high affinity for its receptor. It enters the epithelial cells and forms mineralocorticoid receptor-aldosterone complex, which, upon translocation into the nucleus, binds hormone response elements and increases gene transcription, leading to renal Na^+ retention and K^+ excretion. Spironolactone and eplerenone are structurally similar compounds that compete with aldosterone to inhibit its binding to the mineralocorticoid receptor and render it transcriptionally inactive. Thus, these drugs act both as a diuretic and as an antihypertensive drug. Since spironolactone has structural elements related to progesterone, it causes progestogenic and antiandrogenic adverse effects resulting in gynecomastia, impotence, and menstrual irregularities. On the other hand, eplerenone, a derivative of spironolactone, was designed to avoid such side effects since eplerenone has very low affinity for progesterone and androgen receptors relative to spironolactone [135, 204, 207].

36.3.4.2 Rationale of Using ARAs

Ang II and aldosterone are not always fully suppressed during ACE inhibitor treatment. In the condition of congestive heart failure, such letdown of hormonal suppression was suggested to be associated with increased mortality [208]. The randomized

evaluation of strategies for left ventricular dysfunction (RESOLVD) study showed that the combination of candesartan and enalapril significantly decreased aldosterone levels at 17 weeks of treatment, but not at 43 weeks [209]. This is known as "*aldosterone escape phenomenon*." Such escaped aldosterone might cause cardiovascular abnormalities even during the chronic therapy with ACE inhibitors and ARBs. This justifies the rationale of developing and employing ARAs.

36.3.4.3 Spironolactone

It is a competitive, nonselective ARA. It undergoes extensive metabolism, while the dethioacetylated metabolite canrenone was earlier considered to be the major active metabolite of spironolactone [210]. Later on it was suggested that 7 alpha-thiomethylspirolactone is the main metabolite. Both spironolactone and 7 alpha-thiomethylspirolactone possess anti-mineralocorticoid activity. Concomitant food intake enhances the bioavailability of spironolactone by increasing its absorption and decreasing the first-pass effect [211]. The Randomized Aldactone Evaluation Study (RALES), the first major clinical trial of an ARA, reported that blockade of aldosterone receptors by spironolactone, in addition to standard therapy, substantially reduced the risk of morbidity and mortality among severe heart failure patients [212]. In "resistant hypertension," the blood pressure remains uncontrolled in spite of using at least three antihypertensive medications in effective doses, including a diuretic drug. Although various factors are identified to be involved, hyperaldosteronism is now recognized as the most common secondary cause of resistant hypertension [213]. Addition of spironolactone to standard treatment regimens induced a marked blood pressure reduction in patients with resistant hypertension [213]. The addition of spironolactone, with careful monitoring of potassium levels, is an evidence-based strategy for the treatment of resistant hypertension [214]. See Chap. 42 on *Resistant hypertension* for more information. Beneficial effects were also demonstrated when spironolactone was added to recommended antihypertensive treatment in type 2 diabetic patients with nephropathy [215]. Interestingly, a recent study showed that spironolactone alone was as effective as the combination of spironolactone and losartan in causing reduction in albuminuria in type 2 diabetic patients [205] indicating its therapeutic potential in diabetic nephropathy.

36.3.4.4 Eplerenone

It selectively blocks the aldosterone receptor with minimal effect at other steroid receptors, thereby minimizing the hormonal side effects seen with spironolactone [216]. As compared to spironolactone, eplerenone has up to a 500-fold lesser affinity for androgen/progestin receptors [207, 217] leaving eplerenone to cause much less progestogenic and antiandrogenic effects. Eplerenone further differs from spironolactone by its shorter half-life and the fact that it does not have any active metabolites [218].

Eplerenone either alone or in combination with other antihypertensive agents appeared effective for the treatment of hypertension. Further, the morbidity and mortality were shown to be reduced when eplerenone was added to standard therapy for left ventricular dysfunction complicating acute myocardial infarction [219]. The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure reported that the addition of eplerenone to optimal medical therapy reduced morbidity and mortality [220]. The trial showed that eplerenone (25 mg/day) significantly reduced all-cause mortality 30 days after randomization (when initiated at a mean of 7.3 days after acute myocardial infarction) in addition to conventional therapy in patients with a left ventricular ejection fraction ≤40 % and signs of heart failure. Based on its early survival benefit, it was suggested that eplerenone could be administered after acute myocardial infarction [221]. Importantly, the EPHESUS trial suggested that earlier eplerenone administration (3–7 days) in post-acute myocardial infarction improved outcomes in patients with left ventricular systolic dysfunction and heart failure while this benefit was not observed when eplerenone was initiated later (≥7 days) [222]. In a study by Udelson et al. [223] in clinically stable, well-treated patients with mild-to-moderate heart failure symptoms and left ventricular dysfunction, 36 weeks of treatment with eplerenone at a dose of 50 mg daily had no detectable effect on parameters of left ventricular remodeling, suggesting a need for additional studies to validate the therapeutic efficacy of eplerenone in heart failure patients. However, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial reported that eplerenone, compared to placebo, reduced both the risk of death and hospitalization among patients with systolic heart failure and mild symptoms [224]. The use of eplerenone, however, for hypertension or heart failure may be limited in patients who are at risk for hyperkalemia [219].

36.3.4.5 Therapeutic Uses of ARAs

Both spironolactone and eplerenone are used for the management of essential hypertension and heart failure. Both are indicated for patients with severe heart failure (NYHA class III–IV) with left ventricular systolic dysfunction, while eplerenone is indicated for patients with severe heart failure (NYHA class III–IV) after an acute myocardial infarction. In addition, spironolactone might have a therapeutic potential for the management of primary hyperaldosteronism, edematous conditions associated with cirrhosis and nephrotic syndrome, and hypokalemia [204, 207].

36.3.4.6 Adverse Effects of ARAs

Both drugs cause a marked and life-threatening hyperkalemia. Thus, these drugs should not be administered concurrently with other potassium-sparing diuretics or RAAS inhibitors. Combination of spironolactone with NSAIDs (e.g.,

indomethacin) can cause severe hyperkalemia [225]. The use of spironolactone is associated with gynecomastia, breast tenderness, erectile dysfunction, dysmenorrhea, and amenorrhea. The use of eplerenone is associated with abdominal pain and diarrhea [226]. Eplerenone should not concomitantly be administered with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, nefazodone, troleandomycin, and clarithromycin.

36.3.5 Aldosterone Synthase Inhibitors

In spite of having therapeutic values, ARAs have certain limitations because of their properties such as poor selectivity (spironolactone) and low potency (eplerenone) [227]. Although ARAs efficiently lower blood pressure, they increase circulating renin and aldosterone levels by inhibiting feedback [228]. Additionally, it has been postulated that aldosterone, in addition to its genomic effects (i.e., activation of MR leading to generation of ROS and reduction of nitric oxide bioavailability), also activates non-genomic receptors (mediated via effects on protein kinase C, intracellular calcium, and cyclic adenosine monophosphate). The deleterious organ remodeling was suggested to be mediated by aldosterone via non-genomic receptors pathways. These effects are not inhibited by ARAs [228]. These negative possibilities might limit the clinical uses of ARAs. The alternative way to blunt aldosterone-mediated cardiovascular pathological events that are beyond MR-mediated actions is to inhibit the synthesis of aldosterone. This is accomplished by inhibiting aldosterone synthase (AS, CYP11B2), an enzyme involved in the synthesis of aldosterone.

Aldosterone synthase is a member of the large cytochrome CYP450 family of enzymes. The synthesis of aldosterone is closely related to that of cortisol. The final step in cortisol synthesis is the 11-β-hydroxylation of 11-deoxycortisol to cortisol by 11-β-hydroxylase, which is the product of the CYP11B1 gene. Ang II and potassium regulate the 5′ promoter region of CYP11B2, whereas the promoter region of CYP11B1 includes elements that can respond to ACTH. The sequences of the coding regions of CYP11B2 and CYP11B1 genes are 95 % identical, and the encoded proteins are 93 % identical, although CYP11B2 expression is confined to the zona glomerulosa, while CYP11B1 is expressed in the zona fasciculata and zona reticularis. Such similarity complicates the process of finding a drug that specifically inhibits AS without affecting cortisol production [229].

Aldosterone synthase inhibitors (ASIs) are a new class of drugs currently under development which might offer an additional therapeutic approach to lower blood pressure and possibly prevent activation of both genomic and non-genomic effects of aldosterone [228]. FAD 286 (dextroenantiomer of fadrozole), an ASI, has been shown to decrease urinary free aldosterone and circulating and cardiac aldosterone levels in experimental rats [230, 231]. In rats with congestive heart failure, both FAD286 and spironolactone improved left ventricular hemodynamics, remodeling, and function; however, only FAD286 persistently normalized the left ventricular

redox status, suggesting that inhibition of aldosterone synthase might be a potential therapeutic strategy for the management of congestive heart failure [232]. In rats treated with Ang II and placed on a high-salt diet, aldosterone receptor blockade by spironolactone or aldosterone synthase inhibition by FAD286 similarly decreased hypertrophy and interstitial fibrosis of the kidney and heart [233]. However, FDA286 lacks selectivity for AS as it inhibits 11-β-hydroxylase to a large extent [228]. This led to the introduction of LCI699, another orally active ASI, which in patients with primary hypertension significantly lowered clinic and ambulatory blood pressure, supporting additional research to evaluate the use of ASI in primary hypertension and/or patients characterized by aldosterone excess [234]. LCI699 was well tolerated with no serious adverse events in patients with hypertension [235]. A recent study demonstrated that aldosterone synthesis inhibition with LCI699 lowered blood pressure modestly in patients with resistant hypertension, suggesting aldosterone synthesis inhibition might offer an attractive adjunct to aldosterone receptor blockade [236]. These studies collectively suggest the preliminary therapeutic potentials of ASIs in patients with hypertension and heart failure.

A key to the success of ASIs lies in the selectivity for inhibition of AS over other closely related enzymes. Most of the ASIs have less or equal selectivity for inhibition of 11-ß-hydroxylase (CYP11B1, cortisol synthase) and aromatase (CYP19) versus aldosterone synthase (CYP11B2). Thus, they lack selectivity for AS at a modest rise in clinical doses. Currently, ASIs are in clinical trials.

36.4 Concluding Remarks

The RAAS is one of the most complex systems having important vasoactive substances (Ang II, Ang (1–7), angioprotectin, aldosterone) that regulate cardiovascular and renal function. The major effector peptide of RAAS is Ang II, the excessive generation of which elevates blood pressure and causes cardiovascular abnormalities primarily through activation of AT_1 receptors. RAAS inhibitors represent promising agents in the management of high blood pressure and improving clinical outcomes in patients with high cardiovascular risk. Blood pressure reduction through RAAS inhibition might reduce the risk of stroke to a certain extent as well. The major classes, ACE inhibitors and ARBs, have a potential to prevent the progression of nephropathy in diabetic patients. Some ACE inhibitors are also indicated in the treatment of heart failure following myocardial infarction to reduce the risk of cardiovascular mortality. The ARBs are also indicated for the management of patients with hypertension and heart failure who are intolerant to ACE inhibitors. The renin inhibitor aliskiren is indicated for the blood pressure control in mild-to-moderate hypertensive patients intolerant to first-line antihypertensive therapies. Hypertensive patients can be effectively managed with a combination of an ACE inhibitor and a Ca^{2+} channel blocker or a β-blocker or a diuretic. However, a combination within with another RAAS inhibitor is not recommended because of the risks of hyperkalemia and hypotension. Long-term use of ACE inhibitors might be

associated with Ang II escape phenomenon, which can be prevented using ARBs. However, the long-term use of ARBs might be associated with aldosterone escape, opening a path for the use of ARAs and ASIs (the latter under development) in the management of hypertension and heart failure.

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Chapter 37
Calcium Channel Blockers in the Treatment of Hypertension

Yoshihiko Kanno, Yoichi Ohno, and Tsuneo Takenaka

Abstract Calcium channel blockers are potent and widely used antihypertensive drugs. They act by preventing calcium entry through voltage-gated calcium channels, predominantly the L-type, into cells resulting in the relaxation of vascular smooth muscle. They dilate arteries and arterioles that increase end-organ perfusion and exhibit a few adverse effects especially in the elderly hypertensive patients. The safety of calcium channel blockers is well established. Clinical trials have established non-inferiority of calcium channel blockers as compared to angiotensin-converting enzyme inhibitors, angiotensin-II AT_1 receptor blockers, and diuretics for the prespecified cardiovascular endpoints. Calcium channel blockers can manifest blood pressure-independent cardiovascular protection, but this effect largely depends on their efficacy to lower blood pressure including that of central blood pressure. Calcium channel blockers are essential antihypertensive drugs to reach goal blood pressure and thus the treatment of choice (although not always the first-line agent) for most hypertensive patients, especially for the high-risk population and those with resistant hypertension. An intense treatment of hypertensive patients with adequate doses of calcium channel blockers is mandatory to improve cardiovascular prognosis. In this chapter, important clinical evidence to support the efficacy of calcium channel blockers to improve cardiovascular endpoints will be reviewed.

Keywords Central hemodynamics • Randomized clinical trial • Target blood pressure • Calcium channels blockers

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37.1 Introduction

Hypertension is a leading cause of underlying cardiovascular disease and mortality. Calcium channel blockers (CCBs) are potent drugs used for treating cardiovascular diseases. They lower blood pressure in diverse populations, including hypertension associated with complicating disorders of diabetes mellitus and coronary artery disease. They reduce CV events, potentiate nitric oxide, and are metabolically neutral. CCBs act by preventing calcium influx through voltage-gated calcium channels. Based on the electrophysiological characteristics (high or low voltage), there are five major subtypes of channels: L, N, T, P/Q, and R. L-type calcium channel plays a critical role in the excitation-contraction coupling of skeletal, smooth, and cardiac muscle and contributes to the timing of the cardiac action potential. CCBs preferentially or exclusively inhibit Ca^{2+} flux through the L-type calcium channels in arterial smooth muscle and cause vasodilation; so they are used to treat hypertension. Some CCBs such as verapamil also act on cardiac muscle to reduce the force of contraction of the heart, slow down conduction thereby slowing the heart rate, and are used to treat angina pectoris and arrhythmias. Chemically, CCBs are of three different classes: dihydropyridine (DHP) (e.g., amlodipine, felodipine, nifedipine, nicardipine, etc.), benzothiazepines (e.g., diltiazem, tetrandrine), and phenylalkylamines (e.g., verapamil, devapamil) (Table 37.1). All have considerable differences in their effect on the L-type calcium channels that are differentially expressed in vascular and cardiac tissues. Furthermore, these drugs differ in vascular to cardiac selectivity ratios.

37.2 Pharmacological Characters of CCBs

Dihydropyridines are the prototype CCBs. They are more potent and selective for vascular (over cardiac) smooth muscle than the other two classes of CCBs. DHPs bind to inactive state of L-type voltage-dependent calcium channels to prevent their activation and subsequent calcium influx [1], and are often used to reduce systemic vascular resistance and arterial blood pressure. At clinical doses, DHPs show little inhibitory effects on cardiac conduction and contraction. They slightly increase heart rate, cardiac output, and stroke volume probably through sustained elevation of global sympathetic nerve activity. Sometimes, when short-acting DHPs are used to treat angina, the vasodilation and hypotension can lead to reflex tachycardia which can increase myocardial oxygen demand and worsen ischemic symptoms. The dihydropyridines are useful for esophageal spasm and vasospasm such as angina. For example, amlodipine is the most widely used DHP-type CCB. It manifests less negative inotropic effects and reflexes tachycardia than nifedipine and has established safety to treat patients with angina. Main actions of amlodipine include calcium entry blockade into vascular smooth muscle cells, decreasing systemic vascular resistance and blood pressure. L-type calcium channels are preferentially expressed in artery and arteriole rather than vein. Peripheral edema is a

Table 37.1 Clinically available calcium channel blockers at present

Name	Target channel	Applicability	CYP	Remarks
Dihydropyridines				
Nifedipine	L	HBP, AP	3A4	Slow-release tablets
Nicardipine	L	HBP, HF	2D6, 3A4	Slow-release tablets, intravenous
Nilvadipine	L, T	HBP	3A4	
Nisoldipine	L	HBP	3A4	
Nitrendipine	L	HBP, AP	3A4	
Manidipine	L, T	HBP	3A4	
Benidipine	L, T	HBP, AP	3A4, 3A5	Anti-proteinuric
Barnidipine	L, T	HBP	3A4	
Amlodipine	L	HBP, AP	3A4	
Efonidipine	L, T	HBP, AP	3A4	Anti-proteinuric
Felodipine	L	HBP	3A4	
Cilnidipine	L, N	HBP	3A4, 2C19	
Aranidipine	L	HBP	2C9, 3A4	
Azelnidipine	L, T, P/Q	HBP	3A4	Anti-proteinuric
Benzodiazepines				
Diltiazem	L	HBP, AP, SVT	3A4	Intravenous
Tetrandrine	L	HBP	3A4	
Phenylalkylamines				
Verapamil	L	SVT, AP	3A4	Intravenous
Devapamil	L	SVT	3A4	

CYP indicates cytochrome P450, and the subtypes that metabolize respective drug are shown. HBP, AP, HF, SVT, L, T, N, and P/Q depict hypertension, angina pectoris, heart failure, supraventricular tachycardia, and L-type, T-type, N-type, and P/Q-type calcium channels, respectively. Not all drugs listed here are approved for marketing in all countries

common side effect of DHPs. Amlodipine is metabolized in the liver by CYP3A4; thus, the dosing interval should be adjusted in the patients with cirrhosis. Biological half-life of amlodipine in normal subjects extends to 39 h, which allows once-a-day administration. Compared to verapamil, amlodipine can be used to treat hypertensive patients with cardiac conduction abnormalities.

Verapamil (a phenylalkylamine CCB) is relatively selective for the myocardium, reduces myocardial oxygen demand, and attenuates coronary vasospasm (Chap. 20). It has minimal effect on vascular smooth muscle and therefore causes less reflex tachycardia. The major mechanism of action is causing negative chronotropic and inotropic effects [1]. Verapamil inhibits L-type calcium channels in use-dependent manner. Thus, verapamil can be the treatment of choice for supraventricular tachycardia and is often used to treat angina where tachycardia can be the most important contributor to the high myocardial oxygen demand. Verapamil is categorized as class IV antiarrhythmic agent (Chap. 52). It does not only slow down cardiac conduction including AV node but also reduces contractility. Thus, verapamil

is contraindicated in pregnant patients (Chap. 60) and for patients with heart failure and cardiac conduction defects such as AV nodal block. In contrast, verapamil is the treatment of choice for rate control of atrial fibrillation to increase AV nodal refractory period, whereas it is not effective for Wolf-Parkinson-White (WPW) syndrome or in the conversion or maintenance of sinus rhythm. Verapamil is also effective for atrial flutter and paroxysmal supraventricular tachycardia (AV nodal reentry) (Chap. 50). Verapamil is metabolized in liver with CYP3A4. After perioral administration, its plasma concentration reaches peak at 2 h, and biological half-life is about 6 h.

Diltiazem (a benzothiazepine CCB) is an intermediate class between DHPs and phenylalkylamines in their selectivity for vascular calcium channels. By both cardiac depressant and smooth muscle relaxant actions, diltiazem reduces arterial pressure without producing the same degree of reflex cardiac stimulation caused by DHPs. Diltiazem is prescribed for hypertensive patients or those with non-transmural myocardial infarction [2] (Chap. 20). Diltiazem is metabolized by CYP3A4, and its biological half-life is approximately 5 h following to oral administration. Similarly to verapamil, it is contraindicated for patients with heart failure and cardiac conduction abnormality and for pregnant patients (Chaps. 52 and 60). Depressor actions of diltiazem are weaker than DHP-type CCBs. Large doses of DHPs can be used for hypertension to adequately decrease blood pressure, as DHPs are rather selective for vascular calcium channels. However, dose titration of diltiazem is limited for hypertension because it shows significant affinity for both cardiac and vascular L-type calcium channels, leading to significant cardiac side effects. Of importance, diltiazem does not induce reflex tachycardia, possessing good indication for angina, especially spastic angina.

Although CCBs manifest differing molecular structures (Fig. 37.1), all of the CCBs are metabolized in the liver mainly with the aid of CYP3A4. Thus, any medications that interact with CYP3A4 affect the pharmacokinetics of CCBs. The following substances inhibit CYP3A4 to potentiate or prolong the actions of CCBs: grapefruit juice, cimetidine, sildenafil, triazole antifungals, erythromycin, and HIV protease inhibitors including ritonavir and saquinavir. Flavonoids in grapefruit are reported to reduce the activity of CYP3A4. In contrast, all medications such as rifampicin, phenytoin, carbamazepine, and phenobarbital that activate CYP3A4 weaken the actions of CCBs.

37.3 Clinical Evidence for Calcium Channel Blockers to Inhibit Vascular Injury

In the early 1990s, several retrospective analyses pointed out that short-acting calcium channel blockers may increase the risk of myocardial infarction [3]; however, long-acting calcium channel blockers are safe for patients with coronary artery disease [4]. Observational studies reported that calcium channel blockers may increase the risk of cancer and bleeding [5, 6]. WHO responded to this confusion and published an ad hoc report stating there are no clinical evidences for serious adverse

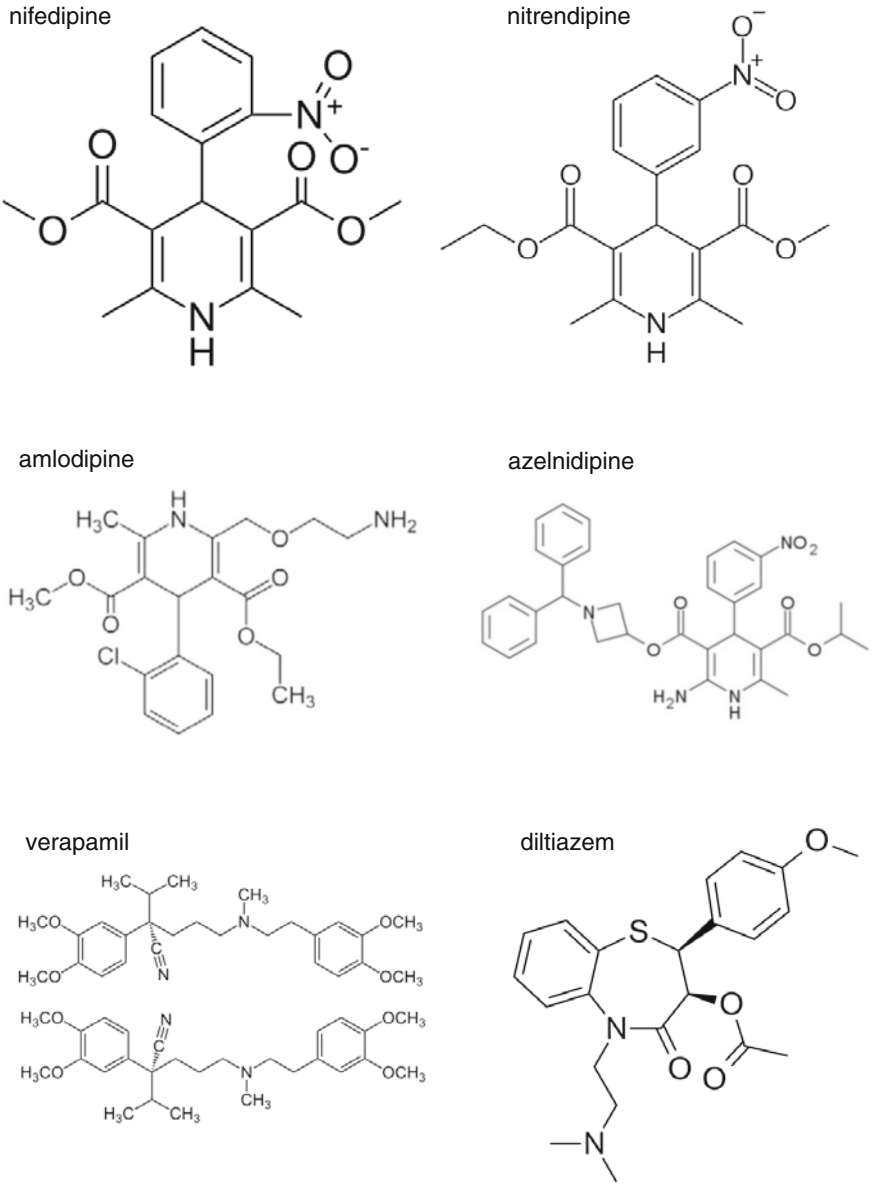

Fig. 37.1 Molecular structures of major calcium channel blockers used in clinical practice. As seen, 1,4-dihydropyridine is a molecule based upon pyridine that has been semi-saturated with two substituents replacing one double bond

effects of calcium channel blockers [7]. Later, these concerns on calcium channel blockers were alleviated in a large-scale prospective randomized controlled trial [8]. Common adverse effects of CCBs include palpitation (reflex tachycardia), flushing (vasodilation), and peripheral edema (arteriolar dilation), related to their potent vasodilatory effects. In contrast to renin-angiotensin system inhibitors, CCBs can be used to control blood pressure during pregnancy.

Although salt restriction is essential for non-pharmacological treatment of hypertension, strict adherence to low dietary salt intake is not easy to achieve. The hypotensive effect of calcium channel blockers is less dependent on salt intake than other drugs, such as angiotensin-converting enzyme inhibitors [9, 10]. Therefore, calcium channel blockers could be prescribed for hypertensive patients who are addicted to salt. Calcium channel blockers established their safety for long-term use in the late 1990s.

37.4 Evidence of CCB to Improve CV Prognosis in Hypertensive Patients

In 1996, the STONE (Shanghai Trial of Nifedipine in the Elderly) study enrolled 1,632 elderly hypertensive patients to assess the effects of slow-release nifedipine on composite cardiovascular endpoints (stroke, heart failure, myocardial infarction, and sudden death) against placebo [11]. Slow-release nifedipine reduced the mean blood pressure by 22/13 mmHg and improved composite CV events. Subanalysis showed that slow-release nifedipine reduced stroke by 57 %.

In 1999, Syst-Eur (the Systolic Hypertension in Europe) study enrolled 4,695 elderly systolic hypertensive patients to compare the effect of nitrendipine against placebo on stroke [12]. Nitrendipine reduced blood pressure by 23/7 mmHg and the risk of stroke by 42 %. Subanalysis also showed that nitrendipine reduced cardiac events including heart failure, myocardial infarction, and sudden death. Collectively, CCBs reduce cardiovascular risk in hypertensive patients, compared to placebo.

37.4.1 Non-inferiority of Calcium Channel Blockers

The ALLHAT (the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) enrolled 33,357 hypertensive patients over 55 years with any coronary risk factors to compare the effects of diuretics (chlorthalidone), calcium channel blocker (amlodipine), and angiotensin-converting enzyme inhibitor (lisinopril) on the composite endpoint of fatal and nonfatal myocardial infarction [8]. The primary results after a mean follow-up period of 4.9 years, published in 2002, showed similar risk reduction regarding the primary composite endpoint in all three groups. However, a statistically significant ($P<0.001$) higher 6-year rate of hospitalized or fatal heart failure (secondary outcome) was observed with amlodipine (10.2 %) compared to chlorthalidone, diaretics (7.7 %).

Similar results were also noted in CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan) study, which enrolled 4,728 Japanese high-risk hypertensive patients to compare the effects of amlodipine and candesartan on composite endpoints of sudden death, cerebrovascular, cardiac, renal, and vascular events [13]. The main results published in 2008 showed that the primary outcome for the composite endpoints did not differ between the two drugs, in spite of the candesartan group exhibiting a reduction in new-onset diabetes. Taking the findings of ALLHAT and CASE-J trials together, CCBs are not inferior to chlorthalidone, lisinopril, and candesartan in reducing cardiovascular risk.

In these clinical trials, the overall adverse event rates of hospitalization for gastrointestinal bleeding, cancer death, and angioedema were not significantly different for the amlodipine treatment group versus the comparator groups.

37.4.2 Superiority of CCB

In 2005, ASCOT-BRLA (the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure-Lowering Arm) study was published comparing the effects between amlodipine with perindopril and atenolol plus thiazide that included 19,257 high-risk hypertensive patients [14]. The primary endpoint was a composite of fatal and nonfatal myocardial infarction, and secondary endpoints were total and cardiovascular death, stroke, and coronary and total cardiovascular events. Although no difference was observed in the primary outcome, amlodipine-based treatment reduced the risk of total death (by 11 %), stroke (by 23 %), and total cardiovascular events (by 16 %) compared with atenolol. The data show that CCB-based treatment is superior to beta-blocker-based treatment in reducing vascular injury. Meta-analysis showed that CCBs are superior to the other antihypertensives including diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in preventing stroke [15]. Even after the differences in blood pressure in each of the drug groups were adjusted, patients treated with CCBs showed a substantial reduction in the relative risk by 33 % for stroke. Of interest, CCBs decreased visit-to-visit variability of blood pressure, which could have contributed to a reduction of cardiovascular events, especially stroke [16].

37.5 CCBs Essentially Attain Target Blood Pressure Goal

Many clinical trials using CCBs have contributed to the determination of target blood pressure levels to which hypertensive patients should be treated [17, 18]. In other words, the use of CCBs helps to achieve target blood pressure levels for most hypertensive patients. Thus, CCBs are considered the basic drugs for the treatment of hypertension. The target diastolic blood pressure that prevents cardiovascular events and death was assessed in the HOT (Hypertension Optimal Treatment) trial,

which enrolled 18,790 hypertensive patients treated with felodipine [17]. Patients were divided into three groups with differing target diastolic blood pressures: <90 mmHg, <85 mmHg, and <80 mmHg. The results showed that patients with diastolic pressures of 83 and 86 mmHg manifested the lowest cardiovascular events and deaths, respectively.

The FEVER (Felodipine Event Reduction) study enrolled 9,711 high-risk hypertensive Chinese patients 50–79 years old to assess the effects of felodipine on stroke against placebo [18]. At the end of study, blood pressure in the felodipine group was 137/82 mmHg, and that in the control group was 142/85 mmHg. The primary endpoint of fatal and nonfatal stroke was reduced by 27 % in the felodipine group compared to placebo ($P=0.001$). Among secondary endpoints, all cardiovascular events were reduced by 27 % ($P<0.001$), all cardiac events by 35 % ($P=0.012$), all-cause deaths by 31 % ($P=0.006$), coronary events by 32 % ($P=0.024$), heart failure by 30 % ($P=0.239$), cardiovascular death by 33 % ($P=0.019$), and cancer by 36 % ($P=0.017$) in the felodipine group compared to placebo. This suggests that systolic blood pressure lower than 140 mmHg is suitable as a target for preventing cardiovascular death and events including stroke, heart failure, and coronary events and that even a small difference in BP (4 mmHg systolic/2 mmHg diastolic) is associated with very substantial reductions in the incidence of most types of cardiovascular events. Do the results from clinical trials agree with epidemiological data? Japanese epidemiological data demonstrated that there is an increase in cardiovascular death or stroke when exposed to blood pressure above 140/90 mmHg [19, 20]. Thus, both epidemiological data and randomized controlled prospective trials provide evidence that 140/90 mmHg is a suitable target blood pressure for antihypertensive drug treatments.

37.6 High-Risk Hypertension

37.6.1 Elderly

Elderly patients may behave differently from young hypertensive patients in lowering of systolic blood pressure below 140 mmHg. To examine the effects of efonidipine on composite endpoint of cardiovascular events including cerebrovascular, cardiac, vascular, and renal events, JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients) study enrolled 4,508 Japanese elderly systolic hypertensive patients aged 65 to 85 years [21]. Patients were randomized into mild (140–160 mmHg) and strict (<140 mmHg) treatment groups and observed for 2 years. The study surprisingly demonstrated that the primary endpoint was similar in both treatment groups.

Another study, J-BRAVE (Japan's Benidipine Research on Antihypertensive Effects in the Elderly) enrolled elderly hypertensive patients and divided them into two age groups: 65–74-year-old (5,092) and >75-year-old (3,804) patients [22]. Blood pressure was controlled with benidipine, and cardiovascular events were

assessed for 3 years. Results indicated that 57 % of patients reached the goal blood pressure of 140/90 mmHg in both age groups. Furthermore, the patients with BP >160 mmHg, despite treatment, showed higher incidence of cardiovascular events. Of note, recently revised guidelines commonly recommend a goal blood pressure 150/90 mmHg and CCBs that dilate both arterioles and arteries to increase organ perfusion for the elderly hypertensive patients who frequently have preexisting end-organ damage [23–25].

37.6.2 Diabetes and Chronic Kidney Disease (CKD)

For young or middle-aged high-risk patients, it seems that the lower the blood pressure, the better the clinical outcomes. Meta-analysis of 61 studies over one million adults indicated that blood pressure above 115/75 mmHg considerably increased cardiovascular mortality [26].

Diabetes is a strong risk factor adding to that of cardiovascular diseases. The UKPDS (United Kingdom Prospective Diabetes Study Group) study divided 1,148 patients with newly diagnosed type 2 diabetes with hypertension into blood pressure goals of tight-control (144/82 mmHg) and less-tight-control (154/87 mmHg) groups [27]. After a median follow-up of 10 years, all diabetic complications, stroke, and microangiopathy were reduced by 24 %, 44 %, and 37 %, respectively, in the tight-blood-pressure-controlled group.

The results of UKPDS trial are generally consistent with those of the HOT trial. Subanalyses of the HOT study in hypertensive patients with diabetes receiving felodipine demonstrated that cardiovascular events were halved in the <80 mmHg group compared with the <90 mmHg group during about 4 years of observation period, and cardiovascular mortality was also decreased in the tight-controlled (<80 mmHg) group [17].

Bakris et al. performed meta-analysis of clinical trials on hypertensive patients with chronic kidney diseases and found that there was a strong relationship between the magnitude of annual decreases in glomerular filtration rate and the blood pressure attained [28]. From this correlation, annual decrease in glomerular filtration rate was nearly zero at 130 mmHg of systolic blood pressure (Fig. 37.2). Regarding target blood pressure, however, hypertension guidelines disagree with one another and recommend 130–140/80–90 mmHg for hypertensive patients with diabetes and/or chronic kidney diseases [23–25].

Practically, CCBs are usually administered to obtain adequate blood pressure control, whereas renin-angiotensin system inhibitors are usually used as the first-line drugs for these high-risk patients to improve renal function. Several studies have shown that renal protective effects of CCBs might be independent of blood pressure lowering. In the CARTER (Cilnidipine Versus Amlodipine Randomized Trial for Evaluation of Renal Disease) study, Fujita et al. reported that cilnidipine, an L/N dual channel blocker, reduced proteinuria following 1-year treatment of 339 Japanese patients with hypertension [29]. They compared cilnidipine- and

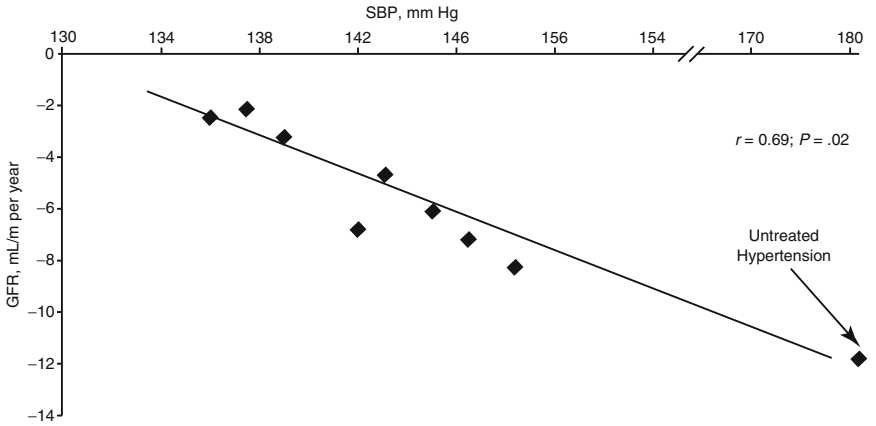

Fig. 37.2 Meta-analysis of ten renal studies (modified after ref [28]): rates of decline in glomerular filtration rate (*GFR*) versus systolic blood pressure (*SBP*) attained in studies extending for 3 years or more in patients with chronic kidney disease

amlodipine-treated patients with equal blood pressure control and showed that cilnidipine reduced, while amlodipine increased, the proteinuria.

In the AVER (Amlodipine Versus Enalapril in Renal Failure) study, Esnault et al. compared amlodipine and enalapril in 263 nondiabetic patients with hypertension who were followed for 3 years [30]. The GFR measured using ^{51}Cr-EDTA showed a similar (statistically not significant) decline in both groups: −4.92 ml/min and −3.98 ml/min in amlodipine and enalapril groups, respectively. The above findings are similar to that reported by us in a 3-year study involving hypertensive patients with IgA nephropathy [31]. Forty-nine Japanese patients of IgA nephropathy with hypertension were divided into benazepril and amlodipine treatment groups, which showed comparable renal protection.

37.7 Effects of Calcium Channel Blockers on Central Hemodynamics

Blood pressure produced by a single heart beat differs from that produced by contraction of the arterial tree [32]. Aortic blood pressure appears to be a more important factor in cardiovascular prognosis than brachial pressure, because major arteries including carotid and coronary arteries are arising from ascending aorta, and for that reason ascending aortic but not brachial pressure is an exact burden on the left ventricle [33]. Recent clinical investigations provided evidence that central aortic blood pressure rather than brachial arterial pressure precisely predicts cardiovascular prognosis in hypertensive patients [34].

Although both diastolic and mean blood pressures are almost identical in all arterial beds, systolic blood pressure differs among the arteries [35]. Wave

amplification and reflection are the underlying mechanisms for these differences in systolic blood pressure. Pressure amplification is important for young people, who may show high systolic brachial blood pressure, whereas their prognoses are pretty good. Reflection pressure is commonly elevated in middle-aged and elderly patients, increasing the central blood pressure that is associated with worsened cardiovascular prognosis. Progress in medical technology enables the estimation of central blood pressure by measuring radial pulse waveform with radial arterial tonometry [36]. As wave reflection becomes large, central systolic blood pressure turns out to be high. In the other words, the greater the stiffness of the artery, the higher the wave reflection.

The ABC-J (Antihypertensives and Blood Pressure of Central Artery in Japan) study is the largest registry of central systolic blood pressure in Japan that included 1,727 hypertensive patients and 848 normotensive subjects [37]. Cross-sectional analysis of ABC-J data demonstrated that sex, height, weight, blood pressure, pulse rate, and antihypertensive drugs are the determinants of central systolic blood pressure. Rather than diuretics or beta-blockers, calcium channel blockers, angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, and alpha-blockers decrease preferentially central systolic blood pressure than brachial systolic blood pressure, suppressing injury of major arteries and improving cardiovascular outcomes in hypertensive patients [14, 34].

37.8 Pressure-Independent Effects of Calcium Channel Blockers on Vascular Damage

Besides an antihypertensive action, dihydropyridines possess strong antioxidative actions [38]. They show scavenging effects on reactive oxygen species and inhibit their production. Reactive oxygen species decrease vasodilatory effects of nitric oxide on vasculature. Thus, the bioavailability of nitric oxide would be acutely improved by calcium channel blockers. Reactive oxygen species also exert influences on the progress of vascular remodeling, inducing the proliferation of vascular smooth muscle cells and fibroblasts [39]. Although antioxidant vitamins seem to lack clinically evident protection on the artery, experimental data do support that CCBs chronically suppress arterial remodeling by reducing oxidative stress.

Clinical evidence of the antioxidative effect of calcium channel blockers was shown in the ENCORE I (effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary disease) study, which was a placebo-controlled trial that involved 343 patients with coronary heart disease. It evaluated the effects of a 6-month administration of long-acting nifedipine and cerivastatin, either alone or in combination [40], on the response of the coronary artery to acetylcholine (change in the diameter of coronary artery measured by quantitative angiography) at baseline and 6 months later. Marked improvement of response to acetylcholine was found with the nifedipine group only. Cerivastatin failed to alter acetylcholine response compared to the placebo group.

Another study using human white blood cells indicated that azelnidipine inhibited interleukin-8 production, thereby suppressing oxidative stress [41]. Collectively, these studies have provided evidence that CCBs improve endothelial function there by suppressing coronary restenosis and cardiovascular events.

37.9 Impacts of Calcium Channel Blockers on the Heart Rate

There is much discussion on the influence of the pulse rate on cardiovascular disease outcome. Sympathetic activation and a high pulse rate would worsen cardiovascular prognosis, but decreasing pulse rate by itself could lead to a reflex elevation in central blood pressure and worsen cardiovascular prognosis [42]. The best antihypertensive drug should share the characteristic of reducing both heart rate and central blood pressure. Most DHPs induce reflex tachycardia via their strong blood-lowering effects. Azelnidipine is the fourth-generation dihydropyridine-type CCB that uniquely reduces pulse rate [43]. Azelnidipine inhibits sympathetic outflow by a direct hyperpolarizing effect on rostral ventrolateral medullary neurons via P/Q channel inhibition and by an indirect action on the medulla via the induction of nitric oxide synthesis [44, 45]. Since azelnidipine also inhibits T channels, it may directly suppress cardiac automaticity and aldosterone release from adrenal glands [43]. Note that azelnidipine is not approved in the USA and Europe.

37.10 Concluding Remarks

Calcium channel blockers are efficacious antihypertensive drugs used in clinical settings. They are not always first-line agents but play a predominant role in the treatment of hypertension associated with complicating disorders of diabetes, coronary artery disease, atherosclerosis, angina, and where other agents are contraindicated. They decrease systemic vascular resistance by inhibiting calcium entry through voltage-gated calcium channels in vascular smooth muscle cells and are useful for treatment of esophageal spasm and vasospasm such as angina. There are three chemically different classes: DHPs, benzothiazepines, and phenylalkylamines. Clinical trials have demonstrated that CCBs reduce cardiovascular risk. Meta-analyses have revealed that CCBs are superior to the other antihypertensive drugs in reducing cardiovascular events, especially stroke. Although some data have shown that CCBs cause preferential decrease in central blood pressure, others have suggested that they reduce peripheral vascular resistance. Cardiovascular protection by CCBs is largely blood pressure dependent, but the effect on pulse rate and antioxidant actions also is involved. Thus, CCBs are the treatment of choice to reach goal blood pressure levels for most hypertensive patients, especially for elderly and high-risk populations. Unfortunately, less than half of hypertensive patients under

antihypertensive medication are able to reach goal blood pressure levels. More intense treatment of hypertension with adequate doses of CCBs is required to improve cardiovascular prognosis.

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Chapter 38
Diuretics for the Treatment of Hypertension

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Abstract Diuretics are agents commonly used in diseases characterized by excess extracellular fluid, including chronic kidney disease, nephrotic syndrome, cirrhosis, and heart failure. Diuretics are also commonly used either as monotherapy or in combination with other antihypertensive agents in the management of hypertension. Multiple diuretic classes, including thiazide-type diuretics, loop diuretics, and potassium-sparing diuretics, are used to treat patients with these diseases. An understanding of what determines a patient's response to a diuretic is a prerequisite to the correct use of these drugs. The response of patients with these diseases to diuretics, which is related to the dose, is best described by a sigmoid curve whose contour can become distorted by any of the several sodium-retaining states that are directly or indirectly associated with renal disease. The pharmacodynamic effect of diuretics as used in the treatment of hypertension involves both a volume removal element and more long-term vasodilation. Diuretic actions are of considerable importance to patients who have renal disease, as their effective use assists in extracellular fluid volume control, reducing excretion of protein in urine and lessening the risk of developing hyperkalemia. Diuretic-related adverse events that involve the uric acid, sodium, and potassium axes are not uncommon; therefore, the clinician must be vigilant in looking for biochemical disturbances. As a result of diuretic-related adverse events, clinicians must be resourceful in the dose amount and frequency of dosing.

Keywords Loop diuretics • Thiazide diuretics • Spironolactone • Hypertension • Diuretic-related side effects • Hypokalemia • Diuretic resistance

38.1 Introduction

Modern diuretic therapy ushered forth out of two apparently unrelated events in the 1930s: the development of sulfanilamide, the first effective antibacterial drug, and the characterization of the enzyme carbonic anhydrase. Clinical experience

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with sulfanilamide showed that this drug increased urine flow as well as enhanced sodium (Na^+) and potassium (K^+) excretion. The recognition that sulfanilamide inhibited carbonic anhydrase fueled attempts to synthesize compounds that might more specifically inhibit carbonic anhydrase. The compound acetazolamide was discovered in the process. The diuretic effect of acetazolamide proved to be short lived in its action leading to a search for more potent diuretic compounds with more substantial long-term effectiveness. The first of its kind of these diuretics was chlorothiazide (CTZ), and its introduction in 1958 ushered in the modern era of diuretic therapy [1].

Diuretics are important therapeutic tools. First, they effectively reduce blood pressure (BP), while at the same time decreasing the morbidity and mortality that follows from being hypertensive. Diuretics are currently recommended by a number of guideline promulgating committees as first line to early therapy for the treatment of hypertension [2, 3] (Chap. 30). In addition, they remain an important component of therapy for volume overload conditions, such as heart failure (HF), nephrotic syndrome, and cirrhosis, to improve the symptoms of edema and congestion [4] (Chaps. 1 and 8). This chapter reviews the mechanism of action of the various diuretic classes and the physiologic adaptations that accompany their use and discusses the basis for their use in the treatment of hypertension and HF. In addition, commonly encountered side effects with diuretics are considered.

38.2 Individual Classes of Diuretics

The predominant site(s) of nephron action of various diuretic classes are represented in Fig. 38.1. Of the diuretic classes available, all have distinctive pharmacokinetics and, in many instances, differing pharmacodynamic responses dependent on both the nature and stage of the underlying disease being treated (Table 38.1).

38.3 Carbonic Anhydrase Inhibitors

Acetazolamide is the only carbonic anhydrase inhibitor with relevant diuretic effects. Acetazolamide binds tightly to carbonic anhydrase, and high concentrations are found in tissues containing this enzyme, particularly red blood cells and the renal cortex. Acetazolamide is mainly renally cleared as the unchanged molecule with approximately 50 % of its renal clearance as the result of active tubular secretion. Its administration is ordinarily accompanied by a brisk alkaline diuresis. Although carbonic anhydrase inhibitors are proximal tubular diuretics (where the bulk of Na^+ reabsorption occurs), their net diuretic effect is modest, since Na^+ reabsorption in more distal nephron segments offsets proximal Na^+ losses. Acetazolamide use is constrained by both its transient action and the development of metabolic

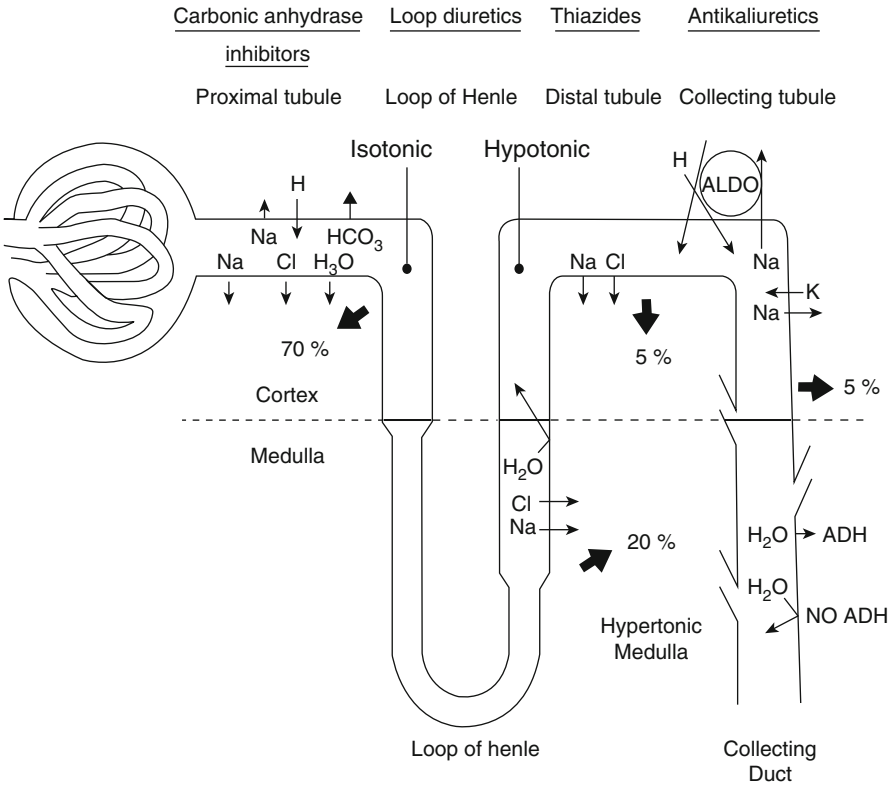

Fig. 38.1 Schematic of the nephron illustrating the handling of water and electrolytes by the different segments and the major nephron sites of diuretic action. Aldosterone effect influences sodium and potassium handling. Heavy *arrows* represent the approximate percentage of sodium reabsorbed by the various nephron segments

acidosis with prolonged use. Acetazolamide (250–500 mg daily) can correct the metabolic alkalosis that derives from chloride (Cl^-) loss with thiazide and/or loop diuretic therapy and can be of some utility in patients with sleep apnea [5, 6].

38.4 Loop Diuretics

Loop diuretics act predominately at the apical membrane in the thick ascending limb (TAL) of the loop of Henle, where they compete with Cl^- for binding to the $Na^+/K^+/2Cl^-$ cotransporter, thereby inhibiting Na^+ and Cl^- reabsorption [7]. Loop diuretics also have effects on Na^+ reabsorption within other nephron segments, which are qualitatively minor compared with their action at the TAL. Other clinically important effects of loop diuretics include a decrease in both free water (H_2O)

Table 38.1 Pharmacokinetics of diuretics

		Half-life		
Diuretic	Bioavailability (%)	Normal subjects (hrs)	Renal failure (hrs)	HF (hrs)
Loop of Henle				
Furosemide	10–>100	1.5–2	2.8	2.7
Bumetanide	80–100	1	1.6	1.3
Torsemide	80–100	3–4	4–5	6
Ethacrynic acid	90–100	1–3	ND	ND
Distal convoluted tubule				
Bendroflumethiazide	ND	5–9	ND	ND
Chlorthalidone	64	50–60	ND	ND
Chlorothiazide	30–50	1.5–2.5	ND	ND
Hydrochlorothiazide	60–80	3.2–13.1	Increased	ND
Indapamide	93	15–25	ND	ND
Metolazone	40–60	15	ND[a]	ND[a]
Polythiazide	ND	26	ND	ND
Trichlormethiazide	ND	1–4	5–10	ND
Distal/collecting duct				
Amiloride	50–60	17–26	100	ND
Triamterene	>80	2–5	Prolonged	ND
Spironolactone	[b]	1.5	ND	ND
Eplerenone	70	4–6	Small↑	ND[c]

Drugs are listed based on the site of action on the nephron
ND not determined, *HF* heart failure, *hrs* hours
[a]Half-life extended based on level of renal or heart failure
[b]Variable based on the formulation being used
[c]Dose adjustment based on serum potassium value

excretion and absorption during H_2O loading and dehydration, respectively, about a 30 % increase in fractional calcium (Ca^{++}) excretion, a significant increase in magnesium (Mg^{++}) excretion, and a transient increase followed by an ultimate decrease in uric acid excretion [8]. The increase in urine Ca^{++} excretion with loop diuretic therapy increases parathyroid hormone release and therein a negative cardiac effect relating to the profibrotic effect of PTH on the myocardium [9].

The available loop diuretics include bumetanide, ethacrynic acid, furosemide, and torsemide. These compounds are heavily protein bound (to albumin), and therefore, in order to gain access to the tubular lumen (site of action), they must undergo secretion (the same applies to thiazide-type diuretics), which in their case is by way of probenecid-sensitive organic anion transporters localized to the proximal tubule [10, 11]. Tubular secretion of loop diuretics may be reduced in the company of elevated levels of endogenous organic acids, such as in chronic kidney disease (CKD), and by drugs that share the same transporter, such as salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs). Loop diuretic protein binding can also be decreased by uremic toxins and/or fatty acids, which can in kind alter diuretic action.

Diuretic excretion rates approximate drug delivery to the medullary TAL and match up well with the observed natriuretic response [2, 4]. The relationship between urinary loop diuretic excretion rate and natriuretic effect is that of an S-shaped sigmoidal curve (Fig. 38.2) [11]. A normal dose-response relationship (as is typically seen in the untreated patient with hypertension) can be distorted (downward and rightward shifted) by a mixture of clinical conditions ranging from volume depletion ("braking phenomenon") to HF or nephrotic syndrome (disease-state alterations) to various drug therapies. As an example of the latter, NSAIDs modify this dose-response relationship by inhibiting prostaglandin synthesis, blunting any expected diuretic effect. Finally, although the diuretic dose-response relationship can flatten in the setting of nephrotic-range proteinuria, the binding of loop diuretics to urinary protein and thereby limiting free drug access to receptor sites seems not to be the basis for this reduction in diuretic effect [12].

38.4.1 Furosemide

Furosemide is the most broadly used diuretic in this class; however, its use is made more difficult by erratic absorption with a bioavailability range from 12 to 112 % [13]. The absorption coefficient of variation varies from 25 to 43 % for different furosemide products; thus, exchanging one furosemide formulation for another will not automatically standardize patient absorption and thus response,

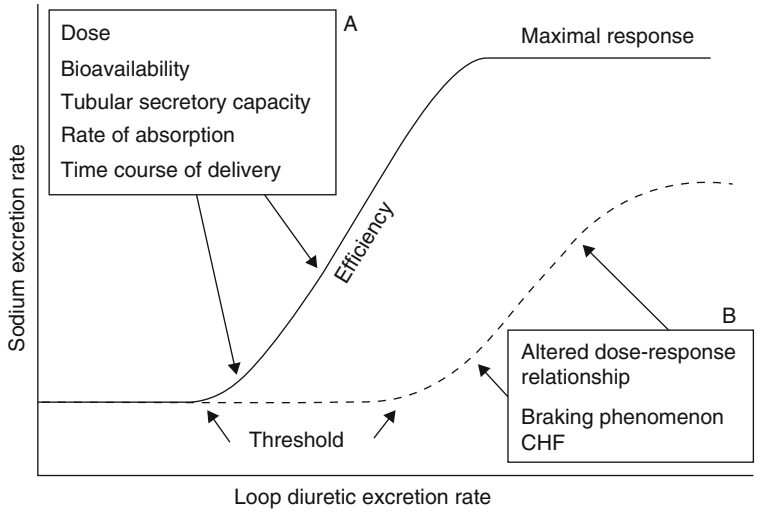

Fig. 38.2 Pharmacokinetic (*A*) and pharmacodynamic (*B*) determinants of the natriuretic response to a loop diuretic. The *broken line* represents a distorted dose-response relationship, as is seen in a patient with diuretic resistance. The amount of diuretic needed to achieve a threshold response can vary quite substantially in the presence of diuretic resistance

when furosemide is given orally. Bumetanide and even more so torsemide are more predictably absorbed than is furosemide. The consistency of torsemide's absorption and its longer duration of action are pharmacologic features to consider when loop diuretic therapy is necessary in the HF patient [14].

38.4.2 Bumetanide/Torsemide

The loop diuretics furosemide, bumetanide, and torsemide are diuretics of choice in the patient with CKD [15]. The pharmacokinetics of loop diuretics are altered in the CKD population: with renal clearance of these drugs being reduced corresponding to the degree of change in renal function. In general, furosemide's pharmacokinetics are more significantly altered in CKD than is the case for other loop diuretics, since furosemide is a renally glucuronidated compound [16]; therefore, both its renal metabolic and intact clearances are dually reduced in CKD. Alternatively, bumetanide and torsemide undergo significant hepatic metabolism; thus, their pharmacokinetic profiles in CKD vary only as the result of decreased renal clearance of the intact molecules (Table 38.1).

38.4.3 Ethacrynic Acid

Ethacrynic acid is structurally different from other loop diuretics. Its diuretic effect is similar to that of other loop diuretics. Ethacrynic acid has little or no effect on glomerular filtration or on renal blood flow, except following pronounced reductions in plasma volume when associated with rapid diuresis. It is used much less frequently than the other loop diuretics mainly because of an increased propensity to hearing changes particularly when given intravenously [17]. Its main use clinically is in those patients with documented sulfa allergies in that it is the only loop diuretic that is structurally different in not having a sulfonamide molecule [18].

38.5 Adaptation to Diuretic Therapy

Diuretic-induced inhibition of Na^+ reabsorption in one nephron segment elicits important adaptations in other nephron segments, which not only limits diuretics' antihypertensive and fluid-depleting actions but also contributes to the magnitude of side effects. Although a portion of this resistance to diuretic effect is an expected consequence of their use, profound diuretic resistance from such adaptations can be encountered in patients with clinical disorders such as HF, cirrhosis, and/or proteinuric CKD. An understanding of how adaptation to diuretic therapy occurs is a prerequisite to minimizing the negative features of this process.

The initial dose of a diuretic ordinarily produces a brisk diuresis and in most instances results in a net negative Na^+ balance. The new equilibrium state established with diuretic therapy is one where body weight decreases and with repetitive dosing stabilizes, since adaptive processes intervene and preclude a continuous volume loss. In nonedematous patients given either a thiazide or a loop diuretic, this adaptation or *braking phenomenon* occurs within a matter of days and limits weight loss to 1–2 kg; this has been demonstrated in normal subjects given the loop diuretics furosemide or bumetanide. Furosemide administered to subjects ingesting a high-Na^+ diet (270 mmol/24 h) produces a brisk natriuresis, which results in a negative Na^+ balance for the following 6 h. This is followed by a prolonged period of time up until the next dose, where Na^+ excretion is reduced to a level considerably below that of intake [19]. This post-diuresis Na^+ retention compensates for initial Na^+ losses, with the result being no net weight loss. In fact, this same pattern of Na^+ loss and compensatory retention can persist for as long as a month after furosemide administration [20]. Sodium intake, prior to and after diuretic dosing, will influence the end results of the *braking phenomenon*. For example, if Na^+ intake is kept low, Na^+ balance will remain negative in the hours after the initial natriuresis with a net fall in body weight.

38.6 Mechanisms and Management of Diuretic Resistance

Diuretic resistance is encountered in a number of disease states, such as CKD, nephrotic syndrome, HF, and cirrhosis with ascites, and most times relates to prominent pharmacodynamic alterations that are derived from disease-state organ dysfunction [11]. Combination diuretic use, which produces sequential nephron segment blockade and thus an additive diuretic response, is frequently necessary and is regularly employed in these conditions. Pharmacokinetic determinants of diuretic response, including the dose administered, absolute bioavailability, and tubular transport rate/capacity are pertinent considerations factors in how a diuretic response is generated [11]. Pharmacodynamic factors, such as improvement in the underlying disease-state condition promoting diuretic resistance, are perhaps more important to overall response and often result in modification of the dose-response relationship. Stratagems used to maximize the diuretic response to loop diuretics include correcting abnormal hemodynamic parameters, utilizing larger doses of well-absorbed orally administered loop diuretics, or using constant intravenous infusions or bolus diuretic therapy [21]. Bolus loop diuretic therapy does not appear to be much different than that of loop diuretic infusions in initiating and maintaining a diuretic response [22]. If these measures fail, then diuretic combinations are useful. Perhaps the most effective is the combination of metolazone and a loop diuretic. The rationale for and use of various diuretic combinations, with particular emphasis on the metolazone-loop diuretic combination, is well established but requires a deft touch in selection of medication doses in that over-diuresis is not uncommon [23].

38.7 Thiazide Diuretics

The main site of action for thiazide-type diuretics is the early distal convoluted tubule where the coupled reabsorption of Na^+ and Cl^- is inhibited (Fig. 38.1). Besides effects on Na^+ excretion, thiazide diuretics also impair urinary diluting capacity (while preserving urinary concentrating mechanisms), reduce Ca^{++} and uric acid excretion, and are modestly magnesuric. The latter can be particularly prominent with long-acting thiazide-type diuretics, such as chlorthalidone [24].

38.7.1 Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is the most widely used thiazide-type diuretic in the United States. Its absorption is dose proportional with a bioavailability ranging from 60 to 80 %. The rapidity and extent of its absorption can be reduced in HF and/or CKD. The onset of diuresis with HCTZ is fairly rapid occurring within 2 h and peaking between 3 and 6 h and sometimes continuing for as long as 12 h; however, only a small fraction of the total natriuretic response to HCTZ occurs beyond 6 h after dosing. The diuretic effect of HCTZ can be extended by administering doses in the 50–200 mg range [25]. Alternatively, if a more extended natriuresis is sought after, a longer-acting thiazide-type diuretic – such as chlorthalidone or metolazone – can be considered.

The half-life of HCTZ and other thiazide diuretics is extended in patients with HF and/or CKD and is particularly lengthening when these disease states are decompensated. Doses of HCTZ in the order of 100–200 mg/day can induce diuresis in patients with CKD, which is contrary to the belief that these drugs are ineffective in advanced stages of CKD [25, 26]. However, in CKD the magnitude of the natriuretic response to a thiazide diuretic has a ceiling controlled by two factors: first, the lowered GFR in CKD reduces the absolute filtered load of Na^+, and second, the distal tubular site of action for a thiazide diuretic is a locus where even under the best of circumstances, only a modest natriuretic response can be anticipated [25, 26].

38.7.2 Metolazone

Metolazone is a quinazoline diuretic with a predominant distal tubular site of action and a minor inhibitory effect on proximal Na^+ reabsorption through a carbonic anhydrase-independent mechanism. Metolazone is lipid soluble and has a large volume of distribution (V_D), which plays a role in its extended duration of action. The pharmacokinetic features of metolazone are a factor in its effectiveness in the setting of either CKD or diuretic-resistant situations, particularly when combined with a loop diuretic [11, 24]. Oral metolazone in its Zaroxolyn form is slowly and

rather erratically absorbed. Diuretic resistance, the failure to respond to a diuretic regimen, is usually taken to signify a worsening of the primary volume-retaining state, but with metolazone, it simply can be a consequence of limited drug absorption [11, 24].

38.7.3 Chlorthalidone

Although chlorthalidone and HCTZ are structurally similar compounds, they are very dissimilar pharmacokinetically. Chlorthalidone is distinguished from HCTZ in having an extremely long half-life and a very large volume of distribution owing to its extensive partitioning into red blood cells [27]. This latter feature creates a substantial depot for chlorthalidone, allowing for a slow streaming effect (red cell → plasma) with subsequent gradual elimination from the plasma compartment by tubular secretion. The extremely long half-life of 40–60 h for chlorthalidone differentiates it from HCTZ, which has a much shorter but wider variation in half-life, from 3.2 to 13.1 h [27]. This plasma half-life difference can be expected to correlate with a more extended effect of chlorthalidone on diuresis and possibly BP. Moreover, the post-diuretic period of antinatriuresis, otherwise termed the "braking phenomenon," is less apt to interfere with net Na^+ loss when a long-acting diuretic, such as chlorthalidone, is administered. Also, chlorthalidone being present in the blood for a longer period of time lengthens more drug exposure in tissue compartments where the drug has its putative effects; however, diuretic blood levels needed to effect direct vessel dilation per se are typically several times higher than what is achieved therapeutically; therefore, it is unclear how the blood level of a diuretic, such as chlorthalidone, might relate to a direct vascular mechanism of action [28, 29].

38.7.4 Indapamide

Indapamide is the first of a class of antihypertensive diuretic agents known as indolines, and it is a mildly natriuretic antihypertensive agent. Indapamide has excellent and almost complete bioavailability, and its metabolism follows linear kinetics with a half-life of ≥15 h. There is little accumulation of indapamide in renal failure presumably because of a shift to greater biliary elimination [30]. At doses of 5 mg or more/day, the diuretic effect of indapamide can be substantial. At 2.5 mg/day fractional Na^+ excretion is unchanged when measured after 4 weeks of treatment; thus, at the usual therapeutic doses of 1.25–2.5 mg/day, the antihypertensive effect of indapamide seems to be related as much to calcium antagonist vasorelaxant effects as to its diuretic property, which has been suggested with its use in end-stage renal disease (ESRD) [31]. Like several other thiazide-type diuretics, indapamide affords the treated patient with hypertension cardiovascular (CVR) risk reduction in the setting of diabetes, left ventricular hypertrophy, and/or stroke [32].

38.8 Distal Potassium-Sparing Diuretics

There are two classes of K^+-sparing diuretics: competitive antagonists of aldosterone, such as spironolactone and eplerenone, and compounds – such as amiloride and triamterene – which work in an aldosterone-independent manner. Drugs in this class inhibit active Na^+ absorption in the late distal tubule and the collecting duct. In so doing, basolateral Na^+- and K^+-ATPase activity drops and intracellular K^+ concentration is reduced. The resultant decrease in the electrochemical gradient for both K^+ and H^+ reduces secretion of these cations. Potassium-sparing diuretics also reduce Ca^{++} and Mg^{++} excretion and can be of some utility in patients prone to the development of calcium-containing stones [33]. Since K^+-sparing diuretics are only modestly natriuretic, their clinical utility resides more in their K^+-sparing properties, especially when more proximally acting diuretics increase distal Na^+ delivery, or in states of primary aldosteronism. Potassium-sparing diuretics do, however, have a significant natriuretic effect when they are one of several components of a diuretic regimen, so-called sequential nephron blockade, and/or when used in suitably titrated doses in patients with cirrhosis/ascites [34].

38.8.1 Spironolactone

Spironolactone is a highly protein-bound and well-absorbed, lipid-soluble K^+-sparing diuretic. 7α-Thiomethylspirolactone and canrenone are two metabolites of spironolactone, which are responsible for much of its antimineralocorticoid activity [35]. The onset of action for spironolactone is characteristically slow, with a peak response at times 48 h or more after the initial dose. Currently, spironolactone is used with increasing regularity in patients with resistant hypertension (Chap. 42), with or without primary aldosteronism, who are receiving multidrug regimens that include a diuretic and any other of the several drug classes, including an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II-AT_1 receptor blocker (ARB), and/or a calcium channel blocker (CCB) [36]. Neurohumoral screening with high plasma aldosterone values and suppressed plasma renin activity values are markers for likelihood of a therapeutic response but not the magnitude of response per se; however, the response to spironolactone can still be significant even without fully suppressed plasma renin activity values and/or elevated plasma aldosterone values. Spironolactone also affords mortality and morbidity benefits in patients with HF and a reduced ejection fraction [37]. Spironolactone remains active in states of reduced renal function because it gains access to its site(s) of action independent of glomerular filtration. The propensity of spironolactone to cause hyperkalemia precludes its use in many HF and/or CKD patients; however, this appears to be less of an issue in patients on maintenance hemodialysis even in the setting of functional anuria [38].

38.8.2 Eplerenone

Eplerenone is a mineralocorticoid receptor antagonist with a molecular structure that affords greater selectivity for the aldosterone receptor; accordingly, its reduced affinity for androgen and progesterone receptors results in less gynecomastia than is seen with spironolactone [39]. Unlike spironolactone, eplerenone does not have any active metabolites, and it is broken down by CYP3A4; thus, coadministration of CYP3A4 inhibitors, such as verapamil and diltiazem, will result in moderate increases in plasma levels of eplerenone. Typically, eplerenone is a very mild diuretic; thus, its antihypertensive effects originate from non-diuretic aspects of its action. Such actions result in a level of BP reduction comparable to that seen with drug classes such as ACE inhibitors (Chap. 36) and CCBs (Chap. 37) [40, 41]. Eplerenone therapy also results in regression of left ventricular hypertrophy (LVH) (either when given alone or when administered with an ACE inhibitor) as well as a prominent anti-proteinuric effect as is similarly observed with spironolactone [42, 43]. In patients with a recent history of acute myocardial infarction (MI) and left ventricular dysfunction or HF, eplerenone reduces morbidity and mortality when added to the pharmacologic standard of care [44].

38.8.3 Amiloride

Amiloride is a K^+-sparing diuretic, which is actively secreted by cationic transporters present in the proximal tubule. Amiloride blocks epithelial Na^+ channels (ENaC) in the luminal membrane of the collecting duct, but only a modest natriuretic response can be expected with its use. Amiloride has but a modest antihypertensive effect when given as monotherapy. Its BP-lowering effect can be considerably enhanced when coadministered with a thiazide diuretic [45]. Unlike HCTZ, amiloride appears not to have a negative effect on glucose homeostasis [46]. Amiloride has a longer half-life than triamterene and, thus, can be administered less frequently than triamterene to utilize its ability to preserve potassium balance in the diuretic-treated patient [47]. Amiloride is extensively renally cleared and will accumulate with its repetitive dosing in the setting of reduced renal function. If amiloride therapy is needed in the setting of CKD (GFR <50 mL/min), either the dose should be reduced or the dosing frequency decreased to lessen the likelihood of developing hyperkalemia.

38.8.4 Triamterene

Triamterene is another K^+-sparing diuretic, which works independently of a direct antagonism of aldosterone effects. Triamterene is metabolized to an active phase II sulfate-conjugated metabolite. Both triamterene and its sulfated metabolite are

cations and gain access to their intraluminal site of action by proximal tubular secretion. Triamterene and its active metabolite accumulate upon repetitive dosing in the patient with CKD. In those unusual circumstances where its use is considered necessary in CKD, empiric dosage adjustment is advisable because of the potential for developing hyperkalemia. Because of its weak BP-lowering properties, triamterene is seldom employed as monotherapy for hypertension. It is usually used in combination with a thiazide-type diuretic with the premise behind such a two-diuretic combination being that triamterene reduces the K^+ and Mg^{++} losses that might otherwise accompany thiazide therapy [48]. Triamterene, given together with a NSAID, has been reported to cause acute kidney injury, which may last for several days. The mechanism behind this interaction is unclear but may relate to triamterene's increasing renal vascular resistance (and as much as a 30 % decrease in RBF) – correspondingly, there is an increase in the urinary excretion of the vasodilator prostaglandins E_2 and F_2 [49]. The decrease in prostaglandin production, which follows NSAID therapy, would then allow for an exaggerated renal vasoconstrictor effect from triamterene [49].

Triamterene can also precipitate a crystalline nephropathy and has been associated with the presence of birefringent fluorescent cases in the urine [48, 50].

38.9 Mechanism of Diuretic Action

The effect of a thiazide diuretic on BP may be divided into three successive phases: acute, subacute, and chronic, which correspond to periods of about 1–2 weeks, several weeks, and several months, respectively [51]. In the "acute" response phase, the BP-lowering effect of a diuretic is coupled to a reduction in ECF volume and a corresponding decrease in cardiac output. The early response (first 2–4 days of treatment) to a thiazide-type diuretic, in the setting of a "no-salt-added" diet (100–150 mmol/day), results in a net Na^+ loss ranging from 100 to 300 mmol, which translates into a 1–2 L decrease in ECF volume. This decrease in plasma volume reduces venous return and diminishes cardiac output, the basis for the initial BP decrease with a thiazide diuretic. In due course the thiazide diuretic effects on volume and cardiac output lessen in importance, although BP remains lowered. During the *subacute* phase of a treatment response (first few weeks), plasma volume returns to slightly less than pretreatment levels, despite the continued administration of a diuretic. The *subacute* response phase with thiazide-type diuretics is a transitional period during which both volume and resistance factors both contribute to the observed BP reduction (Fig. 38.3).

In the *chronic* response phase of therapy, the BP reduction with a thiazide diuretic reverts to that of a reduction in total peripheral resistance (TPR). The decrease in TPR during prolonged therapy has been attributed to several factors including changes in the ionic content of vascular smooth muscle cells, altered ion gradients across smooth muscle cells and/or potassium channel activation, and

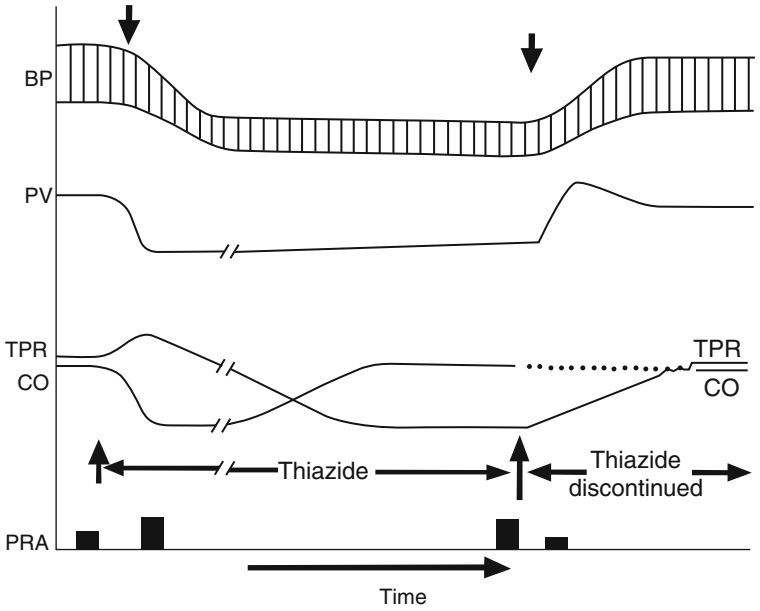

Fig. 38.3 Effects of thiazide administration in an "idealized" patient with hypertension. Early reductions in plasma volume are gradually corrected and supplanted by peripheral vasodilation as the primary BP-lowering effect of these drugs. *BP* blood pressure, *CO* cardiac output, *PRA* plasma renin activity, *PV* plasma volume, *TPR* total peripheral resistance

changes in membrane-bound ATPase activity [28, 52]. The ability of thiazide-type diuretics to reduce BP seems to be linked to the presence of some level of renal function; thus, these drugs do not reduce BP in patients undergoing maintenance hemodialysis [25].

A mechanistic understanding of both diuretic action and the counterregulatory forces triggered by diuresis provide for a well-reasoned approach to the treatment of hypertension. The early action of diuretics to reduce ECF volume is optimized if dietary Na^+ is restricted at the onset of therapy. This limits the repercussions of the braking phenomenon, which is an inevitable occurrence with uninterrupted diuretic use [11]. Some limitation in dietary Na^+ intake may also be relevant to how diuretics might *chronically* reduce TPR. It is thought that intracellular Na^+/Ca^{++} content is favorably adjusted in vascular smooth muscle cells with the *acute* volume reduction observed during the first several days of thiazide diuretic therapy. How the development of volume contraction specifically translates into a reduction in TPR remains unclear [28, 52]. Whatever the mechanism, it can be quite long lived, because a residual BP reduction can be seen several weeks after the withdrawal of thiazide diuretics (even without interposing non-pharmacologic treatments for maintenance of BP control) [53]. This residual BP-reducing effect upon cessation of thiazide-type diuretics has not been specifically compared to that observed with non-diuretic antihypertensive drug classes in the same patient populations.

38.10 Diuretic Class Effect

The concept of class effect has been applied to both loop diuretics and thiazide-type diuretics in respect to the management of hypertension. The loop diuretic effect on BP is a function of at least two processes: first, the manner in which volume removal is effected and, second, the capacity of these compounds to independently reduce total peripheral resistance. Small doses of the long-acting loop diuretic, torsemide, may cause significant BP reduction in essential hypertensives, a process independent of the level of diuresis, and one not seen with sub-diuretic doses of furosemide [54]. Intra-arterially infused furosemide does not directly dilate human forearm arterial vessels even at supratherapeutic concentrations [55]; in bioequivalent doses however, furosemide is just as effective as torsemide in reducing 24-h ambulatory BP in stage II–III CKD patients [56]. Until comparison studies amongst loop diuretics are conducted in diverse populations, it is premature to presume that these compounds are distinguishable, independent of volume removal, in their ability to reduce BP.

The idea of *class effect* for thiazide-type diuretics is still advanced by some, but it has minimal experimental support. Much of the recent debate on thiazide-type diuretic class effect has centered on the similarities and differences between chlorthalidone and HCTZ [57]. The concept of *class effect* with thiazide-type diuretics should be considered in two ways: first the effect on BP and second the event rate reduction. These two compounds are fundamentally different diuretics, in that chlorthalidone has a considerably longer duration of diuretic action than HCTZ [58].

One study evaluated chlorthalidone 25 mg/day compared to HCTZ 50 mg/day. In spite of the lower dose of chlorthalidone, clinic BP was reduced to a similar degree as the higher dose of HCTZ. Notably, nighttime BP was significantly lower with chlorthalidone, which is likely related to its longer duration of action [58]. A recent meta-analysis further compared the effects of chlorthalidone and HCTZ on systolic BP and serum K^+ and found that chlorthalidone had a greater effect on BP with similar effects on serum K^+ at equivalent doses [59]. As to the issues of outcomes, chlorthalidone has been used in several of the major clinical trials in the United States and has had a more consistent pattern of favorable outcomes than is the case with HCTZ [60–62]. These more favorable outcomes with chlorthalidone could be due to a greater reduction in nighttime BP and/or a reduction in the early morning surge in BP [29].

38.11 Clinical Usage

38.11.1 Indications

Thiazide-type diuretics are indicated in the treatment of hypertension, and they provide wide-ranging CV benefits. When used alone in the nonedematous patient, thiazide diuretics are as effective as most other antihypertensive drug classes, an observation which is independent of body mass index [63]. The degree to which diuretics lower BP relates, in part, to the level of counterregulatory system

activation including increased heart rate and activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Head-to-head comparisons amongst the various thiazide-type diuretics have not shown significant differences for BP reduction when equivalent doses are used. The exception to this may be with chlorthalidone, which at a dose of 25 mg is comparatively more potent than 50 mg of HCTZ, particularly as related to overnight BP reduction [58]. Loop diuretics are less effective than thiazide-type drugs in reducing BP in the nonedematous patient [64]; however, as CKD transitions from stage 3 to 5, particularly with extracellular fluid (ECF) volume expansion, loop diuretic therapy becomes the preferred diuretic therapy for management of hypertension [65].

38.11.2 Specific Recommendations by Indication

All thiazide-type diuretics can be administered once daily, which for convenience sake usually occurs in the morning. It is now clear that lower dosages of a thiazide diuretic, such as HCTZ (25 → 50 mg/day), are similarly effective as higher dosages (50 → 100 mg/day) in lowering BP; thus, it is rarely necessary or desirable to use >50 mg/day of a thiazide diuretic. The antihypertensive efficacy of HCTZ in a daily dose of 12.5–25 mg as measured in head-to-head studies by ambulatory BP measurement is consistently inferior to that of all other drug classes, and this should be a consideration when HCTZ is started as monotherapy [66]. In the elderly, a beginning dose of 12.5 mg and a maximum dose of 50.0 mg HCTZ (or its equivalent) are recommended. This cautious dosing occurs, in part, because of the perception of a greater sensitivity to the volume-depleting effects of these compounds. In the Systolic Hypertension in the Elderly Program (SHEP), 12.5–25.0 mg of chlorthalidone controlled more than 50 % of patients for several years without meaningful troublesome consequences [61]; however, chlorthalidone is a long-acting diuretic and should still be used cautiously if there is any doubt whether a patient can adequately take in sufficient replacement fluids if they are becoming dehydrated. It is also generally recommended that diuretic-treated hypertensive individuals should increase their daily intake of K^+, although it is unclear that such an increase either fully compensates for the kaliuretic effect of thiazides or provides for additional meaningful BP reduction [67].

38.11.3 Outcome Considerations with Diuretics in Hypertension

The beneficial effects of BP-lowering treatments on the risks of major cardiovascular disease and/or renal events are without question. What has been argued are the comparative effects of regimens based on different initial drug classes or regimens targeting different BP goals. In a recent analysis undertaken by the Blood Pressure Lowering Treatment Trialists' Collaboration, there were no significant differences observed in total major CVD events between regimens based on initial ACE

inhibitor, CCB, β-blocker, or a diuretic [68]. The results of such analyses tend to shift the argument of which is the preferred first-line drug in the treatment of hypertension to which compound or combination of drugs is most cost effective. In this regard, diuretic therapy as initial therapy or as a component of multidrug therapy has an established and widely accepted position in most guideline promulgating committees (Chap. 30).

38.11.4 Responsive Patient Populations

When used alone in the nonedematous patient, thiazide diuretics are as effective as other antihypertensive drug classes, independent of body mass index. Although it is highly speculative to offer general recommendations about antihypertensive care on the basis of race, age, or gender, this is still customarily done. In general, African American, elderly, and female patients with hypertension typically respond better to diuretic therapy than do other patients. The same can be said for the patient with diabetes and an often-recognizable pattern of salt sensitivity; however, the basis for the interindividual variability in response to a thiazide diuretic is unclear, despite the predictability of responses in the above-cited patient groups [69].

38.11.5 Elderly

A number of studies utilizing diuretic-based regimens have been specifically conducted in elderly hypertensives (age >60 years): the Systolic Hypertension in the Elderly Program (SHEP), the Swedish Trial in Old Patients (STOP), the Medical Research Council Trial in the treatment of older adults (MRC-2), the European Working Party on High Blood Pressure in the Elderly (EWPHE), and the trial of Coope and Warrender. Significant reductions in stroke similar to that observed in younger patients and greater benefits in terms of protection from MI have been demonstrated in these older diuretic-treated patients [70].

The Hypertension in the Very Elderly Trial (HYVET) randomized 1933 patients 80 years of age or older to active treatment and 1912 patients to placebo. Active treatment included indapamide sustained release 1.5 mg. Perindopril 2 or 4 mg was added if BP was not at target (<150/80 mmHg). After a mean of 1.8 years of follow-up, active treatment was associated with a 39 % reduction in death from stroke ($p=0.05$), a 21 % reduction in death from any cause ($p=0.02$), and a 64 % reduction in HF ($p<0.001$) as compared to placebo [71].

Results of these trials establish the benefit of low-dose diuretics and/or β-blockers for the treatment of isolated systolic hypertension in the elderly and amongst other trials have been the basis for current treatment recommendations advocating diuretic therapy in uncomplicated forms of hypertension. This positioning of diuretics in the management of uncomplicated forms of hypertension in the elderly has also been reinforced by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) findings [62, 72].

38.11.6 Blacks

In black patients, hypertension is more prevalent at a younger age, may be more severe, and is associated with a greater incidence of cardiac, central nervous system, and renal complications than in white patients [73]. Although the pathogenesis of hypertension has not been clearly defined in this subgroup of hypertensives, the majority of blacks fall into the low-renin category. This low-renin status cannot be explained by volume expansion alone, and no consistent relationship between these two factors has been unambiguously identified in this population. Although not fully resolved, there appears to be a relationship between a low-K^+ intake and elevated BP in blacks whether they be normotensive or hypertensive [74].

Nonetheless, black patients respond well to diuretic therapy with between 40 and 67 % of young and 58 and 80 % of elderly blacks favorably responding to diuretic monotherapy. The absolute BP reduction (−12/8 mmHg) in black patients given diuretic therapy, although more predictable than is with other drug classes given as monotherapy [such as ACE inhibitors, β-blockers, or ARBs], is often insufficient to bring BP to a value below goal [73, 75]. In blacks, diuretics often need to be added to non-diuretic drug classes if goal BP is to be reached. This practice of administering multiple antihypertensive agents (including a diuretic) to blacks can occur by beginning therapy with a diuretic or with a diuretic as add-on therapy to another drug class, such as an ACE inhibitor, ARB, or β-blocker [76]. A number of morbidity and mortality trials have been conducted in blacks, and diuretic-based regimens have demonstrated noteworthy benefits as regards cardiovascular (CVR) event rates [72, 73].

38.11.7 Combination Use with Other Agents

Diuretics can be successfully combined with β-blockers, ACE inhibitors, ARBs (Chap. 36), centrally acting agents (Chap. 39), and even with CCBs (Chap. 37). In the Veterans Administration monotherapy study, the combination of a diuretic with drugs from any other class provided the best antihypertensive effect as compared to combinations without a diuretic [63]. Diuretics are combined with numerous other drug classes as fixed-dose combination products with most such products utilizing HCTZ [76].

38.12 Diuretic-Related Side Effects

Diuretic-related side effects can be separated into several categories, including those with well-established mechanisms such as electrolyte defects and/or metabolic abnormalities and issues, such as impotence, which are mechanistically more poorly understood [77]. In addition, various drug-drug interactions are recognizable

with diuretics. Diuretic-related side effects are more common and often of a greater intensity with loop diuretics. Thiazide-related side effects are somewhat more common with the longer-acting compounds, such as chlorthalidone and metolazone. Among the thiazide-type diuretics, indapamide has been touted as distinctive in not causing significant metabolic derangements; however, when given in equivalent doses to HCTZ, there is very little that separates these two drugs relative to the development of electrolyte-related side effects [78, 79].

38.12.1 Hyponatremia

Hyponatremia is an uncommon, but potentially serious, complication of diuretic therapy [80, 81]. Thiazide diuretics are more likely than loop diuretics to produce hyponatremia. There is an intraclass risk for hyponatremia with thiazide diuretics with hyponatremia being more common with chlorthalidone relative to HCTZ at equivalent milligram-to-milligram doses per day [82]. Loop diuretics inhibit Na^+ transport in the renal medulla and prevent the generation of a maximal osmotic gradient. Thus, urinary concentrating ability is impaired with loop diuretics. Alternatively, thiazide-type diuretics increase Na^+ excretion and preclude maximal urine dilution, while preserving the kidney's innate concentrating capacity. When diuretic-related hyponatremia occurs, it is typically in elderly females and is usual seen within the first 2 weeks of therapy [83]. However, diuretic-related hyponatremia can occur on a delayed basis even after several years of therapy and can occur quite early in the course of therapy [81, 84]. Multiple factors contribute to the penchant of females to develop diuretic-related hyponatremia, including age, reduced body mass, exaggerated natriuretic response to a thiazide diuretic, diminished capacity to excrete free H_2O, and a chosen low-solute intake. It has also been suggested that the apparent female preponderance of thiazide-induced hyponatremia is related to overrepresentation of females in thiazide-treated cohorts, rather than intrinsic susceptibility to its development [81]. Thiazide diuretic-related hyponatremia, in the 125–135 mmol/L range, can be collectively managed by restricting free H_2O intake, replacing K^+ losses, withholding diuretics, or switching to a loop diuretic if diuretic therapy remains essential.

38.12.2 Hypomagnesemia

Both thiazide and loop diuretics increase urinary magnesium (Mg^{2+}) excretion. All K^+-sparing diuretics diminish the magnesuria that accompanies thiazide or loop diuretic use [85]. Prolonged therapy with thiazide and loop diuretics, on average, reduces plasma Mg^{2+} concentration by 5–10 %, although patients can develop more severe hypomagnesemia in association with similarly sized total body deficits [86]. Cellular Mg^{2+} depletion occurs in up to 50 % of patients receiving thiazide diuretics and can be present despite normal serum Mg^{2+} concentrations. Hypomagnesemia often coexists with hyponatremia and hypokalemia, with one study finding 41 % of patients with hypokalemia to also have low-serum Mg^{2+} concentrations [87].

Hypocalcemia and/or hypokalemia found in association with low-serum Mg^{2+} concentrations can prove refractory to all treatment measures until the underlying Mg^{2+} deficit is corrected.

Several issues arise concerning the treatment of diuretic-related hypomagnesemia beyond empirically normalizing a laboratory value. These include possible favorable effects on BP control, arrhythmia development, and/or coexisting electrolyte or neuromuscular symptoms. In the instance of BP control, there appears to be little additional reduction in BP when Mg^{2+} deficiency is corrected. When quantifiable measures, such as hypokalemia and/or hypocalcemia, are present, the value of treating diuretic-related hypomagnesemia is readily apparent. A variety of oral Mg^{2+} salts are available for the treatment of hypomagnesemia. Mg^{2+} oxide is one commonly employed, but this salt is poorly soluble and acts as a cathartic, which can limit its effect. Mg^{2+} gluconate is the preferred salt for oral therapy, as this agent is minimally cathartic.

38.12.3 Metabolic Alkalosis

Mild metabolic alkalosis is a not uncommon feature of thiazide diuretic therapy, particularly at higher doses. Severe metabolic alkalosis is much less frequent, and when it occurs, it typically follows from loop diuretic use [88]. The occurrence of a metabolic alkalosis with diuretic therapy is primarily due to contraction of the ECF space initiated by urinary losses of a relatively HCO_3-free fluid although several other mechanistic pathways have been suggested [89]. Diuretic-induced metabolic alkalosis is best managed by administration of K^+ and/or Na^+ chloride, although Na^+ chloride administration may be ill advised in already volume-expanded patients, such as those with HF.

38.12.4 Hyperuricemia

Thiazide diuretic therapy increases serum urate concentrations by as much as 35 %, an effect related to decreased renal clearance of urate, and is most prominent at the highest pre-therapy urate clearance values [90]. Decreased urate clearance may be linked to increased reabsorption secondary to diuretic-related ECF volume depletion and/or competition for tubular secretion, since both thiazide diuretics and urate undergo tubular secretion by the same organic anion transporter pathway [91]. Diuretic-related hyperuricemia is dose dependent and is pertinent for two reasons: first, as a precipitant of gout and, second, relative to its effect on CVR event rate. Diuretic-related hyperuricemia does not typically precipitate a gouty attack unless the patient has an underlying gouty tendency or serum urate concentrations are >12 mg/dL [91]. Allopurinol, a xanthine oxidase inhibitor, should not be routinely started, as often occurs with asymptomatic diuretic-related hyperuricemia. If a gouty attack occurs in a diuretic-treated patient, the diuretic use should be

discontinued. Diuretic therapy can often be restarted at a lower and sometimes still effective dose. In the process, careful attention should be paid to avoidance of volume contraction. In the patient with preexisting gout needing diuretic therapy, the xanthine oxidase inhibitor, allopurinol, can be considered, and if intolerant, another xanthine oxidase inhibitor, febuxostat, can be substituted for allopurinol [92].

38.12.5 Hypokalemia/Hyperkalemia

A serum K^+ value of ≤3.5 mmol/L, which is the most common definitional criterion for a diagnosis of hypokalemia, is a not uncommon finding in patients treated with loop and/or high-dose thiazide diuretics [93]. During the first several days of thiazide diuretic therapy, plasma K^+ falls an average of 0.6 mmol/L (in a dose-dependent manner) in subjects not taking K^+ supplements, as compared with a 0.3 mmol/L drop in those taking furosemide [93]. However, it is unusual for serum K^+ values to settle <3.0 mmol/L in diuretic-treated outpatients, apart from a high dietary Na^+ intake, and/or when a long-acting diuretic is being given, as is the case with chlorthalidone. Mechanisms that contribute to the development of hypokalemia during diuretic use include increased flow-dependent distal nephron K^+ secretion (more commonly observed with a high-Na^+ intake), a fall in distal tubule luminal chloride, metabolic alkalosis, and/or secondary hyperaldosteronism [94].

The cardiac implications of diuretic-induced hypokalemia remain debated [95]. This theme is muddled by several factors including the varying relationship between serum K^+ and total body K^+ deficits in the face of diuretic therapy; the fact that in most clinical trials evaluating arrhythmia risk and/or sudden cardiac death (SCD), serum K^+ values have not been measured frequently enough or under sufficiently standardized conditions to allow for only an educated guess as to the K^+ value at the time of an event; and finally the issue of whether hypokalemia produced by transcellular shifts of K^+ manufactures a similar risk as that generated by a reduced serum K^+ with accompanying total body losses [95].

The hazards central to diuretic-related hypokalemia are most apparent in patients with left ventricular hypertrophy, HF, and/or myocardial ischemia, particularly when they become acutely ill and have need of hospitalization [95]. As mentioned previously, outpatient forms of diuretic-related hypokalemia are seldom of a severe enough nature to demand urgent attention; however, these mildly lowered serum K^+ values create a basis for more significant degrees of hypokalemia when transcellular shifts of K^+ are interposed, as occurs during stressful circumstances marked by high endogenous epinephrine levels [94]; therein lies one of the major at-risk scenarios of diuretic-related hypokalemia.

Two additional issues deserve consideration in the milieu of diuretic-related hypokalemia: first, the hemodynamic benefit of normalizing serum K^+ [67] and, second, the consequences of different doses, combinations of diuretics and/or K^+-sparing diuretics on sudden cardiac death [96]. To the former, K^+ supplementation (average increase in serum K^+ of 0.56 mmol/L) in hypokalemic (serum K^+ values

<3.5 mmol/L), diuretic-treated patients has seen a 5.5 mmHg average fall in mean arterial pressure [67]. As to the latter, the risk of SCD among patients receiving combined thiazide and K^+-sparing diuretic therapy has been shown to be lower than that found in patients treated with thiazides alone, with odds ratios for an event increasing significantly as the monotherapy dose of HCTZ increased from 25 to 100 mg/day [96]. Of note in these studies, the addition of K^+ supplements to thiazide therapy had but a slight effect on the risk of SCD, suggesting that other properties of K^+-sparing diuretics, such as a positive effect on Mg^{2+} balance, may have been at play [96].

The K^+-sparing diuretics triamterene and amiloride and the aldosterone receptor antagonists spironolactone and eplerenone are often used for their ability to conserve urinary K^+ particularly when there are increased urinary losses coincident to thiazide and loop diuretic therapy. In certain instances, significant enough K^+ retention can occur so as to result in hyperkalemia. Hyperkalemia with K^+-sparing diuretics is usually encountered in patients with an existing reduction in their glomerular filtration rate (when also given K^+ supplements or salt substitutes), individuals who develop acute-on-chronic renal failure, those on an ACE inhibitor/ARB and/or a nonsteroidal anti-inflammatory drug, or other situations that predispose to hyperkalemia, such as metabolic acidosis, hyporeninemic hypoaldosteronism, or heparin therapy [97].

38.12.6 Hyperglycemia

Prolonged thiazide diuretic therapy can lead to glucose intolerance and may occasionally precipitate diabetes mellitus [62, 98]. Short-term metabolic studies, epidemiologic studies, and a variety of clinical trials suggest a connection between ongoing thiazide diuretic use and the development of type 2 diabetes. However, it should be noted that interpretation of these studies is confounded by multiple factors including differing definitions of new-onset diabetes, small numbers of patients, inadequate comparison groups, relatively limited periods of follow-up, selection criteria that limited the generalizability of the findings, and study designs that prohibited valid comparisons among antihypertensive drug classes [99]. Moreover, in a review of all the placebo-controlled hypertension trials with diuretics, there was only an approximate 1 % increase in new-onset diabetes compared with placebo [100].

Hyperglycemia and carbohydrate intolerance have been linked to diuretic-induced hypokalemia. K^+ deficiency is known to inhibit insulin secretion by β cells; however, diuretic-induced changes in glucose metabolism are not conclusively related to altered K^+ homeostasis, and impaired glucose tolerance occurs even when thiazide-type diuretics in relatively low doses are combined with K^+-sparing agents. The glucose intolerance seen with diuretic therapy can deteriorate further with an increase in sympathetic nervous system activity, which also decreases peripheral glucose utilization. Diuretic-associated glucose intolerance appears to be dose related, less common with loop diuretics, and reversible on withdrawal of the agent, although the data on reversibility in HCTZ-treated patients is somewhat conflicting

[101]. Of note, an overview of this issue found that glucose homeostasis was unpredictably affected by low-dose HCTZ (12.5–50 mg/day) [102]. This is particularly so since the CVR risk with new-onset diuretic-related diabetes parallels that which accompanies existing diabetes [98]. Other drug classes such as ACE inhibitors and ARBs are associated with a lesser incidence of new-onset diabetes. It remains to be determined the extent to which either of these drug classes reduces the diabetogenic potential of thiazide-type diuretics.

38.12.7 Hyperlipidemia

Short-term thiazide diuretic therapy can dose dependently elevate serum total cholesterol levels, modestly increase low-density lipoprotein cholesterol levels, and raise triglyceride levels, while minimally changing high-density lipoprotein cholesterol concentrations [103, 104]. These lipid effects have been noted to be more apparent in blacks, males, diabetics, and nonresponders to diuretic therapy [103, 104]. In nonresponders to diuretic therapy, the observed increase in lipid values likely relates to the higher diuretic doses used/required in such patients. All diuretics, including loop diuretics, cause these lipid changes, with the possible exception of indapamide [104]. The mechanisms of diuretic-induced dyslipidemia remain uncertain but have been related to worsened insulin sensitivity and/or reflex activation of the renin-angiotensin-aldosterone system and/or sympathetic nervous system with volume depletion. Long-term clinical trials however differ in that cholesterol levels are little changed from baseline after 1 year of diuretic therapy [105].

38.12.8 Impotence

Adverse effects of thiazide and thiazide-like diuretics on male sexual function, including decreased libido, erectile dysfunction, and difficult ejaculation, have been reported in several studies with an incidence that varies from 3 to 32 % [106]. Various analyses have suggested that these findings were not mediated by either low-serum K^+ or by the observed fall in BP. In a study by Wassertheil-Smoller et al., problems with sexual interest, erection, and orgasm were greater among men receiving chlorthalidone compared with those given placebo or atenolol with weight loss correcting the problem of chlorthalidone-induced sexual dysfunction [107]. The mechanism by which thiazides affect erectile function or libido is unclear, although it has been suggested that these drugs wield a direct effect on vascular smooth muscle cells and/or decrease the response to catecholamines; however, patients with diuretic-related impotence can respond to sildenafil without any additional drop in BP.

Impotence and decreased libido are the more frequent sexual side effects with spironolactone. Gynecomastia, another fairly frequent complication of spironolactone therapy, may be associated with mastodynia and is typically bilateral. At daily doses of $\leq$50 mg, the incidence of gynecomastia falls between 5 and 10 % [108].

The sexual side effects of spironolactone have been attributed to endocrine dysfunction; spironolactone is structurally similar to the sex hormones and inhibits the binding of dihydrotestosterone to androgen receptors, thus producing an increased clearance of testosterone [108]. Eplerenone is another aldosterone receptor antagonist, which is more selective than spironolactone and is absent in the sexual side effects seen with spironolactone.

38.12.9 Drug Allergy

Photosensitivity dermatitis rarely occurs secondary to thiazide or furosemide therapy [109]. HCTZ more commonly causes photosensitivity dermatitis than do the other thiazides, which may relate to its more frequent use. Cross-sensitivity with sulfonamide drugs may occur with all diuretics, with the exception of ethacrynic acid; however, the frequency with which cross-sensitivity occurs is less common than was first thought, and its occurrence appears to be due to a predisposition to allergic reactions, rather than to specific cross-reactivity with sulfonamide-containing drugs; thus, patients with a sulfonamide allergy that was not "extreme" (such as Stevens-Johnson syndrome or a necrotizing vasculitis) in its original presentation can cautiously receive a thiazide or a loop diuretic [110]. Acute allergic interstitial nephritis with fever, rash, and eosinophilia, although an uncommon complication of diuretics, is one that may result in permanent renal failure if the drug exposure remains prolonged [111]. Allergic interstitial nephritis may develop abruptly or some months after therapy is begun with a thiazide diuretic or, less commonly, with a loop diuretic such as furosemide [112].

38.12.10 Carcinogenesis

A number of cohort and case-controlled studies have evaluated the association between the use of diuretics and renal cell carcinoma. In all case-controlled studies, the odds were greater for patients being treated with diuretics to develop renal cell carcinoma (average odds ratio of 1.55). The risk of renal cell carcinoma appeared to be related to the duration of diuretic treatment and not to the average daily diuretic dose. The issue of renal cell carcinoma occurring with diuretic therapy remains one incompletely resolved at the current time [113–115].

38.12.11 Adverse Drug Reactions

By causing hypokalemia/hyperkalemia and/or hypomagnesemia, diuretics increase the risk of digitalis toxicity [116]. Plasma lithium (Li^+) concentrations can increase with loop diuretic therapy with there being heightened Li^+ absorption in tandem

with developed volume contraction [117]. Whole blood Li^+ should be closely monitored in patients administered Li^+ in conjunction with diuretics. Nonsteroidal anti-inflammatory drugs can both antagonize the effects of diuretics and predispose diuretic-treated patients to a form of functional renal insufficiency. The combination of indomethacin and triamterene may be particularly dangerous, in that acute renal failure can be precipitated [118].

38.13 Concluding Remarks

Diuretics are considered an important component of any treatment plan for hypertension. Of the several diuretic classes that exist, thiazide-type diuretics are the most commonly used in the treatment of hypertension. The safe and effective use of diuretics in the treatment of hypertension/edema requires a thorough understanding of their pharmacokinetics and therein their pharmacodynamics. Thiazide diuretics are generally well tolerated and can be used effectively either as monotherapy or in combination with other antihypertensive agents with the expectation that BP will be lowered and CV event rates reduced. Potassium-sparing diuretics have seen a resurgence in their use particularly as relates to the use of spironolactone in treatment-resistant forms of hypertension. Loop diuretic therapy is more so reserved for CKD and those forms of hypertension that are marked by significantly increased ECF volume.

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Chapter 39
Centrally Acting Antihypertensive Agents in the Treatment of Hypertension

Domenic A. Sica

Abstract Centrally acting antihypertensive agents stimulate α_2-adrenergic receptors and/or imidazoline receptors on adrenergic neurons situated within the rostral ventrolateral medulla and in so doing variably reduce sympathetic outflow. Centrally acting agents also stimulate peripheral α_2-receptors, which for the most part is of marginal clinical significance with the medication doses used in clinical practice. Central α-agonists have an extended usage history, starting with α-methyldopa, which has seen its use dramatically decline, in part, because of significant dose-dependent side effects as well as the arrival of more mechanistically attractive classes of antihypertensive medications. Patients with resistant hypertension requiring multidrug therapy, such as those with chronic kidney disease, are commonly responsive to these drugs as are patients with sympathetically mediated forms of hypertension. Perioperative hypertension is typically responsive to clonidine – a clinical circumstance where the anesthetic- and analgesia-sparing properties of this compound may offer further clinical benefits. Clonidine can be used adjunctively with other more traditional therapies in systolic forms of heart failure, particularly when hypertension exists. Sustained-release moxonidine, however, is associated with early mortality and morbidity when used in the patient with heart failure. Escalating doses of drugs in this class often give rise to salt and water retention in which case diuretic therapy becomes a needed adjunctive therapy.

Keywords Clonidine • Alpha-methyldopa • Moxonidine • Rilmenidine • Guanfacine • Alpha-2-adrenergic receptors

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39.1 Introduction

Although complex, and not fully understood, a relationship exists between the centrally moderated, activated sympathetic nervous system (SNS) and blood pressure (BP)/hypertension. SNS activation is also a central factor in reduced ejection fraction forms of heart failure (HF). Moreover, activation of the SNS has been implicated in various developmental aspects of HF and SNS activation has bearing on various developmental aspects of the metabolic syndrome and progressive chronic kidney disease (CKD) [1, 2] (Chaps. 5 and 8). In more general terms, sympathetic activation, as suggested by an increase in baseline heart rate and/or plasma catecholamine levels, is viewed as a factor in the onset and progression of the hypertensive state and thus emerges as a prospective target for pharmacologic interruption. Yet, centrally acting antihypertensive agents still are demonstrably effective even in the absence of obvious signs of SNS overactivity [3, 4]. Of note, SNS activity can promote/amplify the hypertensive state if merely relatively increased in the context of a patient's unique hemodynamic, volume, and neurohumoral circumstances [5]. In addition, the SNS is connected to other regulatory pathways in a manner such that even a customary level of activity can unduly contribute to baseline and reactive BP changes and/or the development/progression of the structural changes that characterize hypertension. This is particularly the case when the relationship between the sympathetic and renin-angiotensin systems is considered. It has been estimated that as many as 30 % of essential hypertension patients have a neurogenic stimulus primarily contributing to their hypertension [6] (Chaps. 31 and 35).

39.2 Mechanism of Action

39.2.1 Molecular Aspects of Drug Action and Pharmacokinetics

The antihypertensive action of α-methyldopa was originally believed to be via tissue inhibition of dopa decarboxylase with a subsequent depletion of biogenic amines; however, this mechanism likely plays a negligible role in its BP-lowering effect. Instead, α-methyldopa lowers BP by conversion to the active metabolite α-methylnorepinephrine (e.g., the concept of a false neurotransmitter), which unseats norepinephrine from α-adrenergic receptors (Fig. 39.1) [7]. The other agents in this class do not require metabolic conversion and are operationally effective as their intact molecules. The main pharmacodynamic effect of compounds in this class requires that these drugs must be transported across the blood-brain barrier. As such, there is an implicit time lag between any plasma drug concentration and the desired antihypertensive effect. Of note, there may be a small increase in BP shortly after use of these medications relating to peripheral α stimulation, which is quickly superseded by the more dominant central antihypertensive effects. The

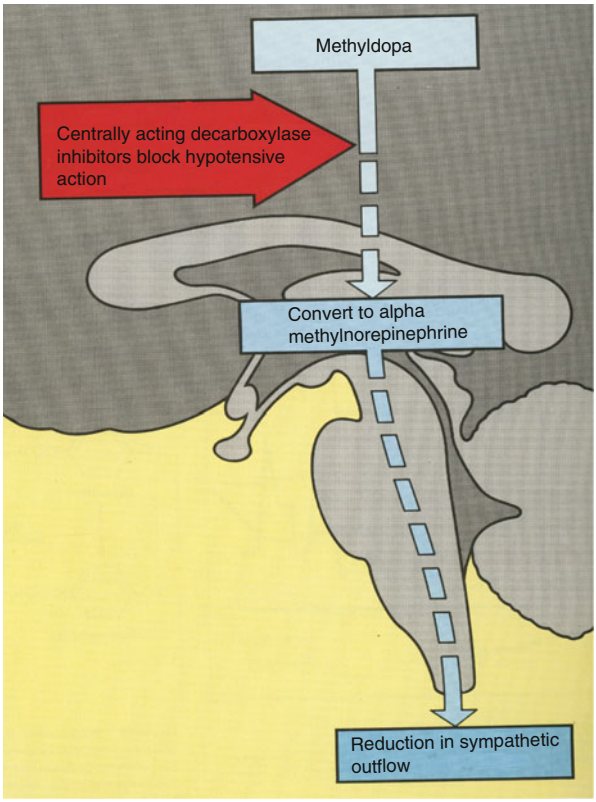

Fig. 39.1 Mechanism of action of methyldopa involving conversion to alpha-methylnorepinephrine and therein stimulation of central α_2-adrenoreceptors and a reduction in sympathetic outflow

pharmacokinetics of the various centrally acting agents is similar with a few noteworthy exceptions (Tables 39.1 and 39.2).

The onset of action varies among the compounds in this class with clonidine showing measurable activity within 15–30 min of intake. These compounds typically have a sizeable volume of distribution, which, in part, relates to their compartmentalization in the brain. The plasma half-life for compounds in this class can vary substantially from their pharmacodynamic half-life. This observation relates to receptor affinity and depot effects in deep tissue compartments. Finally, moxonidine and rilmenidine, compounds that are not available in the United States, are extensively renally cleared, which requires that they be judiciously dose-adjusted in the patient with reduced renal function [8, 9] (Table 39.2).

39.2.2 Pharmacodynamics

Centrally acting antihypertensive medications stimulate central vasomotor adrenergic receptors (e.g., nuclei tractus solitarii) and in so doing inhibit central sympathetic outflow to both the heart and the vasculature in multiple peripheral vascular

Table 39.1 Pharmacokinetics of centrally acting drugs

Drug	Volume of distribution (L/kg)	Absorption (%)	T_{max} (h)	Half-life (h)	Plasma protein binding (%)
α-Methyldopa	0.6	25	2.0	1.7	<15
Clonidine	2.0	75–100	1.5–2.0	6–15	20–40
Guanabenz	7.4–13.4	75	2–5	6–14	90
Guanfacine	6.3	>90	1.5–4.0	17	70
Moxonidine[a]	3.0	80–90	0.5–3.0	2–3	5.8–7.9
Rilmenidine[a]	315–325 L	100	1.7	8.5	10–11

[a]Not available in the United States

Table 39.2 Renal and pregnancy considerations with centrally acting drugs

Drug	Renal elimination[a] (%)	Dialyzability	Dose adjustment in renal failure	FDA pregnancy category
α-Methyldopa	70	Yes	Yes	C
Clonidine	58	Yes, but limited	No	C
Guanabenz	<5	No	No	C[b]
Guanfacine	50	Limited	No	B[c]
Moxonidine[d]	50–75	Not known	Yes	Not classified
Rilmenidine[d]	52–93	Yes	Yes	Not classified

[a]Elimination of the intact molecule
[b]FDA category C – Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other), and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus
[c]FDA category B – Either animal reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women or animal reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)
[d]Not available in the United States, thus the basis for no FDA pregnancy categorization

beds. Plasma catecholamine levels fall with centrally acting therapy, which may relate, in part, to stimulation of peripherally situated presynaptic α_2-receptors [10]. Clonidine stimulates both α_2-receptors and imidazoline (I_1) receptors as the basis for its peripheral sympathoinhibition [11]. Guanfacine is considered a more selective alpha$_2$-receptor agonist than clonidine. Unlike clonidine, guanfacine does not have any measurable effect on dopamine turnover (Fig. 39.2).

The physiologic effects of withdrawal of SNS tone include similar and balanced falls in peripheral vascular resistance and systolic/diastolic BP. The reduction in peripheral resistance that is seen with centrally acting agents is maintained throughout long-term treatment. Despite the vasodilator action of drugs in this class, reflex tachycardia does not occur, and, in point of fact, heart rate may be dose-dependently reduced in the order of 5 % during treatment. Patients with renal insufficiency and clinical sinus node dysfunction and those who had developed bradycardia while taking other sympatholytic agents or who were currently receiving another sympatholytic drug are prone to greater heart rate reductions with clonidine. Cardiac output and renal blood flow typically go unaffected with drugs in this class [12]. Also,

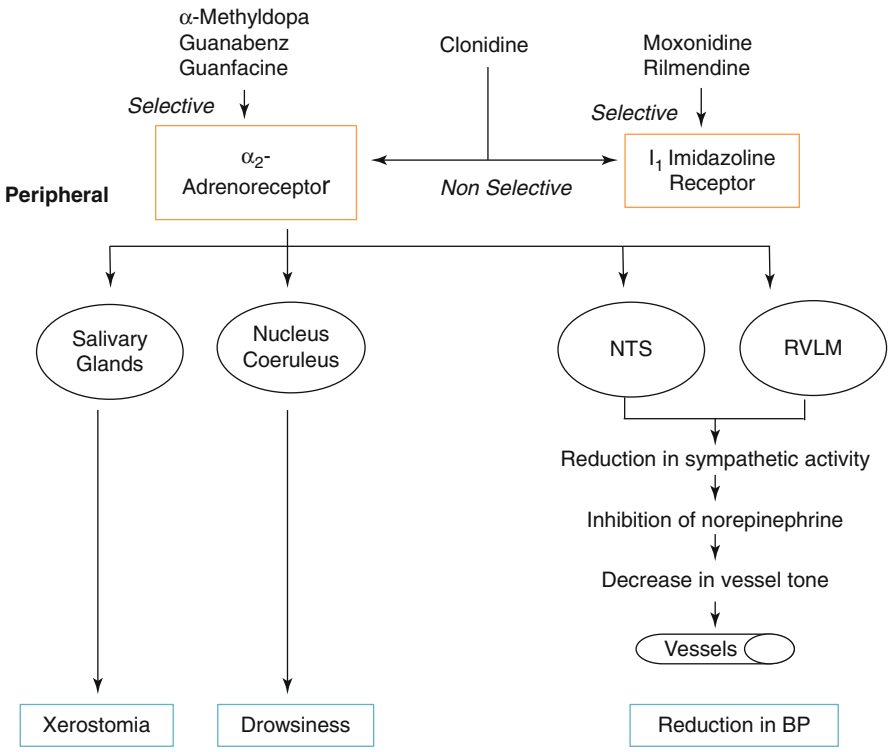

Fig. 39.2 Centrally acting antihypertensive medications working at either the α_2-adrenoreceptor or the I_1 imidazoline receptor. Xerostomia and sedation are mainly α_2-adrenoreceptor mediated and are less common side effects with the I_1 imidazoline receptor antagonists. *NTS* nucleus tractus solitarius, *RVLM* rostral ventrolateral medulla

during exercise, these compounds still reduce peripheral vascular resistance, implying that exercise-related changes in SNS activity are prevented [13]. Centrally acting agents also reduce plasma renin activity and plasma aldosterone and with long-term treatment, left ventricular hypertrophy will regress [14]. Agents in this class tend to dose-dependently foster salt and water (H_2O) retention and, as a result, their effectiveness may wane in the occasional patient over time [12]. This pseudotolerance to a BP-lowering effect can be undone with the addition of diuretic therapy.

39.3 Indications/Contraindications and Objectives of Therapy

39.3.1 Indications

The BP-lowering effect of both central α_2-receptor and I_1-receptor agonists is well established. Clonidine, the most commonly used drug in this class, was shown in the Veterans Affairs Cooperative Study to be an effective antihypertensive agent

particularly in whites and older blacks [3]. Centrally acting compounds compare favorably in effectiveness to several first-line antihypertensive drug classes – such as thiazide diuretics (Chap. 38), angiotensin-converting enzyme (ACE) inhibitors (Chap. 36), and calcium channel blockers (CCBs) (Chap. 37). These compounds however probably find greater use as add-on therapies when sympathetic activation is an ongoing issue, either primary or secondary in nature. The latter might be the case when reflex sympathetic activation as occurs with vasodilators, such as hydralazine and minoxidil, needs to be checked (Chap. 40).

Centrally acting compounds are particularly useful in individuals whose hypertension has a significant anxiety component and is inherently labile. Drugs in this class can be used safely in patients with diabetes mellitus without any deterioration in glycemic control. Patients with pulmonary diseases, such as asthma, also tolerate these compounds even as they can produce xerostomia [15]. Clonidine is often used in the perioperative setting because it lessens sympathetically driven BP increases while also providing both an anesthetic- and analgesic-sparing effect [16].

39.3.2 Drug Differentiation and Mode of Delivery Considerations

All five drugs contained in the centrally acting medication class reduce BP similarly if equivalent doses are used although there are differences in the frequency of dosing between class members (Table 39.3). Clonidine and α-methyldopa are the only two drugs in this class, which are available in a parenteral form. Clonidine is the only compound in this class that is offered in a transdermal delivery system [17]. Differences in the onset and duration of action are two features that distinguish compounds in this class. Clonidine has the quickest onset of action and in most instances the shortest duration of effect. The half-life of drugs in this class widely varies and oftentimes does not predict the duration of effect per se [9, 11].

39.3.3 α-Methyldopa

Methyldopa was first synthesized in 1955 from amino acid derivatives of phenylalanine for treating endocrinologically active neoplastic diseases. From the early 1960s to the late 1970s, α-methyldopa remained a widely used drug in the treatment of all stages of hypertension, in part, because other therapeutic options were lacking [7]. When used in doses ranging from 250 mg to 2.0 g/day, it effectively reduces supine BP without significant orthostatic BP changes. In the more long term, intravascular volume tends to expand diminishing its effectiveness and not infrequently necessitating addition of small doses of a diuretic. With the availability of mechanistically different and inherently better tolerated antihypertensive medications, α-methyldopa

Table 39.3 Dosing considerations with centrally acting antihypertensive agents

Available compounds
α-Methyldopa, clonidine, guanfacine, guanabenz, moxonidine, rilmenidine
Dosing considerations
α-Methyldopa – Oral α-methyldopa is initially given two to three times daily in a dose of 250 mg. Individual maintenance doses are in the range of 0.5–2.0 g/day in two to three divided doses
Clonidine – Oral clonidine is best given two to three times daily. Starting doses are 0.1 mg two to three times daily with dose increase up to as high as 0.6 mg two to three times daily. A small dose of clonidine (0.1–0.2 mg twice daily) augments the BP-lowering effect of most other agents and can be reliably used as add-on therapy. Clonidine is a short-acting compound so patients with excessive sympathetic activity can have a short-lived response to it. If given together with a β-blocker, rebound hypertension is more common when clonidine is abruptly stopped and β-blocker therapy is continued. In some countries, transdermal clonidine is available. The transdermal systems dose range allows for release of 0.1–0.3 mg/24 h. There is a 1–2 days delay in the onset of action after initial patch application with transdermal clonidine, making it inappropriate for the management of hypertensive emergencies; conversely, removal of the transdermal delivery system for clonidine does not immediately eliminate drug effect. Clonidine can also be used intravenously for perioperative hypertension with a dose of 0.15 mg given two to four times daily. The side effects can also occur at lower doses
Guanfacine – The initial response to guanfacine is delayed compared to clonidine but its longer duration of action allows it to be effectively dosed in a range of 1–3 mg given once or twice daily in a split dose. Withdrawal phenomena are significantly less pronounced than observed with clonidine, which may relate to its longer duration of action. Adverse effects increase significantly with doses in excess of 1 mg/day
Guanabenz – Guanabenz is given by mouth as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz. In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4–8 mg every 1–2 weeks according to response. Doses of up to 32 mg twice daily have been used
Moxonidine – 0.2 mg once daily. As needed, the dose can be slowly increased to 0.4 or a maximum of 0.6 mg. The dose must be reduced to 0.2–0.4 mg/day in patients with moderate renal failure (GFR of 30–60 mL/min) and the drug should not be used at GFR values less than 30 mL/min
Rilmenidine – 1 mg once daily, if necessary to be increased to 2 mg in one oral dose. At GFR values <15 mL/min, it should be given in a dose of 1 mg every other day
Overdose
Large overdoses can paradoxically increase BP particularly with clonidine

has fallen out of favor beyond its use in pregnancy-induced hypertension (Chap. 61) and in patients with sympathetically driven forms of hypertension who are clonidine intolerant [18]. As regards the former, α-methyldopa lacks fetal adverse effects in utero (maintains uterine perfusion, not teratogenic) and does not reduce maternal cardiac output, and uterine and/or renal blood flow [19, 20].

Methyldopa is offered in an intravenous formulation (as the parent drug ester) making it one of the antihypertensive medications parenterally available for hypertensive emergencies. The usual intravenous dose range for α-methyldopa is 20–40 mg/kg/day in divided doses given every 6 h. The treatment of hypertensive

emergencies with intravenous α-methyldopa, however, is dated with its having been replaced by more effective and easier to use compounds. In patients with renal failure, urinary excretion of free methyldopa is decreased and plasma levels of methyldopa, particularly the sulfate conjugate, are increased; hence, smaller doses may be indicated in renal failure patients, and this compound is dialyzable. The intestinal absorption of α-methyldopa, and therefore its therapeutic effect, is reduced with the co-ingestion of iron. Common side effects with α-methyldopa include somnolence and depression, which may be linked to a fall in brain biogenic amines [21, 22]. Hypersensitivity reactions, including hepatitis and Coombs-positive hemolytic anemia (due to the appearance of an antibody with specificity for red cell Rh determinants), can occur with α-methyldopa. These reactions occur in 10–20 % of patients receiving ≥1 g/day of α-methyldopa over several months [23]. α-Methyldopa can be continued in the presence of a positive direct Coombs test alone unless anemia develops in which case therapy should be quickly withdrawn. A form of hepatitis with fever, eosinophilia, and increased transaminase values can occasionally develop with α-methyldopa. This is a self-limited process that remits with drug discontinuation. α-Methyldopa may also produce a drug-induced fever with accompanying flu-like symptoms. Its use can be accompanied by an enhance release of prolactin in certain patients, thereby inducing pseudolactation. α-Methyldopa and its metabolic products can interfere with certain catecholamine assays and can interfere with the action of levodopa, bromocriptine, and monoamine oxidase inhibitors.

39.3.4 Clonidine

Clonidine hydrochloride, an imidazoline derivative, was originally developed as a nasal decongestant and vasoconstrictor. Its hypotensive and bradycardic effects were first serendipitously appreciated in 1962. Oral clonidine has an onset of action within 30 min and is particularly useful for managing hypertensive urgencies; however, it is fairly short-acting requiring that it be frequently dosed in managing hypertensive urgencies [24]. A transdermal delivery system for clonidine is available, which provides a programmed daily amount of drug for 7 days. This delivery system needs to be situated on the skin for at least 1 day to achieve steady-state plasma concentrations. Because of the time delay to reach a steady state with transdermal clonidine, oral clonidine should be continued for 1–2 days after the initial patch is first applied. Even after removal of a transdermal clonidine patch, residual drug in the skin maintains the antihypertensive drug effect for 12–24 h [25]. Transdermal clonidine is best absorbed from a chest or upper arm site [26]. Transdermal clonidine is of particular utility for the management of the labile hypertensive patient who requires multiple medications, the hospitalized patient who cannot take oral medications, and the patient with prominent early morning BP surges. At equivalent doses, transdermal clonidine is more likely than oral clonidine to cause dose-dependent salt and H_2O retention [17].

Clonidine can suppress sinus and atrioventricular nodal function, which will sometimes result in significant bradycardia. Also, patients with CKD and sinus node dysfunction are at risk of developing significant bradycardia with clonidine and this drug is best avoided in such individuals [27]. If clonidine is suddenly discontinued during treatment with high doses (usually >1 mg but sometimes lower doses), rebound hypertension may occur [28]. The rebound increase in blood pressure can be quite significant in the occasional patient being treated with clonidine and is characterized by an increase in adrenergic discharge in the setting of upregulated adrenoceptors. Rebound hypertension may be more prominent if therapy with a β-blocker is ongoing when clonidine is discontinued. Such a rebound phenomenon has not been seen with moxonidine and rilmenidine [8, 9]. Clonidine overdose can result in paradoxical hypertension *if* the vasodepressor effect of central α_2-adrenergic stimulation is exceeded by the pressor effects of peripheral α_2-adrenergic receptor stimulation [29].

39.3.5 Guanabenz

Guanabenz is similar to clonidine in its mechanism of action but has a more extended duration of action. Guanabenz is about 75 % absorbed and is 90 % protein bound and its major oxidative metabolites include parahydroxy guanabenz and its glucuronide conjugate. Guanabenz is less often associated with rebound increases in BP, salt and water retention, and/or significant postural reductions in BP [11]. In contrast to clonidine, which undergoes substantial renal clearance as the intact molecule, guanabenz is broadly biotransformed and does not accumulate in patients with significant reductions in renal function [30]. Therapy with guanabenz should generally begin at a 4 mg twice daily dose with titration upwards as might be clinically needed up to a maximum total daily dose of 32 mg. Evening administration of guanabenz effectively suppresses the morning BP elevation in treated hypertensive patients [31]. A noteworthy metabolic action of guanabenz is its ability to reduce total cholesterol levels in the order of 10–20 %. The presumed mechanism for this is an inhibition of hepatic cholesterol production and triglyceride synthesis in addition to the stimulation of fatty acid oxidation [32]. Sedation is a dose-dependent side effect with guanabenz being reported in up to 50 % of patients treated with this compound. Of note, the sedation seen with this compound tends to wane over time. Guanabenz has not been associated with clinically apparent weight gain and/or Na^+ retention. Guanabenz may increase the absorption of hydrochlorothiazide when given concomitantly.

39.3.6 Guanfacine

Guanfacine differs from the other members of this class in that its long duration of action typically allows it to be dosed once daily [33]. Guanfacine appears to compartmentalize in the brain more gradually and thereafter to persist in its

antihypertensive effect longer than does guanabenz. Guanfacine is readily absorbed and 70 % bound to plasma proteins. Strong CYP3A4 inhibitors increase guanfacine exposure levels. Guanfacine is preferably dosed in the evening and in so doing, its peak effect can be brought into line with early morning catecholamine, neurohumoral, and BP surges. Evening dosing of guanfacine also allows any potential sedating effect to play out during sleep. As with other agents in this class, the BP-lowering effect of guanfacine is enhanced when jointly given with a diuretic. Guanfacine is available in an extended release form approved in the United States in 2009, and it is used with some regularity in the treatment of attention deficit disorder [34]. Immediate-release guanfacine tablets should not be substituted on a milligram-per-milligram basis, because of differing pharmacokinetic profiles with sustained-release guanfacine. Guanfacine may be used as an alternative to clonidine in patients intolerant of clonidine because of excessive sedation [35]. Finally, guanfacine has orphan drug status for the fragile X syndrome (the most common inherited cause of mental retardation) as relates to positively affecting the overarousability, impulsivity, and aggressiveness seen in this syndrome. Tricyclic antidepressants, such as imipramine and amitriptyline, attenuate the antihypertensive action of guanfacine (and clonidine) in that these are antagonists of the central α_2-receptors targeted by these compounds.

39.3.7 Moxonidine

Moxonidine belongs to the imidazoline family of compounds and possesses high selectivity for I_1-receptors. This selectivity is important because it is the I_1-receptors that mediate BP reduction in the ventrolateral medulla and the α_2-adrenoreceptors that mediate sedation and dry mouth, typical side effects of clonidine. Moxonidine is well absorbed with bioavailability approaching 90 % and reaches a maximum plasma concentration in about 1 h. Monotherapy or combination therapy of moxonidine with ACE inhibitors, diuretics, or β-blockers effectively reduces BP and in head-to-head studies, it is comparable to clonidine in how much it lowers BP [8, 36]. Moxonidine does not reduce heart rate as can happen with clonidine. The plasma half-life of moxonidine is only 2–3 h; thus, its extended duration of action suggests prolonged binding to central imidazoline I_1-receptors. Moxonidine is extensively renally cleared and its dose has to be adjusted according to the glomerular filtration rate (GFR) [37]. The UK licensed prescribing information states that in patients with moderate renal impairment (GFR 30–60 mL/min), single doses of moxonidine should not exceed 0.2 mg and the daily dose should not go beyond 0.4 mg; moxonidine should not be given in the setting of severe renal impairment (GFR <30 mL/min). Also, moxonidine use should be avoided in advanced HF because a sustained-release form of moxonidine (force titrated to 1.5 mg twice daily) was associated with an early increase in morbidity and mortality in a large cohort of Class II–IV (only 4 % Class IV) HF patients with an average pre-therapy ejection fraction of 25.9 ± 6.5 [38]. Monoamine oxidase inhibitors should not be coadministered with either moxonidine or rilmenidine. Both compounds have fewer

side effects than is the case for clonidine and α-methyldopa, which likely relates to a reduced affinity for α_2-receptors [8, 9].

39.3.8 Rilmenidine

Rilmenidine is the first oxazoline derivative developed as an antihypertensive agent and is a compound with significant affinity for I_1-receptors. Rilmenidine has a large volume of distribution and is mainly renally cleared as the intact molecule. Numerous studies have established that oral rilmenidine, in the 1–2 mg/day dose range, alone or in combination with other antihypertensives, is effective and well tolerated in the treatment of mild to moderate hypertension [9]. A 1 mg daily dose appears to provide the most favorable ratio of efficacy to tolerability. Rilmenidine increases parasympathetic tone, which may account for its not affecting heart rate in the course of reducing BP. Treatment withdrawal relative to rebound hypertension does not appear to occur with rilmenidine. Rilmenidine is much less frequently associated with sedation and dry mouth than is the case for clonidine. The low rate of orthostatic hypotension with rilmenidine may be related to an enhancement in baroreflex sensitivity [39]. Rilmenidine is relatively contraindicated in advance stage chronic kidney disease.

39.3.8.1 Issues Beyond Blood Pressure Reduction

Centrally acting agents and clonidine, in particular, have evolved in their having a wide range of alternative uses beyond merely reducing BP. Clonidine has been used for migraine prophylaxis, for post-traumatic stress syndrome, to reduce postmenopausal flushing, to moderate alcohol and opioid withdrawal symptoms, and to secondarily reduce aqueous humor production in open-angle glaucoma. Clonidine has also been proven modestly effective in reducing fecal output in various diarrheal states including those associated with the short gut syndrome and/or high-output proximal jejunostomies [40]. Clonidine has also been used in the perioperative period as an adjuvant to general and/or regional anesthesia; to improve analgesia with systemic, spinal, or peripheral opioids; as well as to control postoperative sympathetic responses [16, 41]. In so doing, anesthesia and analgesia requirement can often be effectively reduced. Of note, the sympatholytic effect of clonidine is primarily on tonic SNS activity and less so on its reactivity and this is an important physiologic feature in the perioperative setting.

The sympathoinhibition that occurs with clonidine can enhance diuretic effect in cirrhotic patients with ascites and can reduce the sympathetic hyperactivity, which is characteristic of HF [42–44]. Oral clonidine also can control ventricular rate in new-onset atrial fibrillation with an efficacy not dissimilar to that of more traditional agents [45, 46]. Clonidine can also be used in the diagnosis of pheochromocytoma. After administration of 0.1 mg clonidine/h for 3 h, plasma norepinephrine levels decreased in patients with essential hypertension but remained unaffected in patients with a pheochromocytoma [47].

39.4 Complications

39.4.1 Class Side Effect Considerations

As is the case with any antihypertensive agent that reduces SNS activity, postural hypotension, weakness/fatigue, salt and water retention, and gastrointestinal symptoms can arise relating to the adrenolytic action or the resultant override of parasympathetic function, or a combination of both. Somnolence and dry mouth are the most common side effects with central sympatholytics and a major reason for withdrawal of these drugs [21, 22]. I_1-receptor stimulators are in most instances better tolerated with their use being marked by less xerostomia and/or tiredness [8, 9].

Other central nervous system depressants such as sedative-hypnotics, benzodiazepines, antihistamines, and/or ethanol may exaggerate the sedative effects of drugs in common use within this drug class. The dry mouth with centrally acting agents is a function of hyposalivation, a by-product of an α_2-mediated reduction in salivary flow rate. This can be a very bothersome side effect that, if sufficiently long-lived, can increase the chances of developing dental caries, periodontal disease, and/or oral candidiasis [48]. This necessitates particular consideration in children and adolescents who may be given drugs in this class as a means to facilitate sleep [49]. Rebound hypertension is less of a class effect than it is a phenomenon, if seen that would be attributable to the fairly short half-life of clonidine.

39.5 Side Effect Management

The side effects with centrally acting compounds can be managed most effectively by stopping the upsetting compound; however, there are substantial numbers of patients for whom hypertension control is unavoidably dependent on centrally acting agents making discontinuation of any such compound impractical. In such instances, central-acting compounds can be empirically split-dosed so that the same total daily dose remains similar with lower more frequent doses given. In addition, switching from daytime to nighttime dosing is an option, in which case the sedating effects of these medications can be used to enable sleep; however, the decrease in salivary flow that accompanies these therapies, particularly so with clonidine, can be quite unsettling and may foster nocturnal caries development. If this occurs, salivary substitutes or sucking on ice chips can be a consideration but rarely affords a long-term solution to the problem. Also, intraclass switches are occasionally useful considerations; for example, a patient intolerant of the sedating effects of clonidine may have a less-sedating compound, such as guanfacine or guanabenz, substituted.

A final consideration with clonidine-intolerant patients is that they can be converted to the transdermal form of clonidine with which fewer side effects of sedation, fatigue, and/or dry mouth occur [17]. Use of transdermal clonidine also lessens

the chance of rebound hypertension with sudden discontinuation of therapy. Skin reactions to transdermal clonidine are not uncommon. Allergic dermatitis occurs more commonly in whites than in blacks and in women than in men. Skin reactions to transdermal clonidine can include subjective symptoms of pruritus and objective findings such as erythema, scaling, vesiculation, excoriation, and induration. Potential causes of the allergic contact dermatitis could be the active drug, adhesive, diffusion membrane, solvent, or enhancer. Most studies have indicated that the skin reactions are related to the active drug itself and not to other factors. Treatment with hydrocortisone cream or antacids (magnesium-aluminum hydroxide suspension) has been employed as a means to diminish the intensity of skin reactions to transdermal clonidine. 0.5 % hydrocortisone cream, whether applied under or at the edges of the patch, occasionally is effective in diminishing the contact dermatitis; however, this has been inadequately studied beyond the observation that skin pretreatment with hydrocortisone enhances clonidine absorption and thereby increases plasma levels [50, 51].

39.6 Reserpine

Reserpine is an alkaloid found in the roots of *Rauwolfia serpentina* and *R. vomitoria*. Reserpine inhibits the uptake of norepinephrine into storage vesicles resulting in depletion of catecholamines and serotonin from central and peripheral axon terminals. The depression of sympathetic nerve function results in a decreased heart rate and a lowering of BP. Reserpine is extensively bound (95 %) to plasma proteins. Reserpine is almost completely metabolized in the body, and only about 1 % is excreted as unchanged drug in the urine. Reserpine is characterized by a slow onset of action and sustained effects. Reserpine has been employed in several of the early hypertension trials and was effective as mono and more so as add-on therapy [52]. Given as monotherapy, reserpine in general reduces systolic BP by 3–4 mmHg, a level of BP reduction that is considerably enhanced when it is coadministered with a diuretic. Reserpine side effects in the early trials employing 1–2 mg/day were prohibitive in many instances. Contemporary practice now uses doses of 0.1–0.2 mg/day with much better tolerance although nasal stuffiness, abdominal discomfort, edema, and depression are not uncommon side effects. Reserpine is presently available only in a powder form requiring capsules to be made in specialty pharmacies.

39.7 Concluding Remarks

Centrally acting antihypertensive compounds remain a key therapy in the management of assorted forms of hypertension that are commonly linked to the SNS. As such, drugs in this class can be considered as important first-step therapies; yet, centrally acting antihypertensive drugs are used most regularly in an add-on

capacity for broad control of hypertension irrespective of its primary origin. The original compounds in this class – α-methyldopa and clonidine – are now used less often because of a fairly oppressive dose-dependent side effect profile. However, there remain other centrally acting antihypertensive medications, such as guanfacine and guanabenz, that are better tolerated and equally effective compounds. Centrally acting antihypertensive compounds are diversified in their actions both reducing BP and favorably influencing a number of non-hypertensive circumstances coupled to increased SNS activity.

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Chapter 40
Vasodilators and Management of Hypertensive Emergencies

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Abstract Hypertensive emergency is an important clinical entity, which may result in end-organ damage involving neurological, cardiovascular, and renal systems. If not recognized and acted upon promptly, it can result in life-threatening adverse outcomes. Vasodilators form the mainstay of treatment in hypertensive emergencies. There are different classes of vasodilators based on the site and mechanism of action. The most commonly used vasodilators include directly acting drugs that act via the vascular nitric oxide pathway, calcium channel blockers, beta blockers, alpha blockers, and peripheral dopamine agonists. The various classes of vasodilators act via different neurohormonal signaling pathways and reduce the blood pressure by decreasing the peripheral resistance. Despite the availability of several medications, there is still paucity of literature regarding the best antihypertensive medication to be employed as well as the ideal rate of decreasing the elevated blood pressure in a given clinical scenario. This chapter reviews the basic pharmacology and the mechanism of action of commonly used vasodilators. It also reviews the approach to choosing the most appropriate drug based on the target organ involvement in diverse clinical scenarios of hypertensive emergency.

Keywords Vasodilators • Hypertension • Hypertensive emergencies

40.1 Introduction

Hypertension is one of the most common chronic medical problems affecting more than one billion people all over the world [1]. Unfortunately, a majority of these people are not aware that they have hypertension [2]. They often present to the

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emergency room with hypertensive emergency or urgency. Hypertensive emergency is defined as "a severe elevation in blood pressure (>180/120 mmHg) complicated by impending or progressive target organ dysfunction involving neurological, cardiac or renal systems" [3]. Hypertensive urgency is also a severe elevation in blood pressure, but without any end-organ damage [3]. Due to high prevalence of hypertension in our society, hypertensive emergencies or urgencies are encountered in routine clinical practice. In order to prevent permanent end-organ damage, prompt recognition and treatment is essential.

The immediate treatment goal in hypertensive emergency is to limit end-organ injury through blood pressure reduction. Patients should be admitted to an intensive care unit if acute organ damage is present or ongoing (e.g., hypertensive encephalopathy, acute stroke, myocardial infarction). Generally, the mean arterial blood pressure should be reduced by no more than 25 % within 2 h using intravenous therapy and then to a blood pressure of 160/110 mmHg within the first 6 h of treatment [4]. An exception to this recommendation involves patients with aortic dissection whose systolic blood pressure should be lowered to as low as tolerated immediately. In the case of hypertensive urgency, the treatment goal is to minimize the risk of potential end-organ damage. Short-term blood pressure goals during the first 6–12 h in this situation have not been well studied in large clinical trials [5]. Blood pressure should be reduced using oral therapy titrated up over 6–12 h to achieve normal blood pressure ranges as tolerated.

Vasodilators are a group of drugs that reduce the blood pressure by acting via several neurohormonal pathways to change the peripheral vasomotor tone. They form the mainstay of treatment in patients presenting with hypertensive emergency. Based on the site and mechanism of action, vasodilators are divided into various classes. The basic pharmacology of commonly used vasodilators in each of these classes is described in this chapter. In addition, the approach to choosing an appropriate vasodilator depending on the target organ involved is also reviewed.

40.2 Physiology of Vascular Smooth Muscle Contraction and Site of Action of Vasodilators

Adequate blood pressure control requires the work of complex physiological pathways involving all components of the cardiovascular system. Hence, changes in either cardiac output or peripheral vascular resistance will influence the blood pressure. In this chapter, the focus is specifically on the role of peripheral vasculature (both arteriolar and venous systems) in controlling blood pressure. Hypertensive states occur when the homeostatic process controlling the balance between vasoconstriction and vasodilation is impaired [6]. Vasodilators are drugs that cause vasodilation by inducing vascular smooth muscle relaxation. Hence to understand the mechanism of action of these drugs, it is essential to know the basic mechanisms involved in vascular smooth muscle contraction.

Vascular smooth muscle contraction can be caused by mechanical, electrical, or chemical stimuli, all of which result in an increase in the intracellular calcium [7]. The increased intracellular calcium binds to a protein called calmodulin [7]. The calcium–calmodulin complex activates the myosin light-chain kinase (MLCK). This in turn phosphorylates the myosin light chain (MLC) resulting in formation of cross bridges between the myosin heads and actin filaments causing smooth muscle contraction [7]. Myosin light-chain phosphatase (MLCP) negatively impacts this process by dephosphorylating myosin light chains causing vascular smooth muscle relaxation [7]. A small G protein called Rho kinase in turn inhibits MLCP, by phosphorylating a subunit of MLCP, thus inhibiting the phosphatase activity and resulting in contraction [7].

Vascular smooth muscle relaxation is achieved when there is decreased activity of MLCK or increased activity of MLCP. This can be achieved by the following mechanisms (Fig. 40.1) [7]:

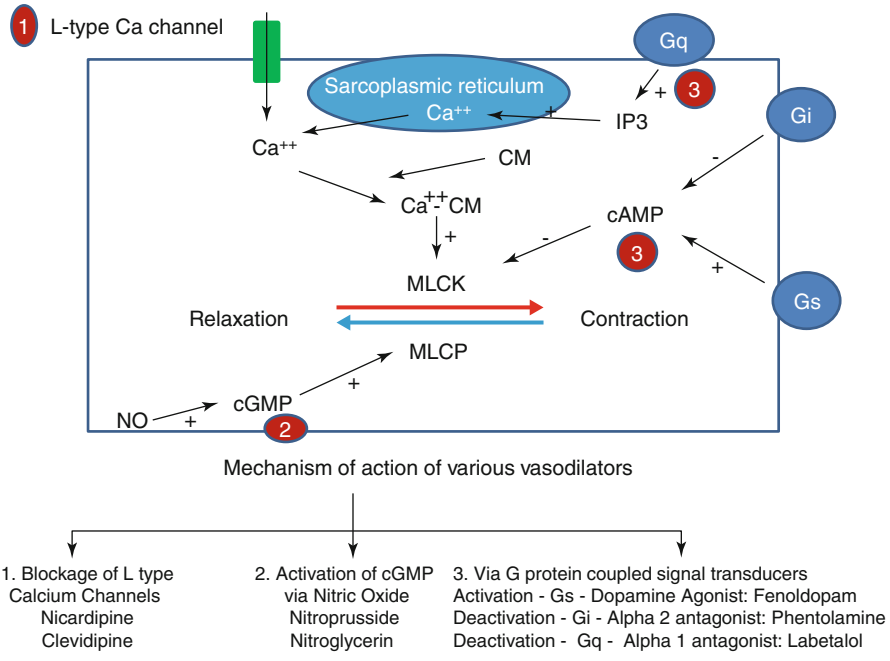

Fig. 40.1 Physiology of vascular smooth muscle contraction and relaxation and mechanism of action of various vasodilators. This figure shows a simplified version of vascular smooth muscle physiology. Activation of MLCK promotes contraction, and activation of MLCP promotes relaxation. Vasodilators act via different signaling pathways as shown in the figure causing inactivation of MLCK or activation of MLCP resulting in vasodilation. *Abbreviations*: Ca^{++} calcium ions, *CM* calmodium, *MLCK* mysoin light chain kinase, *MLCP* mysoin light chain phosphate, *NO* nitric oxide, *cGMP* cyclic gunalyl monophosphate, *cAMP* cyclic adenosine monophosphate, *Gs* stimulatory regulative G protein, *Gi* inhibitory regulative G protein, *IP3* inositol triphosphate, *Gq* class of G protein acting via IP3 pathway

1. Reduction in the amount of available intracellular calcium ions:
   This can be achieved by blocking the voltage-gated L-type calcium channels or by reducing the release of calcium from sarcoplasmic reticulum. Calcium channel blockers such as nicardipine and clevidipine act via this pathway (Chap. 37).
2. Activation of signal transducing pathway via cyclic guanosine monophosphate (cGMP):
   The vascular endothelium, the innermost layer of blood vessels, secretes substances such as nitric oxide and endothelins that act directly on the vascular smooth muscle (Chap. 31). Nitric oxide, produced during the conversion of L arginine to L citrulline, activates guanylyl cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. This results in activation of protein kinase C (PKC) which increases the phosphatase activity of myosin light-chain phosphatase (MLCP). MLCP in turn dephosphorylates the myosin light chains causing relaxation of the vascular smooth muscle. PKC also phosphorylates and inhibits Rho kinase and promotes vasodilation. Sodium nitroprusside and nitroglycerin are the two most commonly used drugs in hypertensive emergencies that act by the production of nitric oxide.
3. Activation of G protein-coupled signal transduction:
   The adrenergic receptors regulate vasodilation via the G protein-coupled signal transducers. Stimulatory regulative G proteins (Gs) are coupled to beta 2 agonists and dopamine D1 receptors in the vascular smooth muscle. These proteins stimulate adenylyl cyclase, which catalyzes the formation of cyclic adenosine monophosphate (cAMP) (Chap. 5). This inhibits MLCK causing deformation of the cross bridges between myosin and actin filaments, resulting in relaxation.
   The inhibitory regulative G proteins (Gi) in vascular smooth muscles are coupled to alpha 2 adrenoreceptors. The activation of these receptors causes a reduction in cAMP, activation of MLCK, and hence vasoconstriction. Peripheral alpha antagonists such as phentolamine and labetalol act by blocking this pathway.
   The Gq proteins are coupled to alpha 1 adrenoreceptors, AT_1 receptors (bind to angiotensin II), and V1 receptors (bind to vasopressin). These Gq proteins are linked to the inositol triphosphate pathway (IP_3) which stimulates the release of calcium from sarcoplasmic reticulum causing vasoconstriction. Alpha-1 antagonists and angiotensin-converting-enzyme inhibitors act as vasodilators by inhibiting this pathway (Chap. 36).

40.3 Pharmacology of Individual Drug Classes

Depending on the site and mechanism of action, vasodilators used in hypertensive emergencies are divided into the following classes:

1. Directly acting vasodilators – act via nitric oxide pathway
2. Calcium channel blockers
3. Beta adrenergic blockers

4. Alpha adrenergic blockers
5. Dopamine agonists

The chemical structures of all the discussed drugs in this chapter are provided in Fig. 40.2 and are listed with their pharmacokinetic properties in Table 40.1.

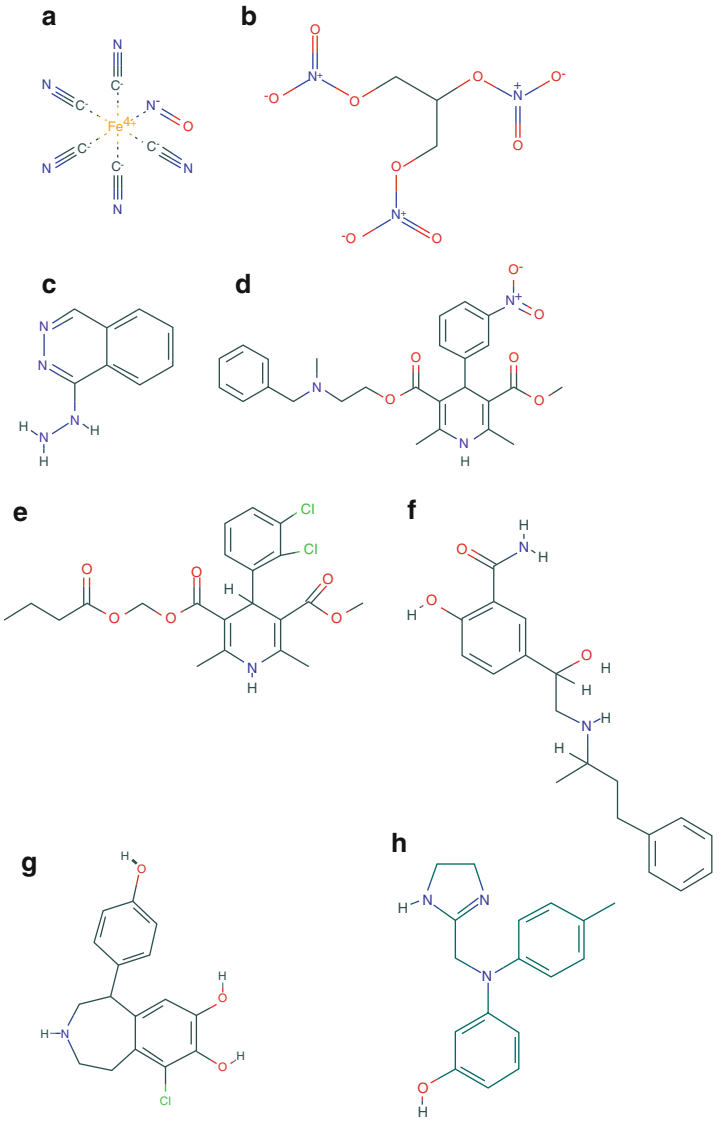

Fig. 40.2 Chemical structures of all the described vasodilators. (**a**) Sodium nitroprusside, Pubchem CID 11963622. (**b**) Nitroglycerin, Pubchem CID 4510. (**c**) Hydralazine, Pubchem CID 3637. (**d**) Nicardipine, Pubchem 4474. (**e**) Clevidipine, Pubchem CID 153994. (**f**) Labetalol, Pubchem CID 3869. (**g**) Fenoldopam, Pubchem CID 3341 h). (**h**) Phentolamine, Pubchem CID 5775 (source: Pubchem, https://pubchem.ncbi.nlm.nih.gov/; Accessed on August 22nd, 2014)

Table 40.1 Vasodilators commonly used in the management of hypertensive emergency

Drug	Mechanism of action	Dose	Onset	Half-life	Clinical situation	Precautions/contraindications
Sodium nitroprusside	Arterial vasodilator via c GMP pathway	0.25–10 μg/kg/min	1–2 min	Nitroprusside, circulatory 2 min; thiocyanate 2 days	All clinical situations of hypertensive emergencies. Caution in neurological emergencies as it decreases cerebral perfusion and in ACS can cause coronary steal phenomenon	Elevated intracranial pressure. Renal and hepatic impairment
Nitroglycerin	Venous vasodilator via cGMP pathway	5–400 μg/min	2–5 min	1–4 min	Commonly used in acute coronary syndrome and decompensated heart failure	Concomitant use of phosphodiesterase inhibitors, inferior ST segment elevation myocardial infarction
Nicardipine	Dihydropyridine calcium channel blocker	5–15 mg/h	10 min	2–4 h	Postoperative hypertension, neurological emergencies	Severe aortic stenosis, advanced heart failure
Clevidipine	Dihydropyridine calcium channel blocker	1–21 mg/h	2–4 min	Biphasic Initial: 1 min (predominant) Terminal: 15 min	Potentially useful in most hypertensive emergencies; extensively studied in post-cardiac surgery patients	Allergy to soy and egg products, advanced heart failure, severe aortic stenosis
Fenoldopam	Peripheral dopamine 1 receptor agonist	0.03–1.6 μg/kg/min	10 min	5 min	Hypertensive emergencies complicated by renal failure	Sulfite allergies, glaucoma
Labetalol	Combined alpha and beta antagonist	IV bolus: 20 mg over 2 min; infusion: 1–2 mg/min	2–5 min	6 h	Aortic dissection, neurological emergencies	Severe bradycardia, advanced decompensated heart failure
Hydralazine	Direct arterial vasodilator	IV bolus: 10–20 mg	5–20 min	2–8 h	Preeclampsia and eclampsia	Dissecting aortic aneurysm
Phentolamine	Alpha 1 and 2 blocker	IV bolus: 1–5 mg; infusion: 1–40 mg/h	1–2 min	19 min	Catecholamine excess states like pheochromocytoma	Acute coronary syndrome Sulfite allergies

40.3.1 Direct-Acting Vasodilators

These drugs act directly on the vascular smooth muscle and cause vasodilation by increasing the endothelial concentration of nitric oxide.

40.3.1.1 Sodium Nitroprusside

Sodium nitroprusside is a complex anion with an octahedral iron center surrounded by five cyanide ligands and one linear nitric oxide ligand [8]. It interacts with oxyhemoglobin and immediately breaks down to release nitric oxide, cyanide, and methemoglobin. The active metabolite, nitric oxide, activates guanylyl cyclase in the vascular smooth muscle, which results in increased production of cGMP. The myosin light chains are dephosphorylated causing vascular smooth muscle relaxation and subsequent vasodilation [8]. Sodium nitroprusside is a nonselective vasodilator acting on both arterioles and venules (arterioles more than venules). Hence, it reduces both the afterload and preload and can sometimes cause reflex tachycardia due to the activation of baroreceptors. Compared to other antihypertensive agents, it has the quickest onset of action (<2 min) and the shortest half-life (2 min) [8]. Hence, it is easily titratable, and its effects are reversible immediately after stopping the infusion. It is excreted renally as thiocyanate, and hence it should be used with caution in patients with renal failure [8].

The use of sodium nitroprusside may be problematic for several reasons. Given the short duration of action, it can precipitously drop the blood pressure. The target blood pressure can be overshot compromising the tissue perfusion. Hence, it is recommended to use sodium nitroprusside only in the intensive care setting, preferably with continuous blood pressure monitoring with an intra-arterial line [9]. The drug is supplied in a lyophilized powder, which is reconstituted and then diluted before use. The resulting solution is sensitive to light and should be wrapped in an aluminum foil set or other opaque material to prevent exposure to light. The drug will remain stable for 24 h if protected from light [10]. A loss of the drug activity is reflected by a change in the solution color from light brown to dark brown, green, orange, or blue [11]. Prolonged exposure to large doses of the drug can result in cyanide toxicity [8]. Signs of cyanide toxicity include mental status changes, seizures, coma, tachyphylaxis, arrhythmias, and metabolic acidosis [8].

Sodium nitroprusside is a nonselective vasodilator and has its effect on most of the vascular beds [9]. In patients with hypertensive encephalopathy, it should be used with extreme caution, as the precipitous drop in the mean arterial blood pressure can result in cerebral hypoperfusion [12, 13]. Similarly in patients with coronary artery disease and ongoing ischemia, it is contraindicated to use sodium nitroprusside because it can potentially cause a substantial reduction in coronary blood flow by causing arteriolar vasodilation and intracoronary steal of blood flow from the ischemic areas [14]. Nitroprusside causes dilation of the resistance vessels. The resistance of the vasculature supplied by a coronary artery with significant stenosis is already very low due to the autoregulation in response to decreased pressure

distal to the stenosis. So, these vessels are incapable of dilating further in response to vasodilators. Hence, when a vasodilator like sodium nitroprusside is used, resistance vessels of the non-stenosed artery are dilated, resulting in shunting or "stealing" of blood from the ischemic areas [14]. Use of sodium nitroprusside within 9 h after the onset of chest pain in patients with acute myocardial infarction and elevated left-sided filling pressures was associated with increased mortality [15]. In summary, though sodium nitroprusside can be used in management of most clinical situations of hypertensive emergency, the need for invasive hemodynamic monitoring, potential for cyanide toxicity, and reduction in cerebral blood flow do not make it the first line of agent in everyday clinical practice to treat hypertensive emergencies.

40.3.1.2 Nitroglycerin

Nitroglycerin or glyceryl trinitrate is an organic nitric acid ester formed by treating glycerol with nitric acid [16]. It also acts on the vascular smooth muscle by producing nitric oxide, however, by a mechanism different from that of sodium nitroprusside. It also has a relatively quick onset of action (2–5 min) and a short half-life (1–4 min) [16]. It undergoes extensive first-pass metabolism in the liver and is converted into inactive glycerol di- and mononitrate metabolites [16].

Nitroglycerin undergoes biotransformation into either its active or inactive metabolites [17]. Glutathione reductase and glutathione-S-transferase are the enzymes involved in degradation of nitroglycerin to inactive metabolites – inorganic nitrite and glycerol 1,3-dinitrate [17]. The mitochondrial enzyme aldehyde dehydrogenase results in bioactivation of nitroglycerin converting it into active metabolites – nitric oxide and glycerol 1,2-dinitrate [17]. The mechanism resulting in nitrate tolerance is complicated and not very well defined. Some of the proposed theories include nitroglycerin-induced activation and increased sensitivity to receptor-dependent vasoconstrictors such catecholamines and vasopressin. Nitroglycerin also increases the mitochondrial NADPH (nicotinamide adenine dinucleotide phosphatase) oxidase activity, producing superoxide and peroxynitrite free radicals which inhibit aldehyde dehydrogenase, resulting in reduced biotransformation of nitroglycerin [16, 17].

Nitroglycerin is more selectively a venodilator resulting in preload reduction and acts on arterioles only in very high doses [18]. It is also a coronary vasodilator and improves collateral blood flow and sub-endocardial perfusion resulting in reduced myocardial oxygen demand [18]. Because of its properties on the coronary arteries, it is the drug of choice in hypertensive emergencies associated with acute pulmonary edema or acute coronary syndromes. In volume-depleted patients, a preload reduction may lead to decreased cardiac output. Similar to sodium nitroprusside, it is a cerebral vasodilator and often causes headache as a side effect. It also should be used cautiously in patients with suspected raised intracranial pressure. Other common side effects include hypotension, dizziness, flushing, and nausea (Chap. 23).

40.3.1.3 Hydralazine

Hydralazine is a synthetic compound prepared by the action of hydrazine hydrate on 1-chloro or 1-phenoxyphthalazine [19]. It is a potent direct-acting arteriolar vasodilator. It causes vascular smooth muscle relaxation by various mechanisms – influx of potassium into the vascular smooth muscle and hyperpolarization, activation of guanyl cyclase and increase in cyclic GMP, inhibition of release of calcium ions from sarcoplasmic reticulum, and finally stimulation of nitric oxide formation by vascular endothelium [20]. The intravenous formulation has a latent onset of action between 5 and 20 min [21]. The half-life is longer compared to other directly acting vasodilators (2–8 h) [21]. It is hepatically acetylated and excreted by extensive first-pass effect [21]. Given the unpredictable antihypertensive effect that lasts for several hours and difficulty in titration, it is not recommended for use in the treatment of hypertensive emergencies. It is used in hypertensive crisis related to pregnancy as it increases the uterine blood flow and is not teratogenic [18].

40.3.2 Calcium Channel Blockers

Calcium channel blockers reduce the blood pressure by causing arterial vasodilation by blocking the calcium ion influx through L-type voltage-gated calcium channels in the vascular smooth muscle cells. The dihydropyridines are a class of calcium channel blockers that mainly act on the vascular smooth muscle, while the non-dihydropyridines act on the myocardium (Chap. 37).

40.3.2.1 Nicardipine

Nicardipine is a second-generation dihydropyridine class of calcium channel blocker. It blocks the L-type voltage-gated calcium channels in vascular smooth muscles [22] and reduces the calcium ion influx causing relaxation and dilation of the peripheral arteries. It has a rapid onset of action (5–15 min), and its effect lasts for about 4–6 h [23]. Nicardipine undergoes extensive first-pass metabolism in the liver. Sequential metabolism of N-benzyl side chain occurs resulting in production of pyridine analogue metabolites [23]. It also has a strong cerebral and coronary vasodilatory effect. Intravenous nicardipine has been shown to reduce cerebral ischemia. In the presence of an acidic pH from cerebral ischemic tissue, there is a high degree of protonated drug which allows for rapid accumulation leading to localized vasodilation [24]. It is often used in patients with hypertensive emergency and stroke after receiving tissue plasminogen activator (tPA) [25]. The most common side effects of the drug include headache, hypotension, nausea, vomiting, and tachycardia [24]. Short-acting calcium channel blockers should be used with caution. Oral or sublingual immediate-release nifedipine has been associated with increased mortality and acute myocardial infarction [26].

40.3.2.2 Clevidipine

Clevidipine is a third-generation dihydropyridine, which blocks the L-type calcium channels. The calcium ion influx through these channels is blocked during arterial smooth muscle depolarization causing vasodilation and reduction in blood pressure [27]. It reduces the afterload without a reduction in preload and, hence, does not cause reflex tachycardia. The product labeling includes a contraindication for use in patients with severe aortic stenosis as afterload reduction can be expected to result in reduced myocardial oxygen delivery [28]. Intravenous clevidipine has a rapid onset of action (1–5 min) and a short half-life (1 min) [27]. Clevidipine clearance does not depend on hepatic or renal function [27]. It is converted into an inactive metabolite by esterases in blood and extravascular tissue [27].

The safety and efficacy of clevidipine has been studied extensively in trials among patients presenting to the emergency room and in cardiac surgery patients [29–31]. In the phase III clinical trial, the Effect of Ultra-Short-Acting Clevidipine in the Treatment of Patients with Severe Hypertension (VELOCITY), among 126 patients who presented to the emergency room with hypertensive crises, 90 % of the patients treated with clevidipine reached target blood pressure within 30 min (median of 10.9 min) [30]. There were no hypotensive episodes related to the use of clevidipine in this study. Clevidipine has also been shown to be safe and efficacious in several randomized trials involving cardiac surgery patients with hypertensive crises in the postoperative period [30, 31].

Clevidipine is manufactured in a lipid emulsion and is contraindicated in patients with an allergy to soy or egg as well as in patients with defective lipid metabolism such as pathological hyperlipidemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia [28]. Due to the lipid formulation of the product, no more than 1,000 ml or an average of 21 ml/h over 24 h is recommended [28]. Additionally, the product is discarded 12 h after the puncture of the stopper to prevent microbial growth [28].

40.3.3 Beta Adrenergic Blocker (see also Chap. 5)

40.3.3.1 Labetalol

Labetalol is a synthetic compound formed by N-alkylation of benzyl amine bromoacetyl salicylamide, which is then debenzylated into labetalol [32, 33]. It is a nonselective beta-adrenergic blocking agent and a selective alpha 1 adrenergic blocking agent [32]. The ratio of α:β adrenoreceptor blocking activity by labetalol was noted to be approximately 1:3 [32]. Alpha 1 activation increases the phospholipase C, which increases the calcium influx into the vascular smooth muscle cells causing vasoconstriction [32]. Hence, labetalol, which acts as an alpha antagonist, prevents the calcium influx and reduces the blood pressure by causing arterial and venous vasodilation. Systemic blood pressure and cardiac output are also further reduced by the negative inotropic action secondary to beta receptor antagonism. Reflex

tachycardia is prevented by beta blockade effect. Intravenous labetalol has a rapid onset of action (2–5 min) with its effect lasting for 2–4 h [33]. It undergoes extensive first-pass metabolism in the liver and is excreted after being converted into an inactive metabolite by glucuronide conjugation [33]. Though labetalol reduces the systemic vascular resistance, it maintains the cerebral and coronary blood flow unlike sodium nitroprusside [34, 35]. Hence, it is recommended for use by the American Stroke Association for management of hypertension in patients with stroke who received tPA [36]. However, sometimes bradycardia already caused by elevated intracranial pressure can be exacerbated by use of labetalol. Also, labetalol has been found to be generally safe and effective in hypertensive emergencies associated with pregnancy [37].

40.3.4 Dopamine Agonist

40.3.4.1 Fenoldopam

Fenoldopam is a synthetic compound that is prepared by the alkalization of the primary amine, halophenethylamine [38]. It is a rapidly acting vasodilator with direct agonistic effect on peripheral dopamine 1 receptors. It has a unique advantage of improving the renal perfusion as it activates the dopamine receptors in the proximal and distal tubules and causes renal arteriolar vasodilation [38, 39]. Sodium absorption is inhibited in the proximal tubule resulting in natriuresis and diuresis. It has a rapid onset of action (within 5 min), and the duration of action lasts for 30–60 min after the infusion is stopped [40]. It is metabolized in the liver by conjugation [41]. Several studies have shown that in patients with hypertensive crisis, fenoldopam is equal in efficacy to sodium nitroprusside in achieving the target blood pressure, but in a selective subgroup of patients with renal failure, fenoldopam may be a better choice as it improves the creatinine clearance by improving the renal perfusion [41–43]. Fenoldopam is known to increase the intraocular pressure and, thus, should be used cautiously or avoided in patients with glaucoma [44]. Other adverse effects include headache, flushing, tachycardia, and dizziness [44]. The drug contains sodium metabisulfite and should be avoided in patients with sulfite allergy [44].

40.3.5 Alpha Adrenergic Antagonists

40.3.5.1 Phentolamine

Phentolamine is a synthetically formed compound by alkalylation of methylanilino phenol group [45]. It nonselectively blocks both alpha 1 and alpha 2 receptors causing vasodilation. It has a quick onset of action (within 2 min) and a duration of action of 10–15 min [6]. It undergoes extensive hepatic metabolism before being eliminated in the urine [46]. Reflex tachycardia often occurs with phentolamine, which can be

managed with administration of an intravenous beta blocker. It is often utilized in catecholamine-induced hypertensive emergencies such as pheochromocytoma, interactions between monoamine oxidase inhibitors and other drugs or food, cocaine toxicity, amphetamine overdose, or clonidine withdrawal [24]. This product also contains sodium metabisulfite and should be avoided in susceptible patients. Serious adverse effects of phentolamine include hypotension, arrhythmias, cerebrovascular spasm resulting in myocardial infarction, or cerebrovascular accident [47].

40.4 Choosing the Appropriate Vasodilator Based on Specific Clinical Scenario

40.4.1 Neurological Emergencies

40.4.1.1 Intracerebral Hemorrhage

The management of blood pressure in patients presenting with intracerebral hemorrhage is complicated, as severe elevation in blood pressure results in expansion of the hemorrhage, and lower blood pressure will impair the cerebral perfusion causing ischemia and worsening the damage. The data regarding the rate of lowering of blood pressure in hemorrhagic stroke is limited. In a recent randomized trial, investigators in the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT 2), involving 2,839 patients with spontaneous intracerebral hemorrhage, early intensive treatment to lower the blood pressure (reducing the systolic blood pressure <140 mmHg within 1 h) compared to traditional treatment (target blood pressure <180 mmHg) did not result in a significant reduction in primary outcomes of death or severe disability [48]. However, functional outcome score was noted to be better in the group treated with intensive lowering of blood pressure [48]. Current guidelines recommend that in patients presenting with intracranial hemorrhage and systolic blood pressure >180 mmHg, the blood pressure should be lowered with intravenous drugs accompanied by continuous blood pressure monitoring. The rate of lowering the blood pressure is still controversial; however, decreasing it to 140 mmHg appears to be safe [49]. The most commonly used vasodilators in this setting include nicardipine and labetalol as both these drugs have minimal effect on cerebral perfusion. Nimodipine is often used in patients with subarachnoid hemorrhage as it prevents cerebral arteriolar vasospasm [50]. Sodium nitroprusside should be used with caution with continuous invasive monitoring given its propensity to cause severe hypotension in a short span resulting in cerebral hypoperfusion [12, 13].

40.4.1.2 Ischemic Stroke

The optimal management of blood pressure in patients presenting with acute ischemic stroke is also not well established. The results of the few randomized trials that were conducted to guide blood pressure management in acute ischemic stroke were

inconclusive [51, 52]. In the China Antihypertensive Trial among Patients with Acute Ischemic Stroke (CATIS), 4,071 patients with non-thrombolyzed ischemic stroke were randomized to receive antihypertensives within the first 24 h to lower the blood pressure to less than 140/90 mmHg within the first 7 days or discontinue all antihypertensives during the hospitalization [51]. There was no difference in the likelihood of death or major disability at 14 days or after hospital discharge between both the groups [51].

Rapid decrease in blood pressure will result in cerebral hypoperfusion and infarct expansion, while elevated blood pressure might result in hemorrhagic conversion. Antihypertensive medications are usually given in ischemic stroke only if the systolic blood pressure is >220 mmHg or diastolic blood pressure >120 mmHg [53]. "Permissive" hypertension is allowed for the first 24–48 h. In patients who received thrombolytics, the blood pressure must be maintained below 180/105 mmHg for at least the first 24 h to prevent hemorrhagic conversion [53]. Intravenous labetalol or nicardipine is the recommended first-line agents in this setting based on consensus, as there are no randomized trials supporting the use of a specific agent in acute ischemic stroke [53].

40.4.1.3 Hypertensive Encephalopathy

In patients presenting with hypertensive encephalopathy, the cerebral vascular autoregulation is disrupted [54]. When there is a sudden and severe rise in blood pressure, breakthrough vasodilation occurs in the cerebral arterioles and capillaries [54]. The vascular endothelium is disrupted with the plasma constituents entering the vascular wall, resulting in the development of cerebral edema [54]. If not recognized and treated immediately, this will progress rapidly to cerebral hemorrhage and death. The systolic blood pressure should be decreased by 20–25 %, or diastolic blood pressure should be reduced to 100–110 mmHg in the first 2–6 h [55]. The drugs that are often used in this situation include intravenous infusion of labetalol, nicardipine, fenoldopam, or clevidipine. Sodium nitroprusside is the second-line agent as rapid reduction in blood pressure can cause cerebral hypoperfusion causing ischemic stroke [12].

40.4.2 Cardiac Emergencies

40.4.2.1 Acute Aortic Dissection

In patients presenting to the emergency room with elevated blood pressure and chest pain specifically radiating to the back, aortic dissection should always be considered as a diagnostic possibility. When the clinical suspicion is high, the blood pressure should be lowered while awaiting further diagnostic workup. Unlike other clinical situations, rapid lowering of blood pressure to normal levels is important in aortic dissection, and the systolic blood pressure should be lowered to less than 100 mmHg if tolerated [56]. Sodium nitroprusside is an excellent first line of agent for this situation. However, it should not be used alone as it

causes reflex tachycardia, which might propagate the dissection [57]. Hence, it should always be combined with a beta blocker such as labetalol. Other agents such as fenoldopam and nicardipine may also be used instead of sodium nitroprusside. Type A dissections (ascending aorta) require prompt surgical management, while type B dissections (descending aorta) can be managed with aggressive blood pressure control [57].

40.4.2.2 Acute Coronary Syndrome

In patients presenting with acute coronary syndrome, the adrenergic surge often results in elevated blood pressure. Sometimes, acute elevation of blood pressure by itself can cause supply demand mismatch secondary to increased cardiac workload and result in elevation of cardiac enzymes. In either scenario, the blood pressure has to be lowered to decrease the myocardial oxygen demand and improve the cardiac output. The first line of agent in this situation is intravenous nitroglycerine. It improves cardiac output by decreasing the preload. It also improves the coronary perfusion. Beta blockers such as intravenous labetalol are also often helpful in this situation to decrease the myocardial oxygen demand. Intravenous sodium nitroprusside should be avoided in acute coronary syndrome patients as it can potentially worsen the ischemia because of coronary steal phenomenon [14].

40.4.2.3 Acute Pulmonary Edema

Patients with preexisting systolic or diastolic congestive cardiac failure, valvular abnormalities such as mitral regurgitation, or renal artery stenosis can present with acute pulmonary edema in the setting of markedly elevated blood pressure. Prompt reduction of blood pressure by at least 20–25 % is required in the first hour of presentation. Along with diuretics, vasodilators such as sodium nitroprusside or nitroglycerin (because of their ability to decrease both arterial and pulmonary capillary wedge pressure) are the drugs of choice to reduce the blood pressure in patients presenting with acute pulmonary edema. Beta blockers and non-dihydropyridine calcium channel blockers are contraindicated in patients with decompensated congestive cardiac failure, especially in the setting of systolic dysfunction given the negative inotropic action of these drugs.

40.5 Acute Kidney Injury

In patients presenting with hypertensive emergencies, acute renal dysfunction is a common finding, specifically in patients with chronic kidney disease. The renal perfusion is adversely affected when the blood pressure is acutely lowered. The optimal rate at which blood pressure should be lowered without affecting the

kidneys is not known. The ideal drug that should be used in hypertensive emergencies associated with renal dysfunction is also controversial. Sodium nitroprusside is renally cleared, and in patients with renal dysfunction, it has increased potential to cause cyanide toxicity. Fenoldopam compared to sodium nitroprusside has been shown to improve natriuresis, diuresis, and creatinine clearance and is currently the preferred drug of choice in patients with renal dysfunction [40, 41].

40.6 Hypertensive Emergency Due to Catecholamine Excess

Hypertensive emergencies due to catecholamine excess occur in the following three clinical scenarios – pheochromocytoma, monoamine oxidase inhibitor crisis, and use of cocaine [58]. Beta blockers should never be used alone as the first-line drugs as blockade of peripheral beta receptors can lead to unopposed stimulation of alpha adrenergic receptors and hence cause a paradoxical elevation of blood pressure [58]. Intravenous alpha blocking agents such as phentolamine in combination with other agents such as nicardipine or fenoldopam are often used in these situations [58].

40.7 Hypertensive Emergency During Pregnancy

Patients with pregnancy-induced hypertension can present with preeclampsia or eclampsia. The blood pressure has to be lowered as soon as possible to a safe level, making sure there is no precipitous reduction that can reduce the cerebral perfusion. The American College of Obstetricians and Gynecologists recommends maintaining the systolic blood pressure between 140 and 160 mmHg and diastolic blood pressure between 95 and 105 mmHg [59]. The common drugs used in hypertensive emergencies are contraindicated in pregnancy. Sodium nitroprusside is converted to cyanide which is toxic to the fetus. Angiotensin-converting enzyme inhibitors are also contraindicated in pregnancy. Hydralazine, magnesium sulfate, methyldopa, and nifedipine have traditionally been used in pregnancy-induced hypertension [60]. Intravenous labetalol and nicardipine have also been shown to be safe and efficacious [37, 61, 62]. Regardless of the drug used, delivery of the fetus is the definitive treatment for both preeclampsia and eclampsia.

40.8 Concluding Remarks

Hypertensive emergency is an important clinical entity with life-threatening adverse outcomes if not acted upon quickly. Vasodilators form the mainstay of treatment by lowering the blood pressure in hypertensive emergencies. The different classes of

vasodilators act on the peripheral smooth muscle causing vasodilation via different signal transducer pathways. Despite the availability of several medications, there is still a paucity of data in terms of randomized controlled trials regarding the ideal rate of lowering blood pressure in each clinical situation. Clinical equipoise should be maintained in choosing the appropriate drug based on the clinical scenario, end-organ involvement, potential side effects of the medication, and ease of administration.

Conflict of Interest None

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Chapter 41
Combination Therapy for the Clinical Management of Hypertension

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Abstract Effective treatment of hypertension represents a key strategy for preventing major cardiovascular events, including myocardial infarction, stroke, congestive heart failure and cardiovascular death. In spite of these well-established concepts, hypertension remains poorly controlled, worldwide. To reduce this gap and to improve blood pressure control at general population level, the use of rational, synergistic and integrated pharmacological strategies have been proposed over the last few years. Indeed, a more extensive use of dual or triple combination therapy, particularly in fixed formulation, is progressively emerging as a cornerstone of a more effective treatment of hypertension in clinical practice. Among different combination therapies currently available for the clinical management of hypertension, those based on the association of drugs inhibiting the renin-angiotensin system, renal tubular reabsorption of electrolytes and transmembrane influx of calcium ions, both in dual- and in triple-fixed combination formulations, have been demonstrated to be very effective in lowering both systolic and diastolic, clinic as well as 24-h ambulatory blood pressure levels with a good tolerability and safety profile. In the present chapter, we provide a systematic and updated overview of the evidence supporting the use of combination therapies with different classes of antihypertensive drugs, with a particular focus on those based on drugs inhibiting the renin-angiotensin system (e.g. angiotensin-converting enzyme inhibitors, angiotensin AT_1 receptor blockers), reabsorption of sodium chloride and water (e.g. thiazide diuretics) and calcium channels (e.g. amlodipine). In addition, we review the currently available

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clinical data addressing the effects of combination therapies on adherence and persistence on prescribed antihypertensive medications compared to monotherapies, as well as safety and tolerability profile of such different treatment strategies.

Keywords Hypertension • Combination therapy • ACE inhibitor • Angiotensin AT_1 receptor blocker • Thiazide diuretic • Calcium channel blocker

41.1 Introduction

A substantial reduction of cardiovascular disease burden represents a major issue in the agenda of healthcare systems around the world. To achieve this goal, early and effective interventions on modifiable cardiovascular risk factors appear to be the most rational and achievable approach in the general population. Among these interventions, blood pressure (BP) reduction in hypertensive patients plays a leading role in any preventive strategy, aimed at reducing the global burden of cardiovascular disease [1].

It is well established that a reduced incidence of major cardiovascular events, mostly stroke, myocardial infarction and cardiovascular death, but also congestive heart failure and renal disease, is strictly related to the degree of BP reduction, both for the systolic and for the diastolic BP [2–4]. In spite of the solid benefits obtained by effective and sustained BP control [5], international surveys continue to report very low rates of hypertension control (i.e. BP levels below 140/90 mmHg) [6–8], so that in the best case, more than half of treated hypertensive patients remain uncontrolled. The persistently high proportions of treated uncontrolled hypertensive patients may be at least, in part, responsible for the unacceptably high incidence of cardiovascular diseases and comorbidities observed over the last decades in both Western and emerging countries [9].

Various factors can be advocated for explaining the relatively low rates of BP control achieved worldwide [10]. These include poor adherence of hypertensive patients to pharmacological prescriptions, insufficient physician-patient communication, clinical inertia, confounding or even contradictory guideline recommendations and extremely complicated therapeutic regimens (i.e. excessive pill burden). Another factor responsible for a substantial proportion of the failure in reaching the recommended BP goals may be linked to the persistently high use of monotherapy, whereas combination therapy is largely viewed as a second-choice option for hypertension management. Unfortunately, monotherapy can provide effective BP control only in 30–40 % of treated hypertensive patients [11]. For this reason, international guidelines recommend to start antihypertensive treatment with combination therapy when BP levels are high (i.e. stage 2–3 hypertension), or when individual cardiovascular risk profile is high or very high [12, 13]. In these cases, combination therapies based on two or three different antihypertensive drug classes, possibly combined in one single pill, may represent a valid option to achieve the recommended BP goals

[12, 13]. In this regard, recent evidence seems to suggest that fixed combination therapies should be preferred compared to free-combination therapies for improving BP control and compliance [14] and reducing treatment discontinuations [15] in the daily clinical practice.

Although different rational combinations of antihypertensive drug classes are currently recommended [12, 13], individual differences and specific advantages have been linked to some therapies as opposed to others. First, not all therapies share the same efficacy and safety profile. For instance, combination therapies of beta-blockers and diuretics or those based on two agents blocking the renin-angiotensin system (RAS) are not encouraged by recent recommendations of European guidelines [12]. In contrast, combination therapies based on RAS-inhibiting drugs, including either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II AT_1-receptor blockers (ARBs) with thiazide diuretics and/or calcium channel blockers (CCBs), which are characterized by sustained and effective BP reductions, low rates of drug-related side effects and discontinuations, are currently recommended [12, 13].

In the present chapter, we provide a systematic and updated overview of the evidence supporting the use of combination therapy with different classes of antihypertensive drugs, with a focus on those based on drugs inhibiting the RAS, including either ACE inhibitors or ARBs (Chap. 36), renal tubular reabsorption of electrolytes (thiazide diuretics) (Chap. 38) and transmembrane influx of calcium (CCBs) (Chap. 37). Overall, the available data indicate that these strategies may provide effective and sustained clinic and 24-h BP control, protection from hypertension-related organ damage and comorbidities and prevention of major cardiovascular and renal complications in a high proportion of individuals over a broad range of hypertensive patients.

41.2 How to Choose the Best Strategy to Achieve Blood Pressure Control in Hypertension

The choice of the best antihypertensive therapeutic strategy should be based on the individual cardiovascular risk profile, as well as on baseline BP levels and treatment tolerability [16]. Proper assessment of additional cardiovascular risk factors, markers of organ damage or concomitant clinical conditions may help customize antihypertensive treatment according to compelling indications [12, 13].

Other factors should be taken into consideration when choosing a given antihypertensive therapy and the subsequent therapeutic algorithm. First of all, a thorough and reliable measurement of BP profile according to clinic, home and 24-h ambulatory BP monitoring should be assessed [17]. This may help in defining different forms of hypertension (e.g. isolated clinic hypertension, ‘early morning’ hypertension, ‘masked’ hypertension, ‘sustained’ hypertension, resistant or pseudo-resistant hypertension) [18], as well as to better identify the most appropriate therapeutic options

among currently available antihypertensive drug classes [19]. In addition, recommendations from national (local) and international guidelines should always be taken into account when starting any antihypertensive strategy, because they are based on the results of randomized controlled clinical trials, which have tested the clinical efficacy, safety and tolerability of different drug classes according to the principles of the modern evidence-based medicine [12, 13]. Also, probability to experience a drug-related adverse reaction or an adverse event to prescribed antihypertensive medication, as well as tolerability and safety profile of each selected drug class or molecule may impact the decision on when, how and how much to treat individual hypertensive patients [19]. Furthermore, these factors may influence persistence and adherence of patients to prescribed antihypertensive drugs [20] (Chap. 30 and 43).

41.3 Monotherapy Versus Combination Therapy

Beyond non-pharmacological options (i.e. lifestyle changes), which should be always applied in each individual patient, a relatively low proportion of hypertensive patients (20–30 %) can be initially treated and maintained on a therapy based on a single class of antihypertensive medication (monotherapy) [12, 13]. However, the vast majority of hypertensive patients (70–80 %) have to be treated with at least two antihypertensive drug classes (combination therapy), in order to achieve the recommended BP targets [12, 13].

International guidelines currently recommend the use of combination therapies in patients with marked BP elevation (e.g. those with stage 2–3 hypertension) and/or high or very high cardiovascular risk profile [12, 13]. A schematic representation of different therapeutic algorithms proposed by European [12] and North American [13] hypertension guidelines is reported in Figs. 41.1 and 41.2, respec-

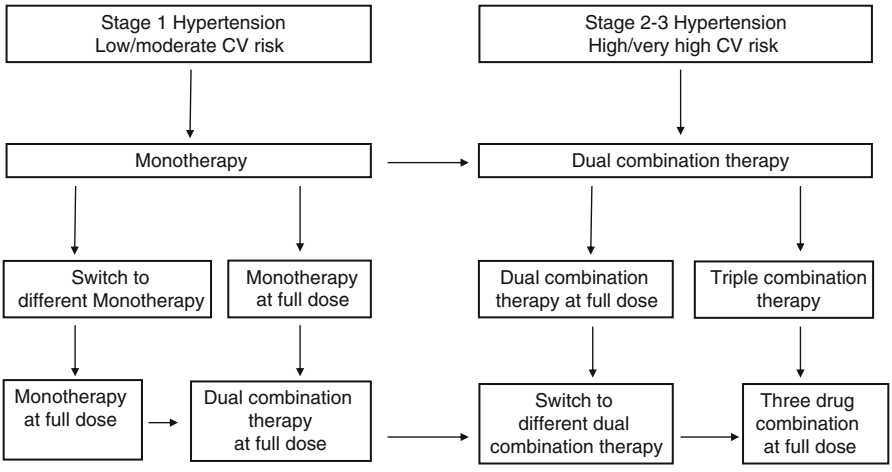

Fig. 41.1 Schematic representation of therapeutic algorithm proposed by ESH/ESC guidelines on hypertension (Modified from Mancia et al. [12])

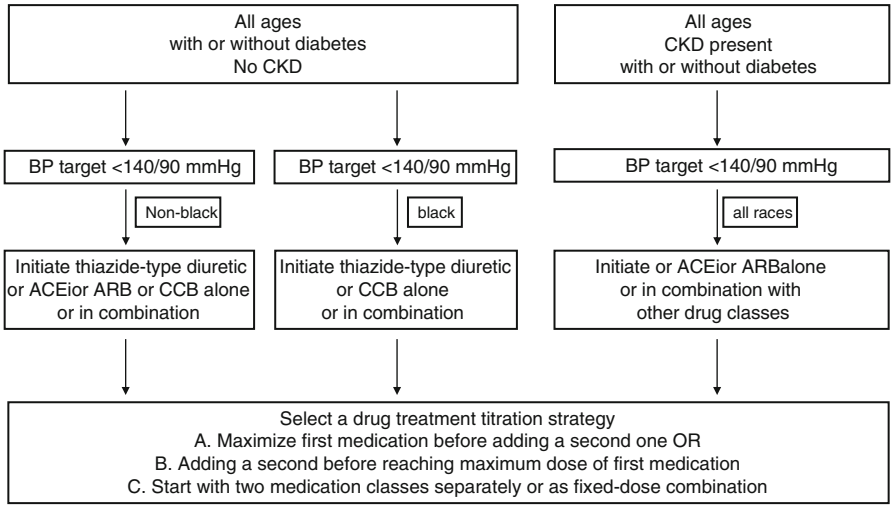

Fig. 41.2 Schematic representation of therapeutic algorithm proposed by JNC 8 guidelines on hypertension (Modified from James et al. [13])

tively (Chap. 30). Possible combination therapies that may be used for hypertension treatment and control are listed in Table 41.1. Within these groups, it is possible to choose the most effective strategy based on the individual global cardiovascular risk profile, effectiveness, safety and tolerability profile. In particular, the use of a combination strategy based on RAS-inhibiting drugs is able to significantly reduce the risk of major cardiovascular events [21] and of discontinuation from prescribed antihypertensive medications [15]. This drug class, which includes ACE inhibitors, ARBs and direct renin inhibitor, can be used in combination with either thiazide diuretics or CCBs, or both, in an effective, safe and well-tolerated way.

In those hypertensive patients who do not achieve satisfactory BP control under monotherapy, a combination strategy based on the use of two classes of antihypertensive drugs including RAS-blocking agents with either CCBs or thiazide diuretics (dual combination therapy) should be used. Randomized clinical trials [22–24] and large meta-analyses [25, 26] confirmed that dual combination therapy is characterized by an antihypertensive efficacy about five times greater than the doubling of the dose of monotherapy. In particular, among different combination therapies, those based on RAS blockers and CCBs are now viewed as the most effective and better tolerated antihypertensive strategy compared to other drug classes in several clinical settings [12, 13].

In those hypertensive patients who do not achieve satisfactory BP control under dual combination therapy, a combination strategy based on the use of three classes of antihypertensive drugs, including RAS blocking agents, CCBs and thiazide diuretics (triple combination therapy) should be used [16]. If the recommended BP targets are not achieved under triple combination therapy, a fourth antihypertensive drug class should be added. The addition of any antihypertensive class different from the previous three classes (beta-blockers, alpha-blockers,

Table 41.1 Potential combination therapies for the clinical management of hypertension

A. Dual combination therapies
1. Based on thiazide diuretics
ACE inhibitors + thiazide diuretics (hydrochlorothiazide, indapamide)
ARBs + thiazide diuretics (hydrochlorothiazide, chlorthalidone)
Calcium channel blockers + thiazide diuretics (hydrochlorothiazide, indapamide)
2. Based on calcium channel blockers
ACE inhibitors + calcium channel blockers
ARBs + calcium channel blockers
Calcium channel blockers + thiazide diuretics (hydrochlorothiazide, indapamide)
B. Triple combination therapies
ACE inhibitors + calcium channel blockers + thiazide diuretics (hydrochlorothiazide, indapamide)
ARBs + calcium channel blockers + thiazide diuretics (hydrochlorothiazide)

aldosterone antagonists, centrally acting agents) has demonstrated to be able to provide additional BP reductions and to achieve effective BP control in a number of patients with moderate-to-severe hypertension and in hypertensive patients who are difficult to be treated. Currently available evidence in the medical literature suggests the additional use of aldosterone antagonists [27, 28]. It should also be acknowledged that some combination therapies with specific drug classes should not be used for the treatment of hypertension. In particular, the use of combination therapy based on ARBs plus ACE inhibitors should not be used in the treatment of essential hypertension because of the additive antihypertensive effect and the potential risk of adverse effects (worsening renal function) [29]. Several studies suggest the use of this combination therapy in order to obtain greater antiproteinuric effect than that achieved with monotherapy with either ARBs or ACE inhibitors; however, a careful monitoring of renal function and plasma electrolytes is always required (Chap. 36).

The use of combination therapies based on ACE inhibitors or ARBs plus direct renin inhibitor (aliskiren) is currently not recommended, since analysis of recent clinical trials reported an increased risk of adverse events (worsening renal function and nonfatal cerebrovascular events) in normotensive patients with diabetic renal failure [30] or congestive heart failure [31]. On the other hand, this potential safety issue does not seem to be confirmed by data derived from extensive monitoring of the clinical practice. In fact, it was reported that in patients with treated uncontrolled hypertension, the addition of aliskiren to an optimal antihypertensive strategy including at least two drug classes may improve BP control rates in the absence of relevant side effects and with the possibility of reducing the use of other concomitant classes of antihypertensive drugs [32].

Combination therapies based on beta-blockers plus diuretics should not be used in the treatment of essential hypertension, unless there are specific indications, because of the potential risk of new-onset diabetes in predisposed

patients [33], except for those beta-blockers with vasodilating action [34, 35] and beta$_1$-selective blockers [36].

41.4 Rationale for Combination Therapies Based on RAS Antagonism

The benefits of RAS-inhibiting drugs in different clinical conditions have been demonstrated in different clinical settings, from asymptomatic patients with cardiac disease to severe refractory heart failure, end-stage renal disease and cardiovascular death [37]. In particular, the favourable effects of RAS-blocking agents, including both ACE inhibitors and ARBs, as compared to conventional treatment (mostly including beta-blockers and diuretics) have been extensively tested in a large, representative population and corroborated by the achievement of reduced cardiovascular morbidity and mortality [37]. On the basis of the observation that in most cases both ACE inhibitors or ARBs were systematically associated with other classes of antihypertensive drugs, mostly thiazide diuretics or CCBs, it has been suggested that implementing the use of combination therapies based on drugs able to inhibit the deleterious effects of abnormal RAS activation may also improve BP control and tolerability, beyond the favourable effects on cardiovascular protection in the clinical management of hypertension.

The rationale of combination therapy based on RAS blockers in hypertension should not be limited only to an increased BP-lowering efficacy due to the synergistic and additive effects on BP reduction provided by different compounds [38–40]. In addition, it may be linked to the favourable impact on several pathophysiological mechanisms of hypertension, as well as to the inhibition of the contra-regulatory mechanisms, thus leading to a reduced incidence of drug-related side effects and hence improved tolerability [38–40]. In addition, these combination strategies can be effectively and safely applied in a number of hypertension-related clinical conditions, such as patients with obesity, metabolic syndrome or diabetes mellitus, coronary artery disease, cerebrovascular disease and renal failure with or without proteinuria [41, 42].

Nowadays, because of the above-mentioned evidence, dual or triple combination therapies based on RAS-blocking agents, thiazide diuretics and/or CCBs appear to be rational for a number of pharmacologic, therapeutic and clinical reasons, as compared to those combinations including beta-blockers and thiazide diuretics. First, these strategies are based on the concomitant use of the most documented antihypertensive agents. Secondly, they are substantially neutral or favourable from the metabolic perspective (i.e. reduced incidence of new-onset diabetes mellitus) when compared with traditional combination therapy. Finally, they have important clinical advantages in terms of tolerability, by providing a substantial reduction of the adverse effects of one component through the antagonistic actions of RAS-blocking agents [43].

41.5 Experience with Combination Therapies in Randomized Clinical Trials: Proven Benefits for Cardiovascular Protection

Results of international, randomized, controlled clinical trials have consistently demonstrated that a reduced incidence of major cardiovascular events is strictly related to the degree of BP reduction. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, the largely prevalent use of monotherapy at the beginning of the trial was associated with only 25 % of patients controlled, whereas 70 % of patients were controlled with the use of combination therapy which progressively prevailed during the course of the study [23]. The same trend was observed in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) trial [22], in which the progressive titration protocol for the use of a combination therapy based on either an ACE inhibitor and indapamide or a beta-blocker and a thiazide diuretic resulted in very high proportions of hypertensive patients who achieved BP control. Despite similar BP reductions between two treatment arms, antihypertensive therapy based on an ACE inhibitor and indapamide induced substantial advantages in terms of reduced incidence of cardiovascular events compared to beta-blocker and thiazide diuretic therapy [22]. More recently, in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [24], the use of combination therapy (benazepril plus amlodipine or benazepril plus hydrochlorothiazide) from the beginning of the study resulted in a very high percentage (72.4–75.4 %) of patients with controlled BP levels at the end of the trial. Even in this trial, antihypertensive therapy based on benazepril (ACE inhibitor) plus amlodipine (CCB) resulted in significantly lower incidence of major cardiovascular events than that of benazepril (ACE inhibitor) plus hydrochlorothiazide (diuretic) [24].

41.6 Experience with Combination Therapy in Clinical Studies in Hypertension: Proven Benefits for Blood Pressure Reductions

41.6.1 Dual Combination Therapy

Several clinical studies, although with limited sample size, duration of the follow-up and different treatment protocol or study design, have demonstrated the efficacy, safety and tolerability of different combination therapies in achieving effective and sustained BP control in hypertensive patients at different risk profile. Potential combination therapies that can be applied for hypertension management and control are listed in Table 41.1. As shown in this table, the choice of drugs in combination therapy is based on their pharmacological properties, lack of pharmacokinetic interaction and their clinical effectiveness. The basis for a combination is twofold

(in addition to patient convenience and compliance): synergistic or additive effect (increases efficacy) and antagonism of other drug's adverse effect(s), e.g. the increase in sodium and fluid excretion induced by hydrochlorothiazide leads to a reflex activation of the RAS characterized by a significant increase in plasma renin and angiotensin. Therefore, RAS inhibitors would indirectly antagonize angiotensin effects and potentiate the antihypertensive effects of hydrochlorothiazide. Hypokalemia, an adverse effect with hydrochlorothiazide, is reduced by ACEi; on the other hand, hyperkalaemia by RAS inhibitors is counterbalanced by diuretics. Also, peripheral oedema induced by CCB is reduced by RAS inhibitors and diuretics. Additionally, reduction of circulating angiotensin II levels and calcium channel blockade has additive effects in lowering BP levels. It may be noted, however, that European guidelines on hypertension recommend the use of combination therapy based on diuretics and dihydropyridine CCBs only in elderly hypertensive patients with isolated systolic hypertension [12]. As previously discussed, despite the availability of numerous clinical trials and observational registries demonstrating the antihypertensive efficacy of aliskiren, both in monotherapy and in combination therapy, in patients with different degrees of hypertension and global cardiovascular risk profile, the same guidelines do not recommend the use of aliskiren as first-line antihypertensive therapy. This is because of the report of increased incidence of serious adverse events in the aliskiren arm of two large, randomized, controlled clinical trials, performed in high-risk normotensive patients with diabetic renal impairment [30] and congestive heart failure [31], respectively.

Overall data confirm that a treatment algorithm based on dual combination represents an effective, safe and well-tolerated therapeutic strategy for improving BP control and achieving BP normalization in the clinical management of patients with mild-to-moderate hypertension. To further improve BP control and achieve BP normalization, triple combination therapy can be implemented. This strategy, in fact, has been tested in open-label extensions of the above-mentioned studies or in randomized clinical trials, which included patients with apparently resistant or challenging hypertension under dual combination therapy or grade 2–3 hypertension, respectively.

41.6.2 Triple Combination Therapy

Several clinical studies have tested the antihypertensive efficacy and safety of triple combination therapy based on the use of dihydropyridine CCBs (mostly amlodipine besylate), thiazide diuretic (hydrochlorothiazide) and ARBs (losartan [44, 45], valsartan [46, 47] and olmesartan [48, 49]).

In the 12-week prospective, open-label, titrate-to-goal Blood Pressure Control in All Subgroups With Hypertension (BP-CRUSH) study [50], treated uncontrolled hypertensive patients on monotherapy were switched to fixed-dose dual combination therapy with olmesartan/amlodipine and subsequently up-titrated every 4 weeks to full-dose dual (i.e. olmesartan/amlodipine) or triple (i.e. olmesartan/amlodipine/

hydrochlorothiazide) combination therapies, if BP control was not achieved. At the end of the study, an overall proportion of more than 75 % of patients reached the systolic BP target.

In the TRIple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in HyperteNsIve PatienTs StudY (TRINITY), a 12-week, multicenter, randomized, double-blind, parallel-group study, performed by Oparil et al. [51], triple combination therapy was compared with dual combination therapy of the individual components in fixed-dose formulations, including olmesartan/amlodipine 40/10 mg, olmesartan/hydrochlorothiazide 40/25 mg and amlodipine/hydrochlorothiazide 10/25 mg in patients with moderate-to-severe hypertension [51]. At the end of the study period, triple combination treatment was associated with markedly greater reductions in seated systolic and diastolic BP levels as compared with dual combination therapy. The number of patients reaching the recommended BP target at week 12 was 69.9 % in the triple combination treatment group and 52.9 %, 53.4 % and 41.1 % in the dual combination treatment groups receiving olmesartan/amlodipine 40/10 mg, olmesartan/hydrochlorothiazide 40/25 mg and amlodipine/hydrochlorothiazide 10/25 mg, respectively ($P<0.001$, triple combination versus each dual combination therapy) [51].

More recently, in a 10-week, multicenter, randomized, double-blind, parallel-group study, performed by Volpe et al. [52], patients with moderate-to-severe hypertension were randomized to receive thiazide diuretic as add-on therapy to a range of doses of different combination therapies based on olmesartan/amlodipine. At the end of the follow-up period, all triple combination therapy induced substantially greater reductions of both systolic and diastolic BP levels compared to the corresponding dual combination therapy. Patients treated with triple combination therapy also had a significantly improved (>70 %) BP control rate by week 10 [52].

Overall, these data demonstrate the efficacy, safety and tolerability of triple combination therapy relative to dual combination or a single antihypertensive agent in patients with moderate-to-severe hypertension or challenging hypertension. Based on these findings, such therapeutic approach is now recommended by international guidelines for the clinical management of high BP levels, even as first-line approaches, when appropriate.

41.7 Fixed-Dose or Free-Combination Therapy for the Clinical Management of Hypertension

Few ‘head-to-head’ clinical trials directly compared the efficacy, safety and tolerability between fixed-dose and free-combination therapies. A recent meta-analysis [14] based on a limited number of randomized and controlled clinical trials demonstrated that fixed-dose combination therapy provides slightly better results than free-combination therapy in terms of a reduction in systolic and diastolic clinic BP levels but without achieving a statistically significant difference. In the same analysis [14], when fixed-dose and free-combination therapies were compared in terms of

compliance with the prescribed antihypertensive treatment, no statistically significant differences were observed. Based on clinical efficacy, the results were slightly favourable to the use of fixed-dose over free-combination therapy. However, this difference was observed mainly in non-randomized clinical trials, whereas no statistically significant difference could be demonstrated in nearly all of the randomized clinical trials that had been considered [14].

A fixed-dose combination strategy has the advantage of providing patients with a simpler therapeutic regimen to be taken in a single dose and therefore, it is absolutely competitive and a winner from the point of view of patient compliance, which is in any case the first and foremost target in the clinical management of hypertension. In other words, no treatment can ever be effective if the patient does not take the prescribed medications, in the correct manner and at the correct dose and time. However, the use of fixed-dose combination therapy often requires progressive dose titration of each medication, in order to achieve and maintain effective and sustained BP control over time. This titration may lead to the onset of dose-related side effects and adverse events, for which physicians may be unable to determine which component of the combination therapy is responsible. In light of these considerations, the use of a free-combination therapy with progressive dose titration may provide a gradual reduction of BP values until effective and sustained BP control is achieved, without resulting in self-discontinuation of the prescribed antihypertensive therapy because of the onset of dose-related side effects or adverse events.

Fixed-dose combination therapy has the advantage of requiring a single daily dose, which also makes it highly competitive in terms of patient compliance. However, it should be mentioned that the use of fixed-dose combination therapy should be able to ensure effective and sustained antihypertensive effects throughout a 24-h period [53]. Also, the use of free-combination therapy may be associated with a higher risk of 'futility' compared with fixed-dose combination therapy, particularly when using not rational and not recommended combination of different antihypertensive drugs [12, 13].

Evidence available to date with respect to the treatment of hypertension has been obtained almost exclusively through the use of free rather than fixed-dose combinations. This evidence does not confirm higher patient compliance with the use of fixed-dose combination therapies versus free-combination therapies, as could be expected, although the studies used are adequately large and rigorously controlled. This could also be attributed to a certain 'mistrust' in patients, when they see that their BP is poorly controlled over the 24-h period, and consequently tend to lose confidence in the treatment. Finally, no evidence exists to date from randomized, 'head-to-head' clinical studies comparing therapies based on fixed-dose combinations versus therapies based on free combinations; this represents a significant limitation that must be taken into account before drawing definitive conclusions.

One last consideration that cannot be omitted is the fact that the components of the fixed-dose combinations currently available in Europe and in the United States (particularly some ACE inhibitors and CCBs) are often generic. Without implying that this aspect may result in reduced antihypertensive efficacy, it should be borne in mind that the wide bioequivalence interval recognized for generic drugs may

result in this class of medications, having a lower antihypertensive efficacy than the non-generic components administered separately in free-combination therapies. Clearly, this aspect should be appropriately investigated, particularly in view of its potentially decisive importance.

41.8 Concluding Remarks

The benefits obtained by achieving effective and persistent BP control in hypertensive patients with different cardiovascular risk profile in terms of reduction of cardiovascular morbidity and mortality have been repeatedly demonstrated. Despite this solid evidence, large international surveys still document persistently low rates of BP control in the general hypertensive population. The relatively low use of combination therapy and the lack of drug dosage optimization during chronic antihypertensive treatment represent two of the plausible reasons for this paradox.

Combination therapies based on RAS-blocking agents and thiazide diuretics or CCBs have demonstrated that this approach may considerably contribute to improved BP control in the presence of a good tolerability profile. In this regard, fixed-dose dual combination therapy based on ARBs and thiazide diuretics or CCBs has proven to be effective and safe. Hence, this strategy could be viewed as a viable way to improve BP control in hypertensive patients. For those patients with difficult-to-treat or grade 2–3 hypertension, triple combination therapy based on the combinations of ARBs, thiazide diuretics and CCBs may represent a rational, effective, safe and well-tolerated antihypertensive strategy. This has been demonstrated to provide further and substantial systolic and diastolic BP reductions compared to dual combination therapy. Additional studies will notably clarify the potential advantages provided by such a combination therapy in terms of organ protection and long-term reduction in cardiovascular morbidity and mortality.

Conflict of Interest MV has received research grants from Novartis, has served in international advisory boards of Daiichi Sankyo, Menarini, Malesci, Guidotti and Novartis Farma and has lectured in symposia supported by several drug companies producing ARBs and ACE inhibitors; GT has lectured in symposia supported by Daiichi Sankyo, Menarini, Malesci and Guidotti.

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Chapter 42
Resistant Hypertension: Definition, Prevalence, and Therapeutic Approaches

Anthony J. Viera

Abstract Resistant hypertension (RH) is defined as blood pressure (BP) above goal despite adherence to at least three optimally dosed antihypertensive medications of different classes, one of which is a diuretic. Not all patients with BP that is difficult to control have RH. Evaluation of possible RH begins with assessment of adherence to medications. White-coat effect should be ruled out by out-of-office BP monitoring. Obesity, heavy alcohol intake, and interfering substances all contribute to RH. Lifestyle modifications including exercise and dietary sodium restriction are important to emphasize. RH may be due to secondary causes such as renal disease, obstructive sleep apnea, and/or aldosteronism. Adequate diuretic treatment is a key part of therapy. Chlorthalidone is more potent and longer-lasting than hydrochlorothiazide and may reduce cardiovascular events to a greater extent. For patients with a glomerular filtration rate <30 ml/min, a loop diuretic is usually needed. In addition to a diuretic, patients with RH should usually be on a dihydropyridine calcium channel blocker and either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II AT_1 receptor blocker (ARB). Spironolactone is an evidence-based fourth-line agent for treatment of RH. Other add-on medication options include a beta-blocker, a long-acting non-dihydropyridine calcium channel blocker, or clonidine. When BP is not coming under control despite the prescription of four or five agents, referral to a hypertension specialist should be considered.

Keywords Hypertension • Resistant hypertension • High blood pressure • Antihypertensive therapy • Secondary hypertension • Spironolactone

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42.1 Introduction

Hypertension continues to be the most common diagnosis in adult primary care practice [1]. In the USA, one out of three adults has hypertension, with a similar prevalence in men and women [2]. The prevalence of high blood pressure (BP) increases with age, from about 7 % among young adults to about 70 % among older adults [3]. Among people living in the USA, there is a 90 % lifetime risk of developing hypertension [4]. The prevalence of hypertension also varies by race/ethnicity, with non-Hispanic Blacks having the highest prevalence at nearly 40 % [2]. While hypertension is the most important risk factor for cardiovascular disease, it is modifiable. BP-lowering treatment markedly reduces the associated risks of heart failure by 50 %, stroke by 40 %, and myocardial infarction by 25 % [4].

The proportion of hypertensive patients receiving BP-lowering treatment has risen from 60 % to 70 % over the past 10 years [5]. However, only about 45 % have their BP controlled (defined as systolic/diastolic blood pressure <140/90 mmHg) [5]. There are many reasons for inadequate control of high blood pressure. Suboptimal therapy is one of the most important reasons [6], but even among patients taking multiple BP-lowering medications, some do not attain control of their BP. Some patients have what is termed resistant hypertension, and this subset of patients can be particularly challenging.

42.2 Definition and Prevalence

Resistant hypertension is defined as BP above goal despite adherence to a combination of at least three optimally dosed antihypertensive medications of different classes, ideally one of which is a diuretic [7]. Patients with controlled BP who require four or more antihypertensive medications are also classified as having resistant hypertension. The term refractory hypertension refers to patients who have uncontrolled BP on five or more antihypertensive medications [8].

An analysis of US National Health and Nutrition Examination Survey data suggests that among hypertensive adults treated with medications, approximately 13 % have resistant hypertension [9]. A recent study of resistant hypertension in Spain found a similar rate of 12 % [10]. Fortunately, only a small proportion of patients with resistant hypertension actually have refractory hypertension. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, among 2,144 participants with resistant hypertension, only 3.6 % had refractory hypertension [8]. Therefore, it should be assumed that most patients with resistant hypertension can achieve goal BP (Table 42.1).

Table 42.1 Six steps of managing patients with resistant hypertension

Step 1. Assess and address adherence to therapy
Step 2. Rule out measurement error and white-coat effect
Step 3. Consider associated comorbidities
Step 4. Reconsider secondary causes
Step 5. Address volume overload and interfering substances
Step 6. Intensify therapy
If BP remains uncontrolled despite treatment with four or five agents, or if uncertainty about diagnosis remains, consider consulting a hypertension specialist

42.3 Assess and Address Adherence to Therapy

Although ascertaining whether a patient is truly adherent to antihypertensive medications can be difficult, it is an important first step in the evaluation of the patient with suspected resistant hypertension. Instructing patients to bring all medicines to their appointment provides the opportunity to reconcile medication lists and review how they take their medications. Asking patients in a nonjudgmental way (e.g., "Many patients will occasionally miss a dose—or even a few doses—of their medication(s); how often is missing medications a problem for you?") about adherence may provide the most accurate answers [11]. Because side effects also may contribute to poor adherence to medications, asking about and addressing them may enhance patients' understanding and adherence.

It is important to keep the medication regimen as simple as possible. Patients may have difficulty adhering to antihypertensive medications due to financial reasons, or they may not understand the medication regimen due to health literacy and cultural or language barriers. A once-daily regimen improves patients' adherence to antihypertensive medications [12]. Fixed-dose combination pills, many of which are available as generics, may also improve adherence [13].

42.4 Rule Out White-Coat Effect

Even before ruling out white-coat effect, it is important to rule out measurement error due to poor office BP measurement technique. Confirm that BP has been measured accurately with the patient correctly positioned and not talking following at least a 5-min rest using an appropriately sized cuff [14, 15]. A cuff that is too small will lead to overestimation of BP. Obese patients, who may have large arms, may prove particularly challenging. The use of a thigh cuff or measurement at the forearm, while not ideal, may be necessary [14].

Approximately one-third of patients with apparent resistant hypertension actually have controlled BP when measured outside the office, i.e., "white-coat" effect. In a study of 611 patients with uncontrolled office BP (systolic >140 mmHg or

diastolic >90 mmHg), nearly 40 % of those on one or two medications and almost 30 % of those on three medications had controlled BP on ambulatory BP monitoring [16]. In another study of over 8,200 patients with resistant hypertension, 38 % had controlled BP based on a 24-h ambulatory BP monitoring [10]. The white-coat effect may lead to unnecessary increases in dosage or number of antihypertensive medications that could result in hypotension or other side effects.

Automated office devices that take several BPs at preprogrammed intervals without an observer present may be useful to mitigate the white-coat response [17]. Generally, however, given the high prevalence of white-coat effect among patients suspected of having resistant hypertension, out-of-office BP measurements should be used to clarify status (Fig. 42.1). Ambulatory BP monitoring (over 24 h) is the ideal strategy, but is not always available. Home (or self-) BP monitoring is an alternative to ambulatory BP monitoring if the latter is not easily available [18]. Before relying on home BP measurements, it is important to ensure that the patient has the appropriate size cuff and to check the patient's monitor against a validated clinical device. Patients should be instructed on how to perform home BP measurements and observed to make sure they perform them correctly, and a systematic approach to collecting the measurements like the one shown in Table 42.2 should be used [19]. If home BP monitoring is used and readings suggest white-coat effect, a 24-h ambulatory BP monitoring, if available, should be considered for confirmation. If the 24-h average BP is <130/80 mmHg (or daytime average <135/85 mmHg), the patient can continue current therapy. If the 24-h average BP is ≥130/80 mmHg (or daytime average is ≥135/85 mmHg), BP is confirmed as uncontrolled, and intensification of therapy should be considered.

42.5 Consider Associated Comorbidities

Certain comorbidities are associated with resistant hypertension. Obesity is common in patients with hypertension and can make hypertension more resistant to treatment due to increased sodium and fluid retention [20]. Therefore, higher doses of antihypertensive medications are often needed. Weight loss must be emphasized not only as an important part of improving overall health but also as an important part of hypertension management. For every kilogram of weight loss, systolic BP is reduced by approximately 1–2 mmHg [21].

Chronic kidney disease (CKD) is also quite common in patients with resistant hypertension [20]. CKD may result from hypertension and, like obesity, makes hypertension more resistant to treatment due to increases in sodium and fluid retention. An emphasis on dietary sodium restriction is therefore particularly warranted in such patients, and a diuretic is almost always required for optimal BP control. Blockade of the renin-angiotensin-aldosterone system with either an ACE inhibitor or ARB (with monitoring of serum potassium levels and glomerular filtration rate) is also part of the hypertension management of the patient with CKD. ACE inhibitors and ARBs should not be used together [22] (Chaps. 36 and 41).

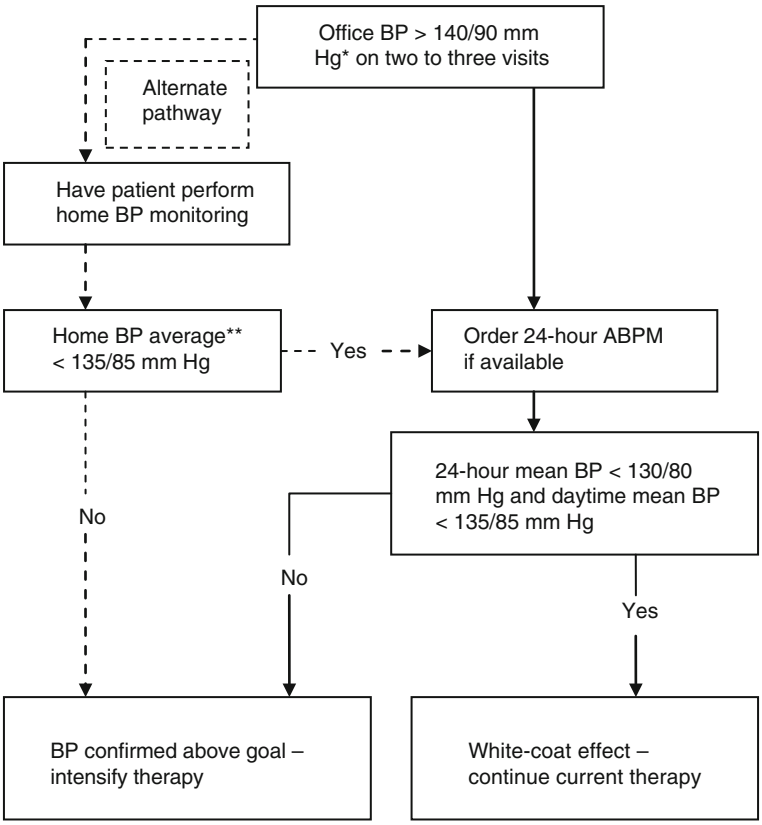

Fig. 42.1 Ruling out white-coat effect in patients with suspected resistant hypertension. If ambulatory BP monitoring is not readily available, home BP monitoring can be used as an initial strategy. If home BP monitoring confirms BP is indeed above goal, no further testing is needed. If home BP monitoring suggests white-coat effect, ambulatory BP monitoring can be used to confirm. *BP* blood pressure, *ABPM* ambulatory blood pressure monitoring. *Target BP may be lower in patients with diabetes or chronic kidney disease or higher in patients 60 years and older. **See Table 42.2 (Adapted with permission from Viera [56]

Table 42.2 Sample home blood pressure measurement protocol

- Verify that patient has appropriate cuff size and understands proper positioning and technique
- On each day for a minimum of five consecutive days, three morning and three evening measurements should be performed approximately 1 min apart without removing the cuff
- Have patient record dates and times of all measurements (or preferably use a device with memory)
- When calculating the average, discard the first 2 days' measurements and the first measurement of each triplicate set of measurements
- Average the remaining measurements

Based on the information from Verberk et al. [19]

Severe atherosclerosis in elderly patients may interfere with accurate BP measurement. When using an upper arm cuff to measure BP, occlusion of the brachial artery should cause disappearance of the ipsilateral radial pulse. If the radial pulse remains palpable despite such occlusion, "pseudohypertension" (falsely elevated BP reading) should be suspected. Clinical clues suggesting pseudohypertension include the development of dizziness or weakness in an elderly patient temporally related to antihypertensive medications and the absence of significant target organ damage despite a very high clinic BP measurement.

42.6 Reconsider Secondary Causes

While possible secondary causes of hypertension are often considered as part of the initial evaluation of a patient newly diagnosed with hypertension, patients with resistant hypertension comprise a subpopulation in which these causes will be more common. Once hypertension is confirmed as resistant, secondary causes of hypertension should be reconsidered (Table 42.3). Primary aldosteronism, obstructive sleep apnea, and renal artery stenosis are the most common secondary causes to reconsider. Even among patients with resistant hypertension, causes such as hypercortisolism and pheochromocytoma are still rare.

42.6.1 Primary Aldosteronism

Primary aldosteronism (PA) is one of the most common causes of resistant hypertension. The diagnosis may have been overlooked when the patient was first diagnosed with hypertension because many of these patients actually have normal potassium levels. In patients referred to hypertension specialty clinics, up to

Table 42.3 Secondary causes of hypertension

- Aldosteronism[a]
- Carcinoid syndrome
- Coarctation of aorta
- Cushing's disease
- Hyperparathyroidism
- Obstructive sleep apnea[a]
- Pheochromocytoma
- Polycythemia
- Renal artery stenosis[a]
- Renal parenchymal disease (can be cause or consequence)[a]

Adapted with permission from Viera [56]

[a]More common causes among patients with resistant hypertension

20 % demonstrate PA [23–25]. In a study of 1,616 patients with resistant hypertension, 182 (11 %) had PA. Among that 11 %, however, only 83 (46 %) had hypokalemia [26]. Patients with resistant hypertension ought to be considered for testing for PA. The best initial test is a morning plasma aldosterone/renin ratio. A ratio below 20 (when plasma aldosterone is reported in ng/dL and plasma renin activity is in ng/ml/h) effectively rules out PA. A ratio of 20 or higher with a serum aldosterone >15 ng/dL suggests PA, but the diagnosis must be confirmed by a salt suppression test [27]. In the study mentioned above, half of the patients with a high ratio did not have PA. The optimal diagnostic strategy for distinguishing adrenal adenoma from bilateral adrenal hyperplasia is controversial. Therefore, if a patient screens positive for PA, referral for confirmatory testing and evaluation should be considered.

42.6.2 Obstructive Sleep Apnea

Among patients with resistant hypertension, obstructive sleep apnea (OSA) is very common. In obese patients and/or those who report a history of snoring, witnessed apnea, or excessive daytime sleepiness, OSA should be suspected. In some patients, however, resistant hypertension may be the only sign. In one study of patients with resistant hypertension, 83 % were diagnosed with unsuspected OSA based on polysomnography (sleep study test) results [28]. Therefore, a polysomnogram should be considered in patients with resistant hypertension. In those found to have OSA, treatment with continuous positive airway pressure (CPAP) may help improve BP control [29].

42.6.3 Renal Artery Stenosis

In older adults, renal artery stenosis is usually due to atherosclerosis. In younger adults fibromuscular dysplasia, which is a systemic disease, can cause renal artery stenosis. Particularly among young women, renal artery stenosis due to fibromuscular dysplasia is one of the most common causes of secondary hypertension. An audible high-pitched holosystolic renal artery bruit on physical exam would raise suspicion and warrant imaging. Either computed tomography angiography (CTA) or MRI with gadolinium can be used to visualize renal artery stenosis. If it is available, MRI might be preferable because it does not use radiation and can determine the physiologic degree of stenosis. MRI can also be used for patients who have poor renal function. If MRI and CTA are contraindicated or not available, renal Doppler can be used. Renal Doppler also provides useful information regarding blood flow, but its accuracy is hampered by body habitus and operator skill [30].

While identifying renal artery stenosis due to fibromuscular dysplasia is important, identifying renal artery stenosis due to atherosclerosis (usually in older adults) is less critical because evidence does not show a benefit of revascularization over medical management [31].

42.7 Address Volume Overload and Interfering Substances

42.7.1 Volume Overload

Volume overload, which frequently contributes to resistant hypertension, may be related to a high-sodium diet, chronic kidney disease (leading to sodium retention), or both. Patients with resistant hypertension should be encouraged to reduce their dietary sodium intake as much as possible since they may be more sensitive to sodium than the general hypertensive population. In one study in which patients with resistant hypertension were randomized to low-salt vs high-salt diet, mean office BP was reduced 23/9 mmHg greater in the low-salt diet group [32]. Consider a nutrition consult to help patients learn how to adequately reduce the sodium content of their meals.

Appropriate diuretic therapy is a key to treating patients with resistant hypertension (Chap. 38). An early step in management, sometimes the only one necessary, is to increase the dose of the diuretic or change to a more potent diuretic. Chlorthalidone was the thiazide-like diuretic used in several of the large clinical trials with patient-oriented outcomes {the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack *Trial* (ALLHAT [33]); the Systolic Hypertension in the Elderly Program (SHEP [34])}. It is longer-acting and provides a greater BP reduction than equivalent doses of hydrochlorothiazide [35, 36]. Also, it reduces progression to left ventricular hypertrophy and cardiovascular events to a greater degree than does hydrochlorothiazide [37, 38]. Therefore, changing from hydrochlorothiazide to chlorthalidone, if applicable, is often a good initial step. Low-dose thiazide-type diuretics are only effective when renal function is adequate. Therefore, in patients with a serum creatinine value >1.8 mg/dL or glomerular filtration rate (GFR) <30 ml/min, a loop diuretic should be used [7]. Short-acting loop diuretics like furosemide and bumetanide need to be given two to three times per day. Torsemide is a longer-acting alternative.

42.7.2 Interfering Substances

Many substances can interfere with BP control either by directly raising BP, interfering with the mechanisms of antihypertensive drugs, or both (Chap. 36). For example, nonsteroidal anti-inflammatory drugs (NSAIDs) raise BP directly and can interfere with the mechanism of nearly every type of antihypertensive drug. For

Table 42.4 Examples of drugs and other substances that may interfere with blood pressure control

• Alcohol
• Amphetamines
• Antidepressants (e.g., bupropion, tricyclic antidepressants, selective serotonin reuptake inhibitors, venlafaxine, monoamine oxidase inhibitors)
• Cocaine
• Corticosteroids
• Cyclosporine
• Decongestants
• Dietary and herbal supplements (e.g., ginseng, ephedra, ma huang, bitter orange)
• Diet pills
• Erythropoietin
• Licorice (including some types of chewing tobacco)
• Nonsteroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitors)
• Oral contraceptives

Adapted from Viera [56]

patients with resistant hypertension NSAIDs should be discouraged or limited to the extent possible. Other agents that should be considered but that are less commonly involved in resistant hypertension include oral contraceptives, some antidepressants (e.g., bupropion, venlafaxine), appetite suppressants (e.g., ephedra, phentermine), sympathomimetics (e.g., amphetamines, cocaine, pseudoephedrine), and herbal supplements (e.g., ginseng) (Table 42.4). Eliminating or reducing a possible interfering substance may help reduce the patient's BP.

Heavy alcohol intake also can make hypertension much more difficult to control. Many hypertensive patients do not even recall getting advice to limit their alcohol intake, and compliance with advice to reduce alcohol intake is poor at about 30 % at 3 years [39, 40]. The acceptable amounts of alcohol intake are no more than two drinks (1 oz (30 ml)/of ethanol) per day for men or one drink (0.5 oz (15 ml) of ethanol) per day for women. Patients drinking in excess of these amounts should be advised to reduce their intake.

42.8 Intensify Therapy

It is important to remember that in addition to antihypertensive medications, the management of hypertension includes lifestyle modifications. A recent study examined healthy lifestyle factors and risk of cardiovascular events in patients with resistant hypertension [41]. Patients who exhibited a greater number of healthy lifestyle factors had a lower risk of cardiovascular events over a mean follow-up of 4.5 years. Thus, for patients with resistant hypertension, lifestyle modifications should be reemphasized. In particular, regular physical activity should be encouraged. Of

course, smokers should also be strongly encouraged to quit and offered cessation medications or programs. Patients may not appreciate that the Dietary Approaches to Stop Hypertension (DASH) eating plan combined with low sodium intake can be as effective as a single antihypertensive medication in reducing BP [42]. The importance of weight loss for overweight patients should be emphasized as well.

For patients with resistant hypertension, in addition to a diuretic, other medication classes among the first three agents would usually include an angiotensin-converting enzyme (ACE) inhibitor or ARB and a long-acting dihydropyridine calcium channel blocker. As mentioned earlier, fixed-dose combination pills are available (Table 42.5) and may be useful to enhance adherence to multidrug regimens. Unfortunately, chlorthalidone is not available in many of these combinations. Spironolactone is an evidence-based fourth agent to consider for patients with resistant hypertension. Spironolactone is an aldosterone antagonist that has been shown to reduce systolic BP by as much as 20 mmHg in patients with hypertension that is resistant to three or more drugs [43, 44]. Because it is potassium-sparing, when using spironolactone,

Table 42.5 Examples of fixed-dose combination pills for hypertension treatment

Combination	Generic agents (trade name)	Dose ranges available (mg)[a]
ACE inhibitor with dihydropyridine CCB	Amlodipine/benazepril (Lotrel)	2.5–10/10–50
ACE inhibitor with nondihydropyridine CCB	Trandolapril/verapamil extended release (Tarka)	1–8/180–240
ACE inhibitor with diuretic	Benazepril/HCTZ (Lotensin HCT)	5–20/6.25–25
	Enalapril/HCTZ (Vaseretic)	5–10/12.5–25
	Fosinopril/HCTZ (Monopril HCT)	10–20/12.5
	Lisinopril/HCTZ (Zestoretic)	10–20/12.5–25
	Quinapril/HCTZ (Accuretic)	10–20/12.5–25
ARB with diuretic	Candesartan/HCTZ (Atacand HCT)	16–32/12.5
	Irbesartan/HCTZ (Avalide)	150–300/12.5
	Losartan/HCTZ (Hyzaar)	50–100/12.5
	Olmesartan/HCTZ (Benicar HCT)	20–40/12.5
	Telmisartan/HCTZ (Micardis HCT)	40–80/12.5–25
	Valsartan/HCTZ (Diovan HCT)	80–320/12.5–25
Beta-blocker with diuretic	Atenolol/chlorthalidone (Tenoretic)	50/25
	Bisoprolol/HCTZ (Ziac)	2.5–10/6.25–12.5
	Metoprolol/HCTZ (Lopressor HCT)	50–100/25–50
	Nadolol/bendroflumethiazide (Corzide)	40–80/5
Diuretic with another diuretic	Spironolactone/HCTZ (Aldactazide)	25–50/25–50
	Triamterene/HCTZ (Maxzide, Dyazide)	37.5–50/25
Vasodilator with diuretic	Hydralazine/HCTZ (Hydrazide)	25–50/25–50

Adapted with permission from Frank [57]
ACE angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker, *HCTZ* hydrochlorothiazide
[a]Note maximum dose may be higher

careful attention must be paid to potassium levels, especially in patients who are also taking an ACE inhibitor or ARB. Spironolactone can cause gynecomastia in men. Eplerenone is an alternative aldosterone antagonist/mineralocorticoid receptor antagonist that does not cause gynecomastia. Amiloride is another alternative agent that functions as an indirect aldosterone antagonist [45]. These drugs are contraindicated in patients with severe renal impairment (Chaps. 36 and 38).

Other pharmacologic strategies for treating resistant hypertension include a beta-blocker (e.g., metoprolol), a vasodilating beta-blocker (e.g., labetalol, carvedilol, nebivolol), a direct vasodilator (e.g., hydralazine), or a centrally acting agent such as clonidine (transdermal or oral) or guanfacine. Another strategy that may be particularly useful in patients with comorbid diabetes or chronic kidney disease is adding a CCB of the alternate class (e.g., adding a nondihydropyridine to a dihydropyridine) [46, 47]. A nondihydropyridine CCB combined with a beta-blocker may promote bradycardia, which can be worsened by clonidine. Consider referral to a hypertension specialist when a patient's BP is not controlled adequately despite four or five agents.

42.9 Use of Plasma Renin Testing

Because of a possible paradoxical BP response, some patients with resistant hypertension may actually benefit from having medication withdrawn. Pressor responses to diuretics may be due to reactive increases in renin secretion, similar to that seen in sodium deprivation [48]. Pressor responses to other drugs may be related to unopposed alpha-adrenergic activity or blockade of the renin-angiotensin system. Measurement of plasma renin activity (PRA) may help guide withdrawal vs add-on therapy. In one trial of 77 hypertensive patients who were all uncontrolled despite treatment with an average of three medications, patients were randomized to either PRA-guided treatment or cared by clinical hypertension specialists [49]. Approximately one-third of participants in the PRA-guided group had low PRA levels during treatment, and they had anti-renin drugs withdrawn and received anti-volume drugs (diuretic or CCB) if needed. Converse strategies were applied to patients with medium or high PRA levels. At the end of the study, the number of antihypertensive drugs remained similar in the two groups. However, systolic BP declined significantly more in the PRA-guided group (−29 mmHg vs −19 mmHg), and the proportion of patients who had their BP controlled was 74 % vs 59 %. Given these promising results, further trials evaluating the use of PRA-guided treatment for patients with uncontrolled hypertension are needed.

42.10 Device-Based Interventions

Renal sympathetic activity contributes to hypertension in part through simulation of renin release, increased sodium reabsorption, and neurogenic mechanisms. Selective denervation of the renal nerves may therefore reduce BP. Much

enthusiasm was generated for catheter-based renal denervation after the publication of the Symplicity HTN-2 (renal sympathetic denervation in patients with treatment-resistant hypertension) trial, which showed resistant hypertension patients with a mean baseline BP of 178/96 mmHg randomized to catheter-based radiofrequency denervation had a 6-month mean reduction of office BP that was 31/12 mmHg greater than controls [50, 51]. Unfortunately, the Symplicity HTN-3 trial, which compared renal denervation to a sham control procedure and had stricter BP measurement enrollment criteria, showed no significant difference in BP outcomes (−14 mmHg office systolic BP in denervation group and −12 mmHg office systolic BP in sham group at 6 months) [52]. It, therefore, appears that renal denervation using the current technology may not be effective in the general population of patients with resistant hypertension. However, research with newer devices and using carefully selected subgroups of patients is still warranted.

Electrical stimulation of the carotid sinus baroreceptor has also been shown to decrease BP. A few small studies have demonstrated that an implantable baroreflex stimulator is feasible and may be effective [53, 54]. In one study, 45 patients with resistant hypertension and an average BP of 179/105 mmHg had reductions in BP of 21/12 mmHg at 3 months, and some had persistent effect at 2 years following device implantation [54]. However, in a study in which 265 patients with resistant hypertension were randomized 2:1 to baroreceptor stimulation vs a delayed group (had the device but it was not activated until the primary endpoint was determined), 54 % in the "on" group vs 46 % in the "off" group were responders, defined as at least a 10 mmHg reduction in systolic BP at 6 months [55]. Further studies of baroreceptor stimulation are going to be needed to clarify its potential role in treatment of resistant hypertension (Chap. 6).

42.11 Concluding Remarks

Resistant hypertension is relatively common, affecting approximately 13 % of patients treated for hypertension. The first step for managing patients with suspected resistant hypertension is to assess and address adherence to therapy. Next, it is important to rule out white-coat effect using out-of-office BP monitoring. Associated comorbidities and possible secondary causes should be considered. Volume overload often plays a role in resistant hypertension, and substances that interfere with BP control should be discontinued if possible. The final step in managing patients with resistant hypertension is to intensify therapy with strong consideration given to adding spironolactone to the multidrug regimen. With this six-step approach, the majority of patients should be able to achieve BP control. Further trials investigating approaches—both pharmacologic and device-based—for patients with resistant hypertension will help clarify optimal management strategies.

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Chapter 43
Drug Adherence in Hypertension

Michel Burnier

Abstract The treatment of essential hypertension is based essentially on non-pharmacological recommendations and on the prescription of blood pressure lowering drugs and/or diuretics. Because of the silent nature of hypertension, long-term adherence to therapy is one of the major issues of the management of hypertensive therapy. Indeed, it is well recognized that many patients interrupt their antihypertensive treatment completely after 1 year, and this lack of persistence has a major impact on our ability to control blood pressure in the hypertensive population. Today, there are multiple ways of assessing drug adherence in patients, but only very few of them are accurate, and the most accurate ones are difficult to implement in clinical practice. Thus, physicians have no real capacity to establish a correct diagnosis of nonpersistence or poor adherence even in high-risk patients such as patients with resistant hypertension. Therefore, there is an urgent need to develop new techniques or devices to help physicians in their ability to handle adherence to therapy and to improve blood pressure control in the population.

Keywords Persistence • Electronic monitoring • Drug measurements • Resistant hypertension • Multidiscipline • Healthcare system

43.1 Introduction

Lowering blood pressure (BP) below the targets recommended by most international guidelines for the management of hypertension is the most effective way to reduce the risk of hypertensive patients to develop target-organ damages and to lower their cardiovascular mortality [1–3]. However, it is well recognized that in most countries around the world, only less than 50 % of treated hypertensive patients actually reach the recommended target BP; hence, uncontrolled patients remain at high risk of suffering from hypertension-induced complications [4]. Indeed, surveys

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have clearly demonstrated that the survival of treated hypertensive patients not at goal is equivalent to that of untreated hypertensives [5]. In a post hoc analysis of a clinical trial, Mancia et al. [6] found that the higher the number of clinical visits with a normal BP, the lower the incidence of clinical outcomes. These observations suggest that there is an important gap between the rate of BP control obtained in clinical trials and the rate reported in national surveys reflecting the real life, and many factors can contribute to this gap [7]. Among them, medical inertia and drug adherence are probably two of the most important factors contributing to the poor control of BP in the hypertensive population. Indeed, drugs that are not prescribed adequately by physicians and not taken appropriately by patients cannot be effective and will certainly not provide the expected clinical benefits. In fact, poor adherence to therapy is not a specific issue of the management of hypertension. Indeed, in a recent analysis of drug adherence in a very large group of patients treated for the primary and secondary prevention of cardiovascular diseases, a low adherence to therapy was found with antihypertensive agents as well as with lipid-lowering treatments suggesting that a poor adherence is common to most if not all silent diseases [8]. See also Chap. 21.

The purpose of the present chapter is to review the role of drug adherence in the management of hypertensive patients. We shall revise the definitions, the methods available to measure drug adherence in clinical practice and in studies, and, finally, discuss the impact of drug adherence on BP control in the general hypertensive population but also in patients with so-called resistant hypertension (Chap. 42). At last, strategies to improve drug adherence will be discussed.

43.2 Definitions and Taxonomy of Drug Adherence

In the literature, several terms are used to describe different aspects of drug adherence such as adherence, compliance, concordance, or persistence. Some of these terms are sometimes used as synonyms, and what they actually represent is not always well understood. According to the World Health Organization, adherence is the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider. In recent years, a particular effort has been made in the field of adherence to clarify the terms and their exact definition. To this purpose, a consensus conference was held to generate a new taxonomy [9]. Thus, *adherence to medication* is the process by which patients take their medications as prescribed. Adherence has three components: *initiation*, *implementation*, and *discontinuation. Initiation* is the time from prescription until first dose of the medication is taken. The *implementation* of the dosing regimen is defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken. *Discontinuatio*n marks the end of therapy, when the next dose to be taken is omitted, and no more doses are taken thereafter. Persistence is the length of time between initiation and the last dose, which immediately

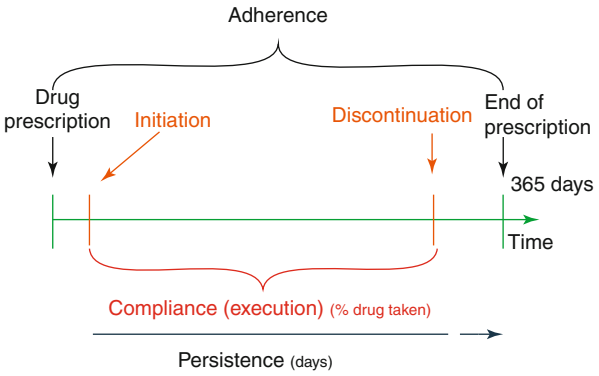

Fig. 43.1 Illustration of the different components of drug adherence. Adherence to drug therapies includes several aspects following the prescription. It starts with the initiation of therapy (4–5 % of patients do not start their therapy). Then the patient has to execute his/her treatment every day, and he/she has to persist on treatment. Discontinuation may occur at any time and signs the end of persistence. As discussed in the text, poor persistence is the major problem in hypertension

precedes discontinuation [9]. Practically, three types of deviation from prescribed dosing instructions are particularly frequent, i.e., non-initiation, short persistence, and poor execution of the dosing regimen [10]. About 4–5 % of patients never start their treatment and represent the non-initiation process. Short persistence, which consists of all patients ceasing their engagement with the dosing regimen on their own initiative, is definitively the most common problem of adherence in hypertension with 50 % of patients being nonpersistent at 1 year [11]. At last, the poor execution is illustrated by the lapses in implementation (or execution), which are the typical consequence of forgetfulness or negligence resulting in more or less prolonged period of treatment interruptions. Each of these aspects of adherence to medication has a direct impact on the quality of BP control of hypertension, the most critical ones being of course a non-initiation and a lack of persistence. The different processes are illustrated in Fig. 43.1.

43.3 Methods of Measuring Drug Adherence

Many techniques have been published and are being used to estimate drug adherence in patients (Fig. 43.2). The simplest one is undoubtedly a careful interview of the patient leading to a physician's impression on what the patient is actually doing with his/her medications. This method is quite imprecise, and in our experience, the ability of a physician to detect nonadherence is about 30 %. The only exception may be patients who did not initiate their treatment at all and are often ready to admit that they did not accept the treatment for one or another reason. Thus, per se the physician's impression is a very weak indicator of the level of adherence of a patient. The occurrence of drug-induced adverse effects, the clinical response, and the respect of

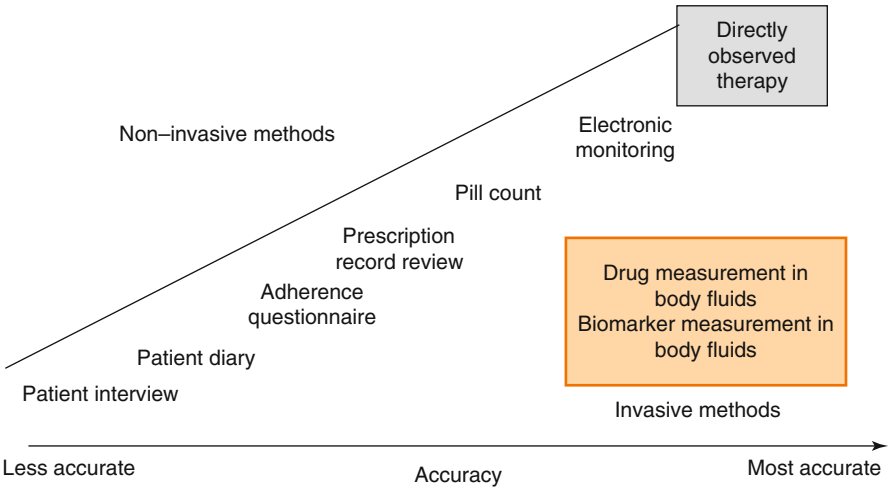

Fig. 43.2 Methods of assessment of drug adherence according to their accuracy. Several methods reported in the figure have been used to assess drug adherence in hypertension. Most noninvasive methods except electronic monitoring and direct-observed therapy are unreliable and tend to overestimate drug adherence

consultations have also been used as indirect markers of adherence, but it appears that the adequacy of these methods is as good as tossing a coin. Several questionnaires have been built to assess adherence. These questionnaires are generally used in clinical studies but their results tend to overestimate the adherence, as patients tend to forget the episodes when no medication was taken. The most popular questionnaire is the Morisky questionnaire, which is easy and rapid to use in practice in its simplified version [12]. However, when compared to electronic measurements of adherence, the Morisky questionnaire has been found to overestimate drug adherence as well.

The most common method of assessing drug adherence in clinical trials is the pill count. This method provides a relatively good overview of what has been taken by the patient during a time period but again the general trend of this method is an overestimation. This is due to the tendency of patients to return empty boxes. This is confirmed by the observation that patients receiving more pills than actually needed generally return an empty box. In large epidemiological studies, a careful monitoring of prescription refills is sometimes used. This approach enables to calculate the percentage of days covered by the prescriptions [13]. This method also gives a rough estimate of drug adherence over a long time period and may be useful if an electronic monitoring of drug prescriptions by pharmacies is available. Such continuous registries may be helpful to evaluate drug persistence and the risk factors associated with a poor adherence [14, 15]. However, this approach assumes that patients take their drugs adequately every day, which is certainly not the case. Moreover, patients may use different pharmacies to obtain their medications. Thus, the monitoring system should cover all sources of medication delivery.

Two methods actually provide very interesting and reliable information on drug adherence: the electronic monitoring and the direct measurements of plasma or urinary drug levels. The former gives very interesting dynamic information on adherence and is based essentially on the fact that if the pillbox is not open, the drug is not taken, but it does not prove the ingestion, whereas the latter ascertains drug intake but the information obtained with drug levels is only punctual. The fact that electronic monitoring systems do not prove that the medication was actually taken is often seen as a major limitation of these devices. Yet, in our experience, one has to admit that it is very difficult and very rare that a patient opens the pillbox every day and throws the medication each day during several months. Thus, information gathered with the electronic monitoring are considered reliable provided the monitoring is performed long enough (at least several months). As far as drug measurements are concerned, positive results confirm that some drug has been taken, but physicians obtain no information on when the drug was taken and how often doses were missed between consultations as illustrated in Fig. 43.2, and this may limit the interpretation of the results. In fact, although measurements of drug levels tend to become popular, for example, in patients with resistant hypertension [16, 17], this approach may be affected by the *white coat adherence* bias according to which patients tend to improve their adherence a few days before and after a consultation [18]. Thus, if patients are informed that blood or urine will be taken to measure drug levels, which should be done ethically, the method may be of limited interest. Moreover, chemical methods are costly and labor intensive. Nonetheless, recent studies using this methodological approach without informing patients have clearly demonstrated that drug adherence is particularly low among patients with resistant hypertension [16, 17, 19].

As mentioned in a recent review article, the ideal method to assess drug adherence in clinical practice should "*provide a reliable capture*, *storage*, *analysis*, *and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data*" [20]. Nowadays, three methods are close to fulfill these criteria, i.e., the retrospective analysis of prescription refill records, the analysis of chemical markers of drug exposure, and the automatic electronic monitoring of adherence [20].

43.4 Risk Factors of Poor Adherence in Hypertension

Hypertension is a disease that can be treated but rarely cured. Thus, patients are usually informed that therapy will be maintained quasi for the rest of their life (Chap. 31). The long-term management of hypertension actually generates many obstacles that may affect the capacity of patients to stay on therapy. The first obstacle is the acceptance of the diagnosis and the difficulty for some patients to initiate a course of lifelong treatment for a silent asymptomatic disease. Depending on the quality of the information they received, patients may not be motivated. Thereafter, patients may be confronted with the first side effects of the prescribed drugs. In the

absence of symptoms before treatment, side effects may not be accepted and tolerated. With time, the treatment scheme may become more and more complex as it is well recognized that 70 % of patients will need more than one drug to reach the target BP recommended by guidelines (Chaps. 30 and 41). Later, patients may be exposed to the delayed side effects such as sexual dysfunction. These factors will further decrease the motivation to remain under treatment, and for many patients, the necessity to pursue the treatment will be questioned leading in most cases to a discontinuation of therapy due to a low persistence. A recent analysis by Simpson et al. has actually shown that patients with an excellent adherence to therapy have a global positive attitude toward all preventive recommendations for a better health [21]. Thus, this type of patients has a better survival even if they receive a placebo as demonstrated recently in the post hoc analysis of a heart failure trial [22]. However, it is also important to notice that in some cases, a good adherence may have damaging effects if the drug has serious adverse effects, and patients continue to take them as, for example, nonsteroidal anti-inflammatory drugs or antiarrhythmic agents (Chap. 42).

Besides these therapy-related factors, several other barriers and risk factors for interrupting treatments have been identified (Table 43.1). These barriers come not only from the patient him-/herself but also from the family, the physician, the nature of the treatment, and the healthcare system. These include depression, other comorbidities, personal as well as family beliefs on hypertension and on the necessity of treatment, lack of knowledge about hypertension, cost of medications, the use of alternative medicines, memory problems in elderly patients, and poor quality of life.

Several studies have clearly identified the characteristics of patients at high risk of not being adherent to their treatment. These are essentially young, active men, hypertensive patients of Afro-American origin, and elderly patients with cognitive dysfunction [23]. Gender does not seem to be a major determinant although some studies have suggested that adherence to therapy is better in females than males. The same is true of the educational level. The health system per se and particularly the copayment has also a major impact on the long-term persistence of patients

Table 43.1 Factors associated with an increased risk of poor adherence

• Age and gender (young man at higher risk)
• Elderly patients with cognitive impairment
• Personal and family beliefs
• Asymptomatic nature of hypertension
• Understanding of the benefits of treatment
• Lower socioeconomic status
• Cost of treatments and copayments
• Severity of disease
• Number of drugs and complexity of treatment
• Drug tolerability (acute and long-term side effects)
• Efficacy on blood pressure control
• Family support
• Physician-patient relationship
• Depression and comorbidities

treated for hypertension [24]. Thus, it is very important for physicians to identify these high-risk factors, as strategies may be developed to prevent any interruption of therapy as will be discussed later in this review.

43.5 Adherence in Hypertension

It is well recognized that adherence to medication is an important determinant of the BP response to treatment and hence of the clinical benefits of antihypertensive therapies. In the last two decades, many clinical studies have investigated drug adherence in patients with hypertension in most cases using the medication event monitoring system (MEMS) which enables to follow the adherence on a day-to-day basis for a long time period. These studies aimed not only at defining adherence in hypertension but also at investigating the ability of the monitoring system to support drug adherence [25, 26]. Recent reviews have confirmed that adherence is highly variable but relatively high when measured in hypertension. This high adherence may be due to the measurement bias, as adherence tends to increase as soon as it is measured. In addition, a careful monitoring of adherence might help. However, in one control study, it did not really improve BP control but rather prevented from changes in drug therapies [26]. Nonetheless, many interesting aspects of the adherence process have been described with this approach. The first and probably the most important one is that drug adherence is a very *dynamic process*, which can hardly be summarized with a single number. Indeed, patients may be adherent for some periods and less adherent in other circumstances, for example, during weekends and holidays. Second, it is very difficult to define a cutoff point above which drug adherence is sufficient and acceptable. Indeed, in the literature, an arbitrary cutoff of 80 % is used to define a good adherence, but it is obvious that 80 % can be achieved in many ways with different clinical impacts, for example, missing 1 day every 5 days or 1 week every 5 weeks. Moreover, the impact of missed doses on BP control and risk reduction depends largely on the pharmacological profile of the prescribed drugs [27]. This is the reason why it is generally recommended to use long-acting medications in patients at risk of poor adherence. Thirdly, many investigators have tried to demonstrate a correlation between the level of BP achieved under treatment and the percentage of doses taken. These correlations have sometimes been obtained [28] but they have generally been very weak. In fact, there are many good reasons why this type of correlation should not be very high. Indeed, high BP values can be obtained in nonadherent hypertensive patients as well as in adherent patients insufficiently or inadequately treated.

Despite many of these limitations, increasing evidence gathered from large databases has shown that patients with a good adherence have a better BP control [29]. Moreover, highly persistent hypertensive patients have a greater reduction of their cardiovascular risk than patients interrupting their treatment [30]. At last, a good adherence to antihypertensive medications has been associated with a significant reduction of the risk of coronary heart disease and congestive heart failure and cerebral diseases [31–33].

43.6 Adherence in Resistant Hypertension

Apparent resistant to therapy is one clinical situation in which the question of drug adherence becomes particularly important. Indeed, when the prescribed antihypertensive drugs do not lower BP as expected, physicians are confronted to two crucial questions: is the patient a *nonresponder* to therapy or is the patient not taking his/her drug as recommended thus being a *nonadherer*? In the absence of any adequate tools to measure drug adherence, physicians are left with only one option, i.e., to consider the patient as a nonresponder. Thus, physicians will probably increase the drug doses or add another drug in order to achieve the therapeutic targets. However, it is obvious that if poor adherence is the real problem, adding new drugs is a completely wasted action, which will only aggravate the situation.

With the recent development of renal denervation and baroreflex activation to treat patients with resistant hypertension, a sudden interest for resistant hypertension and its causes has emerged [34] (Chap. 42). Several analyses have investigated the potential causes of apparent resistance to drug therapy in hypertension. Not surprisingly, poor drug adherence has been identified as one important factor of pseudo-resistance. Yet the true incidence of poor adherence remains largely unknown in this patient population because adherence was rarely measured adequately. Thus, published figures range between 10 and 50 % [16, 17, 35–39]. In our experience, using electronic monitoring of drug adherence, about one third of patients with resistant hypertension had adherence problems leading to uncontrolled hypertension [40]. More recently, three studies have been conducted among hypertensive patients with uncontrolled BP or candidates to renal denervation to assess drug adherence using measurements of either urinary or blood concentrations of drugs [16, 17, 19]. Two of these studies reported almost 50 % of partial or complete nonadherence and the other 23 % of nonadherence in renal denervation candidates. These figures are important and may well be underestimations as they do not take into account the white coat adherence phenomenon discussed earlier in this review [41]. Figure 43.3 illustrates the limits of this approach on the nature of adherence. Interestingly, poor adherence to the medication has been found in inpatients as well as in outpatients [19]. In hypertensive patients with coronary heart disease, resistant hypertension also appears to be common (38 %) and to be associated with a worst cardiovascular prognosis [42].

In any case, it is now increasingly accepted that poor adherence is a real concern in resistant hypertension. Despite the availability of adequate noninvasive methods, adherence to therapy remains largely underdiagnosed and almost never measured in clinical practice. In recent studies, some investigators have used the directly observed treatment (DOT) or “tablet feed” which is commonly used in the management of tuberculosis, to evaluate the role of poor adherence in mediating uncontrolled BP [43, 44]. Although a small number of patients were enrolled in some of these studies, it clearly showed that many patients actually normalized their BP when the treatment was given under control. Thus, taken together, these new data suggest that adherence to the drug regimen is clearly a critical issue in resistant

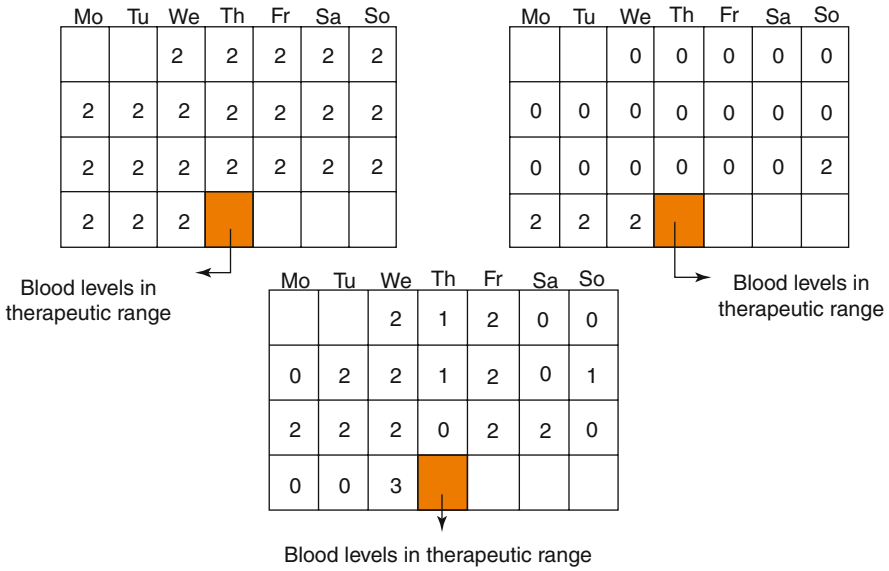

Fig. 43.3 Illustration of the limits of measuring drug levels in blood or urine using three clinical cases in which a positive measurement has been obtained suggesting good adherence. In all three cases, drug levels measured in the blood (or urine) are found to be positive. Numbers denote the quantity of tablets taken by the patient for that day. The first patient is fully adherent, whereas the second patient takes his/her therapy only a few days before the consultation leading to a positive test. The third patient has a rather erratic execution although he/she stays on therapy. The day before the consultation, the patient took three instead of two tablets causing a positive test in blood. This illustrates that measuring drugs in blood or urine provides only a limited information on adherence because of the dynamic nature of adherence

hypertension, and we believe that a good assessment of adherence in patients not responding to drug therapy is essential to take rational therapeutic decisions [40]. However, today, physicians are still limited by the lack of cheap and easy to use methods of monitoring adherence in clinical practice.

43.7 Strategies to Improve Drug Adherence in Hypertension

Multiple ways to improve drug adherence have been investigated in hypertension and chronic diseases in general. The proposed strategies concern the patient, drug therapy, pharmacist, physician, and the entire healthcare system.

The first and certainly the most important step is providing careful information to the patients on the goals of therapy and on the means to achieve the objectives. Indeed, in order to be motivated to stay on therapy, patients need to know the risks linked to their disease and to consider them as serious. They have to know the BP goals and the effects expected from therapy. They also have to be informed on the

means to achieve these goals to acquire specific competences and to develop a set of strategies to reach the targets, to cope with the disease, and to autoregulate their actions. Finally, patients have to believe in their personal efficacy. Thus, the empowerment of the patient is critical [45]. In this respect, recent studies have suggested that self-monitoring and even self-uptitrating of drugs by the patients may be helpful to improve BP control even in high cardiovascular risk patients [46]. Thus, home BP monitoring may be a good recommendation in patients who have difficulties with their treatment and are at high risk of not staying on therapy [47]. On their side, physicians also need to be motivated and should avoid medical inertia in order to show patients that they are eager to achieve the BP goals in order to preserve their patients' health [48].

One can also act on the prescribed regimen to support drug adherence over time. Indeed, it is well recognized that the number of drugs patients received and the dosing frequency have a major impact on persistence [49–51]. Several studies have demonstrated that simplifying the drug regimen with the use of fixed-dose combinations has a positive impact on adherence and persistence [52–55]. A recent meta-analysis confirmed that simplification of therapy is an effective therapeutic approach in hypertension that improves adherence though the impact on BP control is relatively modest [54]. This finding was actually confirmed in a Cochrane analysis of different strategies to improve adherence in hypertension [56]. Interestingly, it seems that beyond the number of tablets per day, the perception of the burden of the disease and of the therapy is predominant [57]. Indeed, patients may accept to follow a treatment including a high number of tablets per day provided they are convinced of the clinical benefits. Regarding the adaptation of drug therapy, it is also recommended to prefer the prescription of combinations of long-acting drugs which blunt the effect of isolated missed doses. Studies have shown that BP is more likely to remain adequately controlled despite the omission of one or two doses if the antihypertensive drug has a long half-life [58].

Several other tools can be used to support drug adherence in hypertensive patients. This includes the use of organizers, recalls using telephones or emails, rewards, special packages, and behavioral interventions. All of these tools have been shown to have some positive effect on drug adherence, but in general, the magnitude is rather small in the order of 4–11 % [59]. The most effective way to support drug adherence and improve persistence during a long period is probably to monitor drug adherence continuously, for example, with an electronic monitoring system such as the medication event monitoring system (MEMS) (Fig. 43.2). Indeed, the use of such devices enables to obtain real data on the patients' adherence and allows a discussion between the physician and patient on adherence data [60]. Unfortunately, the MEMS device is used essentially in clinical trials, and very few hospitals or reference centers are using them as a clinical tool. For many years now, telemonitoring of BP measured at home by the patient with the possibility of an interaction between the caregiver and the patient in case of problems has been reported as an effective and cost-effective way to support drug adherence. However, in our opinion, this approach should be used essentially in patients at very high risk of developing a cardiovascular complication when missing several drug doses [61, 62].

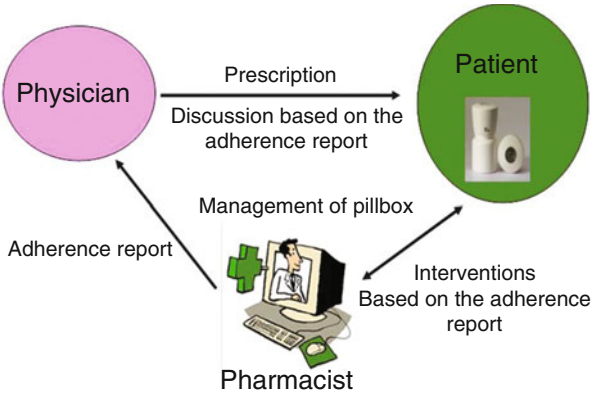

Fig. 43.4 Illustration of a physician-pharmacist network based on adherence monitoring and the availability of an adherence report, which links the patient to the pharmacist and the physician. Note that the central part of the collaboration is the adherence report. The data are collected by the patient with the electronic monitoring system that was prescribed by the physician. The collected data are then analyzed by the pharmacist and discussed once with the patient. Then the patient brings the report to the physician for a second analysis and adaptation of therapy and discussion about adherence if needed

In some countries, a multidisciplinary approach which includes pharmacists and/or nurses has been shown to be effective in improving adherence and hence clinical parameters [63, 64]. The multidisciplinary approach as illustrated in Fig. 43.4 is very interesting, but it is often subject to major problems such as the constantly difficult collaboration between physicians and pharmacists in some countries and, more importantly, the reimbursement of pharmacists' activities by the healthcare system. Moreover, the cost-effectiveness of this approach has been questioned as well as that of a sustained nurse support [60, 65, 66].

In the end, the health system and its ability to reimburse activities linked to the management of drug adherence and also to limit the copayment of drugs in patients with financial difficulties is an important issue [24]. A recent literature review on this topic shows that reduced medication copayments were associated with improved hypertension control and treatment adherence, mainly evaluated in American settings [24].

43.8 Concluding Remarks

Although cardiovascular mortality tends to decline in developed countries [67], hypertension remains a major risk factor for the development of cardiovascular events such as stroke, coronary heart disease, congestive heart failure, and chronic kidney diseases. Today, few if any new drugs are being investigated in order to improve our ability to treat and control blood pressure in the population.

New invasive techniques such as renal denervation and carotid baroreflex stimulation are being tested in patients with resistant hypertension, but most recent results have produced more questions than answers, and one still has to define more precisely who will benefit the most from these interventions. Therefore, physicians have no other choice today than to use actual available drugs including fixed-dose combinations as effectively as possible. In this context, one cannot do without addressing the issue of drug adherence and persistence. Blood pressure control cannot only be improved by recruiting more untreated hypertensive patients but also by improving drug adherence in the treated hypertensive patients. To this purpose, there is an urgent need to develop new methodologies or devices enabling detection and monitoring of drug adherence in order to provide physicians with reliable data on which they can build their therapy and support their patients in their effort to achieve the therapeutic goals and hence to reduce their patients' risk of cardiovascular complications.

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Chapter 44
The Glycemic Consequences of Antihypertensive Medications

Joshua I. Barzilay, Paul K. Whelton, and Barry R. Davis

Abstract Thiazide and thiazide-like diuretics are among the oldest and most widely used medications for the treatment of hypertension. They are effective in lowering blood pressure and for preventing cardiovascular disease. The use of these agents has been questioned owing to their metabolic side effects, chief among which are rise in glucose levels and incident diabetes mellitus. Newer antihypertensive agents are preferred by many medical societies since they are considered metabolically neutral or advantageous. In this chapter, we examine the effects of the thiazide-like diuretic, chlorthalidone, on glucose levels through our experience with its use in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). We show that hyperglycemia develops in people treated with chlorthalidone, but elevated glucose levels also occur in people treated with amlodipine and lisinopril. After several years of use, there is no statistically significant difference in glucose levels between them. We further show that incident diabetes mellitus associated with diuretic use has a less severe effect on coronary artery disease than does diabetes mellitus which develops with calcium channel blocker and angiotensin-converting enzyme inhibitor use.

We also discuss the use of first-generation beta-blockers. They, too, have a diabetogenic effect, but, like thiazides, offer many benefits.

We conclude that thiazide and thiazide-like diuretics and older beta-blockers have an important role in hypertension management in the present age of medical care despite their perceived negative metabolic effects.

Keywords Renin-angiotensin system • Fasting glucose • Hypertension management • Insulin resistance • Thiazide-like diuretics • Beta-blocker • Diabetogenic effect • Calcium channel blockers

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44.1 Introduction

Small increases in fasting glucose (FG) levels can be associated with an increased risk of cardiovascular disease (CVD). As one example, people with impaired FG levels (100–125 mg/dL) have an approximately 25 % increased risk of coronary heart disease (CHD) as compared to people with normal fasting glucose levels (less than 100 mg/dL) [1]. Thus, any medication that increases glucose levels, either through impaired insulin release/production or through insulin resistance, could potentially increase the risk of CVD. Such considerations have played a major role in the selection of antihypertensive drug therapy. Almost 50 % of hypertensive individuals have insulin resistance [2], and the majority of people with hypertension (HTN) are overweight or obese [3–6], which are risk factors for diabetes mellitus. Thiazide diuretics and first-generation beta-blockers are considered diabetogenic and are frequently avoided by the medical community [7]. In contrast, renin-angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are metabolically favorable and have been recommended by many medical societies and opinion leaders as the preferred drug classes for controlling HTN in individuals at risk for glucose disorders [6, 8–10].

While these assumptions are logical, they do not necessarily lead to better cardiovascular outcomes. Diuretics are time-proven for the control of blood pressure and for cardiovascular protection [11–14]. This is especially so in the elderly [15], in whom HTN has its highest prevalence and incidence. Thiazide diuretics also potentiate the effects of newer blood pressure medications [16], on account of which they are frequently combined with newer antihypertensive medications. Likewise, older beta-blockers are effective for CHD protection [17–19] and are still widely used. Avoiding the use of a diuretic or a first-generation beta-blocker in an attempt to prevent an increase by a few points in blood glucose levels is unwise if the resulting blood pressure control is suboptimal, which can lead to an increased risk of a CHD event.

In this chapter, we review the results of clinical trials which have examined the glycemic effects of thiazide diuretics, ACEIs, ARBs, and calcium channel blockers in patients with HTN.

44.2 Thiazide and Thiazide-Like Diuretics

Soon after their introduction into clinical practice (1960s), it became clear that the use of thiazide and thiazide-like diuretics was associated with an increased incidence of impaired glucose metabolism and new onset of type 2 diabetes mellitus (T2DM). At the time, hydrochlorothiazide (HCTZ) doses of 25–100 mg were commonly prescribed since there were few other medications for the treatment of HTN and higher doses were believed to be more efficacious than lower doses. With greater experience and the realization that hypokalemia from high doses of

thiazides could lead to sudden death [20], diuretic doses were lowered, generally to 12.5–25 mg of HCTZ or to 25 mg of the thiazide-like diuretic chlorthalidone. Nonetheless, glucose abnormalities persist [21] (see Table 44.1 in reference [21]). In general, the increases in FG levels as compared to placebo or another medication are modest, about 2–5 mg/dL (Chap. 38).

It is believed that glucose abnormalities in association with thiazide diuretic use are through loss of urinary potassium with consequent diminished serum potassium levels [22]. The latter inhibits or impairs the release of insulin from the pancreatic beta cells. It is also hypothesized that diuresis can lead to decreased blood volume and cardiac output, which activates the sympathetic nervous system, leading to reduced blood flow to the skeletal muscle and ultimately to peripheral insulin resistance [23] (Fig. 44.1).

To gain insight into these concepts, we examined the Antihypertensive Lipid-Lowering Heart Attack Prevention Trial (ALLHAT) study database. ALLHAT was a large (>42,000 participants) multicenter randomized clinical trial designed to determine whether the occurrence of fatal CHD or nonfatal myocardial infarction would be lower for high-risk patients with HTN assigned to first-step therapy with the calcium channel blocker (CCB) amlodipine (Chap. 37), the ACEI lisinopril, or the α-adrenergic receptor blocker doxazosin compared to the thiazide-type diuretic chlorthalidone during 5 years of treatment [24]. The doxazosin arm was discontinued after only 3.3 years because of futility of finding a significant benefit for CHD incidence and also because doxazosin was associated with a significantly higher incidence of CVD and especially heart failure as compared to chlorthalidone [25]. Following the full 5 years of treatment, there were no differences in the incidence of the primary outcome (fatal CHD and nonfatal MI) or all-cause mortality for amlodipine or lisinopril as compared to chlorthalidone. However, the thiazide-based treatment resulted in a clinically important significantly lower risk of heart failure [3].

We conducted a post hoc analysis of ALLHAT to investigate differences in elevated FG levels, change in FG levels, and incident diabetes mellitus in the three

Table 44.1 The odds of diabetes with the use of ACE inhibitor vs. diuretic and CCB vs. diuretic for baseline to 2 years, years 2–4, and years 4–6 in the ALLHAT

	Baseline to year 2	*P* value	Year 2 to year 4	*P* value	Year 4 to year 6	*P* value
Characteristic						
Subjects without diabetes mellitus at the beginning of the interval	6,486		4,076		753	
Randomized treatment						
ACE inhibitor vs. diuretic	0.550 (0.431–0.704)	<0.001	0.816 (0.586–1.138)	0.23	0.863 (0.403–1.851)	0.71
CCB vs. diuretic	0.727 (0.579–0.913)	0.006	0.0740 (0.536–1.023)	0.07	0.955 (0.579–1.902)	0.90

Based on Ref. [26]. Reproduced with permission from the American Medical Association

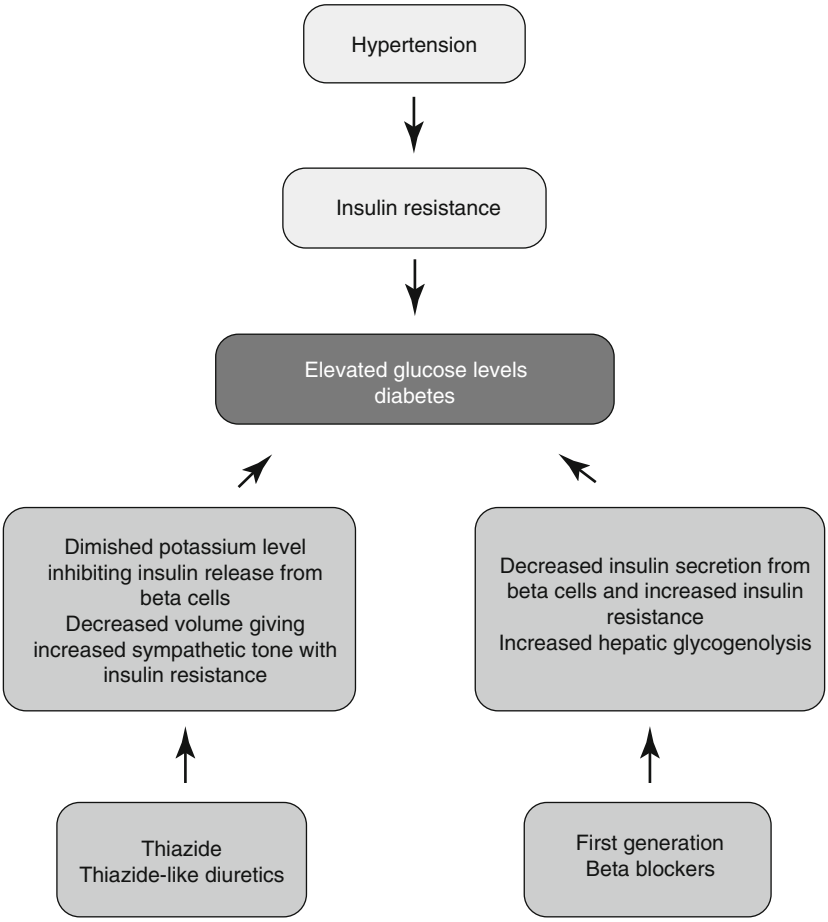

Fig. 44.1 Proposed diabetogenic mechanisms of thiazide and thiazide-like diuretics and first-generation beta-blockers

treatment groups. Unlike previous studies, we were able to examine the impact of any glucose changes associated with treatment assignment to the risk of CVD and renal disease in participants without diabetes at baseline. By design, there was little overlap in the use of the three classes of antihypertensive medications so valid comparisons could be made. In addition, the number of participants and events in each arm of the study was sufficiently large to provide adequate statistical power.

In the first part of our analysis [26], we found that FG levels increased steadily during a mean follow-up of 4.9 years, regardless of the antihypertensive therapy assignment. Participants randomized to treatment with chlorthalidone had a significantly higher level of FG and a higher incidence of new-onset diabetes mellitus at years 2 and 4 of follow-up compared with those randomized to lisinopril or amlodipine treat-

ment. However, the differences in mean FG level change between the treatment groups were small (3.0 and 1.5 mg/dL between chlorthalidone and amlodipine and 5.0 and 4.0 mg/dL between chlorthalidone and lisinopril at years 2 and 4, respectively). Further analyses found little association between serum potassium levels or changes in serum potassium levels and FG elevations in those taking chlorthalidone.

These small differences in FG levels translated into higher odds of new-onset diabetes mellitus (FG > 125 mg/dL) at 2 years in those taking chlorthalidone compared with those taking amlodipine or lisinopril. In other words, a small change in FG levels moved many participants over the 125 mg/dL cutoff point used to define diabetes mellitus. During the first 2 years, the odds for developing new-onset diabetes were lower for those assigned to lisinopril (odds ratio [OR], 0.55 [95 % confidence interval [CI], 0.43–0.70]) or amlodipine (OR, 0.73 [95 % CI, 0.58–0.91]) compared to their counterparts assigned to chlorthalidone. At years 4 and 6, assignment to amlodipine or lisinopril was still associated with a lower OR of developing new-onset diabetes, but the ORs were no longer statistically significant (Table 44.1).

The 4- and 6-year cumulative incidence of new-onset diabetes among participants without diabetes at baseline was 11.0 and 13.8 % in those assigned to chlorthalidone, 9.3 and 12.0 % in those assigned to amlodipine, and 7.8 and 11.0 % in those assigned to lisinopril. These rates allow for a calculation that provides an important perspective on thiazide-associated diabetes. If amlodipine is assumed to be metabolically neutral, then (based on the 4-year rates) 85 % (9.3/11.0) of the new-onset diabetes associated with a thiazide diuretic is not "causally related" to the use of a thiazide diuretic, at least in an older, mostly overweight, ethnically diverse population.

Findings similar to these have been reported in two other studies that reported on change in FG levels with antihypertensive medications [27, 28]. In both these studies, the changes in FG levels were small (mean, 2.0–3.5 mg/dL), but the relative risk of developing new-onset diabetes was significantly increased.

We next examined whether these differences in FG impacted CVD and renal disease outcomes. We failed to find an effect of the changes in FG level on any study end point, both for an exploration of all the treatment groups combined and for the chlorthalidone group separately. Further, the hazard ratio for a 10 mg/dL change in FG level was no larger for chlorthalidone than for amlodipine or lisinopril. For incident diabetes mellitus, CHD was the only outcome with a statistically significant increased hazard ratio, and this did not differ significantly across the three treatment groups (Fig. 44.2).

These ALLHAT findings are consistent with other studies. In a 14-year follow-up of the Systolic Hypertension in the Elderly Program [27], diabetes mellitus diagnosed during chlorthalidone therapy was not associated with a significant increase in CVD mortality (HR, 1.04 [95 % CI, 0.75–1.46]) when compared with diabetes mellitus that occurred in the absence of diuretic administration, which was associated with a significant increase in CVD mortality (HR, 1.56 [95 % CI, 1.12–2.18]). In a second study, a 15-year follow-up of 686 middle-aged adults with HTN treated with diuretics [28], incident diabetes mellitus did not have a significant effect on CVD mortality, whereas prevalent diabetes mellitus at baseline did.

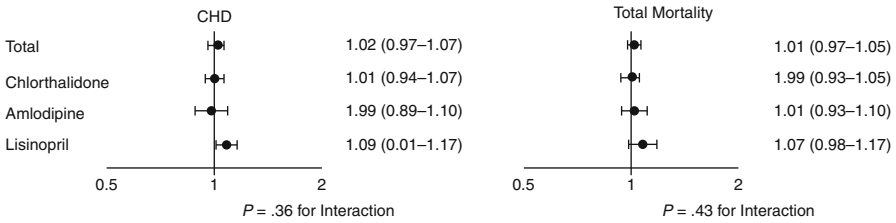

Fig. 44.2 Cox regression models showing the hazard ratio and 95 % confidence intervals associated with a 10 mg/dL (0.56 mmol/L) increase in fasting glucose during the first 2 years of follow-up for subsequent CHD and total mortality (Based on Ref. [26]. Reproduced with permission from the American Medical Association)

An explanation can be proposed as to why increased blood glucose and diabetes mellitus in association with thiazide-like diuretic treatment did not lead to an increase in CVD risk. Previous studies have shown that glucose levels decrease when diuretic therapy is discontinued [22]. In contrast, "classic" diabetes mellitus is characterized by persistent elevation of blood glucose levels. This suggests that the elevation in glucose levels, which can occur during diuretic therapy, is likely to have been caused by mechanisms other than insulin resistance – the underlying pathway for "classic" diabetes mellitus. As discussed above, only a small proportion of the cases of diabetes mellitus that arises during diuretic therapy actually appears to be "causally related" to the diuretic. On the other hand, incident diabetes mellitus in participants treated with lisinopril was associated with a significantly high risk of CHD. Also among those treated with amlodipine, patients who developed diabetes had a higher total mortality and stroke. Given that these medications are "glucose protective" or "glucose neutral," respectively, the development of diabetes in association with their use suggests the presence of a high degree of insulin resistance. It should also be remembered that a rise in FG levels associated with thiazide diuretics occurs most often in people who would probably have developed diabetes mellitus anyway (insulin resistant, overweight, or obese) over time.

In a subsequent analysis [29], we employed administrative data sets to explore the impact of antihypertensive medications on glucose metabolism in the ALLHAT participants during 4–5 years of observation after completion of the trial. During the period of posttrial observation, the ALLHAT participants were no longer required to continue their assigned first-step study medication. We conducted this analysis because it could be argued that the mean follow-up period of 4.9 years during the trial might be insufficient to detect the detrimental effects of elevated glucose levels on CVD outcomes. An increase in blood glucose might lead to an increase in CVD risk only over a longer period of time. Posttrial monitoring of participants in the UK Prospective Diabetes Study (UKPDS) [30] suggested that a sustained period of glycemic control in patients with newly diagnosed diabetes mellitus reduced cardiovascular morbidity and mortality, but two decades or more of follow-up were required before the effects achieved statistical significance. The converse could be true for recognition of new-onset diabetes as an adverse effect of antihypertensive therapy.

In our analysis of health experience during extended follow-up of the ALLHAT participants, those with diabetes mellitus at baseline experienced higher rates of CVD as compared to their counterparts without diabetes mellitus. Those with incident diabetes generally had outcome rates that were intermediate between those with and without baseline diabetes. A more provocative finding was the comparison between those who did and those who did not develop diabetes during the trial, based on treatment assignment. The HRs in the chlorthalidone cohort with versus without incident diabetes for CVD mortality (HR, 1.04 [95 % CI, 0.74–1.47]), all-cause mortality (HR, 1.04 [95 % CI, 0.82–1.30]), and non-CVD mortality (HR, 1.05 [95 % CI, 0.77–1.42]) were consistently lower than the comparable HRs in the corresponding amlodipine and lisinopril cohorts (HRs, 1.22–1.53). For example, those who developed diabetes in the chlorthalidone cohort had a statistically insignificant increase in the risk for total CHD events when compared with those who remained nondiabetic (HR, 1.18 [95 % CI, 0.77–1.81]), whereas the opposite was true for participants with versus without incident diabetes who had originally been assigned to lisinopril (HR, 2.57 [95 % CI, 1.45–4.54]). Similarly, the HRs (CIs) for all-cause mortality and stroke were not significantly different in the chlorthalidone cohort based on incident diabetes status: 1.04 (0.82–1.30) and 0.91 (0.49–1.67), respectively. Thus, the results were similar to and confirmed the results of the first-phase (in-trial) period of ALLHAT.

In summary, the treatment experience in ALLHAT and other studies suggests that low-dose thiazide and thiazide-like diuretics are associated with small increases in FG levels as compared to the ACEI lisinopril and the CCB amlodipine. These differences diminish over time. The magnitude of the FG difference does not appear to result in a clinically significant increase in CVD risk.

44.3 Renin-Angiotensin System Blockade: ACEIs and ARBs

Upregulated bradykinin and nitric oxide, both of which promote increased skeletal muscle and pancreatic blood flow, are suggested to be the mediators of the improved glycemia noted during ACEI and ARB therapy [31]. Use of agents from these drug classes is also reported to improve angiotensin-II-mediated oxidative stress in the beta cell [32]. On account of their favorable glucose effect, ACEIs and ARBs are considered the “preferred” antihypertensive medications in people at high CVD risk (Chap. 36).

In the preceding section, we showed that lisinopril was associated with a slightly lower FG level as compared to the thiazide-like diuretic chlorthalidone with little or no clinical impact. The next question we address is whether RAS blockade prevents new-onset glucose disorders or ameliorates prevalent glucose disorders better than placebos.

In the Heart Outcomes Prevention Evaluation (HOPE) trial [33], the risk of self-reported incident diabetes was less in those assigned to the ACEI ramipril compared to placebo (3.6 % vs. 5.4 %; relative ratio [RR] 0.66 [95 % CI 0.51–0.85]; $P < 0.001$).

In the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial [34], the risk of incident diabetes was less in those assigned to the ARB valsartan compared to placebo (33.1 % vs. 36.8 %; RR 0.86 [0.80–0.92]; $P<0.001$). In contrast, treatment with ramipril did not reduce incident diabetes in people with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (17.1 % vs. 18.5 %; RR 0.91 [0.80–1.03]; $P=0.15$) in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial [35]. This study was specifically designed to investigate the effects of RAS blockade on diabetes prevention. The Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial [36] also found no evidence that the addition of telmisartan to usual care prevented incident diabetes or led to regression of IFG or IGT in persons at high risk for cardiovascular disease but free from diabetes. During a 56-month median period of treatment, 21.8 % of the participants treated with telmisartan compared to 22.4 % of their counterparts on placebo developed diabetes (RR 0.95 [95 % CI 0.83–1.10]; $P=0.51$). Participants with IFG and/or IGT at baseline were equally likely to regress to normoglycemia (26.9 % vs. 24.5 %) or to progress to incident diabetes (20.1 % vs. 21.1 %; $P=0.59$) during telmisartan or placebo therapy.

Variation in patient age and prior history of CVD may have played important roles in explaining study outcome differences. The NAVIGATOR trial (which used an ARB) enrolled individuals who were younger than those in TRANSCEND (which also used an ARB) and had a much lower prevalence of CVD (24 % vs. 80 %). Increasing age and prevalent CVD are associated with increased insulin resistance [37, 38].

Many of the ACEI studies were post hoc analyses in which incident diabetes was not a prespecified outcome. The results relied on physician-reported or self-reported incident diabetes rather than measures of FG or 2-h post-challenge levels of blood sugar. This makes it likely that many of the study participants with seemingly normal glucose metabolism would have been diagnosed with new-onset diabetes had they been thoroughly investigated.

In summary, there is no strong evidence that RAS blockade has an important antidiabetic effect when added to other cardiovascular agents for the treatment or prevention of atherosclerotic heart disease (ASHD) in people at high risk, most of whom have HTN.

44.4 First-Generation Beta-Blockers

First-generation β-blockers, such as propranolol and metoprolol, have been associated with worsening of glycemia and an increased risk of diabetes mellitus. The possible mechanisms include inhibition of pancreatic insulin secretion through nonselective blockade of β2-adrenergic receptors, inhibition of peripheral glucose uptake, and resultant unopposed α2-adrenergic receptor-mediated stimulation of hepatic glycogenolysis [39] (Fig. 44.1). Newer-generation beta-blockers, such as

carvedilol and nebivolol, have fewer metabolic effects than first-generation beta-blockers and are considered metabolically favorable [40].

Despite their glycemic effects, first-generation beta-blockers such as propranolol, metoprolol, and atenolol are still widely used. They are effective for HTN management and for preventing ischemic cardiovascular disease and sudden death. In the UK Prospective Diabetes Study [41], atenolol-based therapy was as effective in cardiovascular protection as was ACE-based therapy. In the Beta-Blocker Heart Attack Trial [17], a first-generation beta-blocker (propranolol) was effective for preventing recurrence of ischemia compared to a placebo in people with diabetes mellitus. In other studies, diabetic people prescribed first-generation β-blockers had significantly lower 1-year mortality rates than those not receiving these agents, regardless of type and severity of diabetes mellitus [18, 19].

In the Atherosclerosis Risk in Communities (ARIC) study [42], an observational cohort, there was an increase in the risk of diabetes associated with the use of beta-blockers (RR, 1.28; 95 % CI, 1.04–1.57). Similar findings have been noted in other observational studies [43, 44], In contrast, a retrospective, observational cohort study [45] of previously untreated patients, aged ≥66 years, identified as new users of an antihypertensive drug class, found that neither ACE inhibitor use (HR 0.96 [95 % CI 0.84–1.1]) nor beta-blocker use (0.86 [0.74–1.0]) was associated with a statistically significant difference in type 2 diabetes mellitus incidence when compared with the CCB control group ($n=76,176$). In the secondary analysis ($n=100,653$), compared with CCB users, T2DM incidence was not significantly different between users of ACE inhibitors (0.97 [0.83–1.1]), beta-blockers (0.84 [0.7–1.0]), or thiazide diuretics (1.0 [0.89–1.2]).

Clinical trials of beta-blockers have yielded mixed results regarding hyperglycemia. The Veterans Administration Cooperative Study Group on Antihypertensive Agents [46] identified a hyperglycemic effect following 12 months of propranolol that persisted for 1 month after the discontinuation of drug therapy. The Medical Research Council Working Party on Mild to Moderate Hypertension [47] found that the rate of withdrawal from the trial because of hyperglycemia was higher in the propranolol group than in the placebo group, but this difference was not statistically significant. In the Oslo study [48], fasting serum glucose levels were significantly higher in the group treated with propranolol in combination with a thiazide diuretic compared to the placebo group, whereas there was no difference in serum glucose concentrations between the thiazide diuretic and placebo groups. On the other hand, the Systolic Hypertension in the Elderly Program [49] did not show an increased risk of hyperglycemia or diabetes mellitus in subjects taking beta-blockers with thiazide diuretics. Differences between these study outcomes may stem from differences in the dosage of medication, the type of beta-blocker used (e.g., cardioselective vs. nonselective), and the duration of treatment. In the Women's Health Initiative Observational Study [50] (93,676 women, aged 50–79 years at baseline), among women with hypertension but no history of CVD, a 2-drug-class regimen of CCBs plus diuretics was associated with a higher risk of CVD mortality compared to beta-blockers plus diuretics. Risks were similar for ACEIs plus diuretics and beta-blockers plus diuretics with or without diabetes mellitus.

44.5 Parallels with Statin Therapy

Much like thiazide medications, statin medications – among the most commonly used medications in the world – have been linked to an increased risk of diabetes mellitus. A meta-analysis of six trials [51] that included 57,593 participants found a 13 % increase in the relative risk of new-onset diabetes. Another meta-analysis of 13 randomized statin trials [52] with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes mellitus. The mechanism by which statins impair glucose metabolism is uncertain, but it is believed that secretion of insulin by the beta cells of the islets of the pancreas is impaired [53], the same mechanism implicated in incident diabetes mellitus associated with the use of thiazide diuretics. These findings, however, have not dissuaded medical societies and government agencies from recommending statins, their beneficial effects outweighing concerns about possible risk (Chap. 28) [54].

Contrary to this quick and decisive stand regarding the dysglycemic consequences of statins, the uncertainty regarding the dysglycemic adverse effects of low-dose thiazide or thiazide-like diuretics and of older beta-blocker medications as treatments for HTN has persisted for many years. Importantly, this uncertainty continues despite their proven clinical efficacy. To judge the efficacy of a medication, the positive and negative effects need to be weighed against one another. It is our opinion that the CVD-protective effects derived from thiazide diuretics and older beta-blockers outweigh their negative metabolic effects. Mostly the same conclusions have been arrived at regarding the diabetogenic effects of statins [52]. The salutary effects of ACEIs and ARBs on glucose metabolism are small and, in our opinion, not sufficiently powerful to be used as a principal criterion for the choice of antihypertensive drug therapy in individuals with hyperglycemia or predisposition to hyperglycemia. Efficacy in lowering blood pressure and preventing CVD should play a more important role in determining the choice of medication.

44.6 Concluding Remarks

We have reviewed the diabetogenic effects of thiazide and thiazide-like diuretics and of first-generation beta-blockers and found their effects not to be harmful. We note that the current widespread use of combination therapy for the management of HTN makes the concern regarding the diabetogenic effects of thiazides and beta-blockers somewhat moot. ACEIs are now frequently combined with thiazide diuretics. Beta-blockers are often added to multidrug regimens when blood pressure control has not been achieved. In one of the few studies to explore the effects of combinations of antihypertensive medications on glucose disorders, an examination of a large cohort [55] ($n = 134{,}967$) found that the combinations of ACEIs with beta-blockers or with thiazides resulted in a lower risk of biochemical diabetes than thiazide or beta-blocker monotherapy. One medication appeared to have canceled the glycemic effects of the other.

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Chapter 45
Pathophysiology and Treatment of Pulmonary Arterial Hypertension

Nina Rol, Christophe Guignabert, and Harm Jan Bogaard

Abstract Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure above 25 mmHg at rest. Pulmonary arterial hypertension (PAH; precapillary PH) is an incurable progressive form of PH characterised by sustained remodelling of the lung vasculature leading to increased vascular resistance. The right ventricle (RV) adapts to the increased afterload with thickening of the RV wall and increased contractility. RV dilatation and an ultimate functional decline of the RV result in right heart failure and the death of most patients. Median survival is only 3 years, despite therapeutic advances. PAH-specific therapies induce relaxation of small pulmonary arteries and include calcium channel blockers that are used in a small group of patients responding to acute vasodilators. Most PAH-specific medication modulates abnormalities in three main pathophysiologic pathways for PAH: the nitric oxide, prostacyclin and endothelin pathways. Lung transplantation is the last therapeutic option when medication has failed. In this chapter, we discuss the pathogenesis of PAH and the development of associated right heart failure. Subsequently, we provide an overview of currently approved medications and treatment options under investigation.

Keywords Pulmonary arterial hypertension • Right heart failure • Inflammation • Endothelial cells • Nitric oxide • Prostacyclin • Endothelin

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Abbreviations

5-HT	5-hydroxytryptamine; serotonin
6MWD	6 minute walk distance
ACE	Angiotensin-converting enzyme
ACVRL1	Activin A receptor type II-like kinase 1
Ang II	Angiotensin II
BCL2	B-cell lymphoma 2
BCL-xL	B-cell lymphoma-extra large
BMPR2	Bone morphogenetic protein receptor type 2
CCB	Calcium channel blockers
cGMP	Cyclic guanosine monophosphate
CTEPH	Chronic thromboembolic pulmonary hypertension
DC	Dendritic cell
EC	Endothelial cell
ECM	Extracellular matrix
EGF	Epidermal growth factor
ENG	Endoglin
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
FC	Functional class
FCS	Fetal calf serum
FDA	Food and Drug Administration
FGF-2	Fibroblast growth factor-2 (basic)
HIF	Hypoxia-inducible factors
HIV	Human immunodeficiency virus
hPAH	Heritable PAH
i.v.	Intravenously
ICAM-1	Intercellular adhesion molecule-1
IL	Interleukin
iPAH	Idiopathic PAH
KCNK3	Potassium channel subfamily K, member 3
MAPK	Mitogen-activated protein kinase
MIF	Macrophage migration inhibitory factor
mmHg	Millimetre of mercury
mPAP	Mean pulmonary artery pressure
NF-κB	Nuclear factor-kappa B
NK cell	Natural killer cell
NO	Nitric oxide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PDE-5	Phosphodiesterase type 5
PDGF	Platelet-derived growth factor
PGI2	Prostacyclin
PH	Pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn

PVR	Pulmonary vascular resistance
RAAS	Renin–angiotensin–aldosterone system
RHC	Right heart catheterisation
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
RV	Right ventricle
SMC	Smooth muscle cell
TGF- β	Transforming growth factor-β
TKI	Tyrosine kinase inhibitors
Treg	Regulatory T cell
VCAM-1	Vascular adhesion molecule-1
VEGF	Vascular endothelial growth factor

45.1 Introduction

Pulmonary hypertension (PH) is not a single disease, but a haemodynamic feature found in a rather large group of diseases. PH is defined as a mean pulmonary artery pressure (mPAP) above 25 mmHg at rest. Based on current aetiological perceptions of the condition, PH is classified into five clinical groups (Table 45.1). Increasing resistance in the pulmonary vasculature (PVR) leads to a high right ventricular (RV)

Table 45.1 Clinical classification of pulmonary hypertension based on 5th WSPH Nice 2013

1 Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, ENG, Smad9, Cav1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 Pulmonary hypertension of the newborn
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1″ Persistent pulmonary hypertension of the newborn (PPHN)
2 Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

(continued)

Table 45.1 (continued)

3 Pulmonary hypertension due to lung disease and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4 Chronic thromboembolic pulmonary hypertension (CTEPH)
5 PH with unclear multifactorial mechanisms
5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosis mediastinitis, chronic renal failure, segmental PH

Adapted from Simonneau et al. [1]
ALK1 activin receptor-like kinase 1 gene, *APAH* associated pulmonary arterial hypertension, *BMPR2* bone morphogenetic protein receptor, type 2, *Cav1* caveolin-1, *ENG* endoglin, *HIV* human immunodeficiency virus, *KCNK3* potassium channel, subfamily K, member 3, *PAH* pulmonary arterial hypertension

afterload, and the RV either adapts to the high pressures with hypertrophy or dilates and fails. RV failure is the cause of death in the vast majority of patients [2].

Patients present with nonspecific symptoms, like breathlessness, fatigue, weakness, angina and syncope [3]. The New York Heart Association (NYHA) Functional Class (Table 45.2), based on clinical symptoms, is a strong predictor of survival [4, 5]. At physical examination, a left parasternal heave can be felt and auscultation may demonstrate an accentuated pulmonary component of the second heart sound, a pansystolic murmur of tricuspid regurgitation, a diastolic murmur of pulmonary insufficiency or a RV third sound. Different imaging techniques, including electrocardiography, chest radiography, echocardiography and cardiac magnetic resonance imaging, may raise the suspicion of the existence of PH, and these tests are also useful to identify possible underlying causes and to monitor treatment responses. Right heart catheterisation (RHC) is always needed to confirm the diagnosis, to evaluate the severity of the disease and to determine the effectiveness of drug therapy. The acute vasoreactivity test aids in determining drug therapy [2].

The current PH clinical classification gathers groups of PH that share similar haemodynamic criteria and types of pulmonary vascular lesions to optimise therapeutic approaches, predict patient outcomes and facilitate research strategies (Table 45.1) [1]. Group 1 PH corresponds to pulmonary arterial hypertension (PAH). PAH is characterised by precapillary PH (mPAP $\geq$25 mmHg, with a normal pulmonary capillary wedge pressure $\leq$15 mmHg) due to major pulmonary arterial remodelling. The lowest reported prevalence and incidence of PAH are 15 cases/million adult population and 2.4 cases/million adult population/year, respectively.

Table 45.2 Pulmonary hypertension New York Heart Association (NYHA) Functional Classification (FC) [75]

I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope
II	PH patients with slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope
III	PH patients with marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope
IV	PH patients with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

The prevalence of PAH in Europe is estimated between 15 and 50 subjects/million population [6]. In 70 % of the heritable PAH cases, a germ line mutation of the bone morphogenetic protein receptor 2 (*BMPR2*) is found [7, 8]. The same mutation is found in 11–40 % of sporadic PAH patients, indicating the genetic predisposing factor for PAH [9].

In the year 2000, exonic mutations in the gene encoding for *bone morphogenetic protein receptor type 2* (*BMPR2*) were found in 54 % of PAH patients, or more specifically 58–74 % of patients with heritable PAH (hPAH) and in 3.5–40 % of patients with sporadic PAH [8, 10–14]. *BMPR2* is a member of the receptor family of transforming growth factor-β (TGF-β). The penetrance of mutations of *BMPR2* is below 20 %, indicating that the *BMPR2* gene is not the only gene responsible for PAH and that the pathophysiology of this disease is multifactorial. Therefore, many laboratories have investigated possible mutations in other members involved in the signalling cascade of TGF-β, and two genes were found mutated: *ACVRL1* (*activin A receptor type II-like kinase 1*) and *ENG* (*endoglin*). However, these mutations account for only a small proportion of cases of hPAH. Recently, mutations have also been described in *Smad 1*, *Smad 4*, *Smad 8* and *Smad 9* [15, 16]. All these mutations disrupt the BMP/*Smad* signalling pathway and promote endothelial and smooth muscle apoptosis and proliferation, resulting in loss of the endothelial barrier function and pulmonary vascular remodelling. These mutations could also increase the susceptibility to inflammatory stimuli [17]. Recently, Ma et al. [18] demonstrated the involvement of the potassium channel subfamily K member 3 (*KCNK3*) *missense* mutations in the pathophysiology of PAH. Indeed, mutations in this gene were identified in six unrelated patients with PAH (three patients displaying heritable form of PAH out of 93 patients [3.2 %] and three patients with sporadic PAH out of 230 patients [1.3 %]) [18]. To date, all identified *KCNK3* mutations are missense mutations and are responsible for a loss of function of the two-pore-domain potassium channel TASK-1 and its signalling pathway in PAH. The reduction in potassium channel activity may enhance calcium channel-mediated vasoconstriction and vascular remodelling [19, 20].

Pulmonary vascular remodelling, occurring mostly in the small- to midsized pulmonary arterioles (≤500 μm), is a hallmark of most forms of PH. This process is ascribed to the increased proliferation, migration and survival of pulmonary vascular

cells within the pulmonary artery wall, i.e. pulmonary vascular smooth muscle cells (SMCs), endothelial cells (ECs), myofibroblasts and pericytes. PAH is associated with excessive production of vasoconstrictive mediators such as endothelin (ET)-1 concurrent with a reduced bioavailability of vasodilator molecules nitric oxide (NO) and prostacyclin (PGI2). Pulmonary vascular remodelling is also under the control of various key growth factors such as platelet-derived growth factor (PDGF), serotonin (5-hydroxytryptamine; 5-HT) and fibroblast growth factor (FGF)-2. Abnormalities in the expression and function of calcium and potassium channels are also involved in pulmonary vasoconstriction and remodelling of the pulmonary vasculature. Recent findings highlight the critical role of the close and complex relationship between the pulmonary vascular endothelium and inflammation/autoimmunity in PAH. Indeed, circulating levels of certain cytokines and chemokines are abnormally elevated, and some have been reported to correlate with a worse clinical outcome in patients with PAH [21–24]. Altered regulatory T (Treg) cell function has been demonstrated in patients with PAH, a phenomenon that has been demonstrated to be partly leptin-dependent [25, 26]. Similarly, natural killer (NK) cells have recently been implicated [27]. An accumulation of immature dendritic cells (DCs) has been demonstrated, suggesting that they may contribute to PAH immunopathology [28]. Furthermore, ectopic lymphoid follicles that develop in contact with remodelled pulmonary arteries could be the site of a local autoimmune reaction, leading to the production of autoantibodies directed notably against pulmonary vascular cells. Circulating autoantibodies are commonly detected in idiopathic PAH (iPAH) patients without evidence of an associated autoimmune condition [29–32]. However, despite the many arguments supporting a role of inflammation in the pathogenesis of PAH, only some patients respond to anti-inflammatory and/or immunosuppressive therapy. It is therefore necessary to understand the complexity of the immune mechanisms of PAH to improve the transfer of knowledge to the clinic.

Although PAH is still a disease without a cure, there are approved drug therapies that at least temporarily stabilise or improve the symptoms in the majority of patients. In this chapter, we will first outline the pathophysiological mechanisms that underlie PAH and PAH-associated RV failure. Subsequently, we will discuss the major therapeutic targets which are currently available or under development (Chap. 59).

45.2 Pathophysiology of PAH

The extensive structural and functional remodelling of the vasculature in lungs of patients with PAH takes place sequentially and includes medial hypertrophy, muscularisation of small arterioles, intimal thickening and the formation of plexiform lesions. These processes involve changes in all three layers (intima, media and adventitia) of the vessel wall and are the consequence of cellular hypertrophy, hyperplasia, inflammation, apoptosis, migration and accumulation of extracellular matrix (ECM).

45.2.1 Pulmonary Endothelial Cell Dysfunction

Pulmonary endothelial dysfunction is a critical element in the development and progression of PH, irrespective of disease origin. In PAH, the dysfunctional endothelium shows several abnormalities: (a) a transition from a quiescent state (having no adhesiveness) to an activated state, expressing specific markers and proteins, such as E-selectin and key adhesion molecules [e.g. intercellular adhesion molecule (ICAM-1) and vascular adhesion molecule (VCAM-1)] (submitted data); (b) a reduced ability to produce vasodilatory mediators such as NO and PGI2; (c) an excessive production and release of vasoconstrictive mediators such as 5-HT, ET-1 and Ang II [33]; (d) an important qualitative and quantitative remodelling of components of the ECM; and (e) an increased production of various factors affecting the control of proliferation, differentiation and migration of pulmonary vascular cells such as FGF-2 (basic), interleukin (IL)-6 and leptin [26, 34–36]. Furthermore, the pulmonary ECs derived from iPAH patients exhibit an aberrant cell phenotype which is characterised by an excessive proliferation and resistance to apoptosis induction [35, 37]. Tu et al. [35] have demonstrated that an excessive FGF-2 autocrine loop is one of the mechanisms involved in this aberrant endothelial phenotype, explaining the constitutive activation of the mitogen-activated protein kinase (MAPK) signalling pathway and the overexpression of two key anti-apoptotic factors B-cell lymphoma 2 (BCL2) and B-cell lymphoma-extra large (BCL-xL).

In PAH pulmonary ECs, many other intrinsic abnormalities were also described including $p130^{cas}$ overexpression, a key amplifier of receptor tyrosine kinase (RTK) downstream signals, altered energy metabolism and a constitutive activation of hypoxia-inducible factors (HIF)-1α [38, 39]. In addition, the abnormal cellular crosstalk between ECs and the other pulmonary vascular cells in the pulmonary vascular wall in PAH represent a key feature of PAH pathogenesis. We have shown that dysfunctional pulmonary ECs from patients with iPAH, through an aberrant release of FGF-2 and IL-6, contribute to increased pericyte coverage of distal pulmonary arteries in PAH, an abnormality that is a potential source of smooth muscle-like cells [36]. Indeed, activated TGF-β in pulmonary arterial walls in PAH can promote human pulmonary pericyte differentiation into contractile smooth muscle-like cells. Multiple lines of evidence therefore suggest that neutralisation of FGF-2, IL-6 and TGF-β1 may be beneficial against the progression of PAH. A better understanding of the underlying mechanisms is critical to slow down and reverse this obliterative pulmonary vascular remodelling in PAH. Experimental work strongly supports the fact that the obstructive vascular remodelling may be limited by strategies which, at a time, promote vasodilation and inhibit cell proliferation/survival and inflammation. Because many of these tools have been developed and are available through cancer treatment, there is a growing interest for the transfer of these tools to PAH. However, several studies are needed not only to identify the best strategies/molecules for use in PAH but also to better understand the risk/benefit of these anti-proliferative treatments, especially vis-à-vis the maintenance of cardiac function.

45.2.2 Pulmonary Smooth Muscle Hyperplasia

Mechanisms underlying the excessive pulmonary vascular SMC proliferation in PAH are partially understood and result from two complementary mechanisms: inherent characteristics and dysregulation of molecular events that govern SMC growth, including signals originating from pulmonary ECs. Cultured pulmonary arterial SMCs from patients with iPAH grew faster than SMCs from controls at basal conditions or when stimulated by 5-HT, FGF-2, epidermal growth factor (EGF), PDGF or fetal calf serum (FCS). For example, 5-HT transporter (5-HTT) activity is associated with pulmonary artery smooth muscle cell proliferation, and the L-allelic variant of the 5-HTT gene promoter, which is associated with increased expression of 5-HTT, is present in homozygous form in 65 % of patients with iPAH compared with 27 % of controls [40].

These observations explain the fact that interest has been growing in the potential use of anti-proliferative approaches in PAH [41]. Excessive release of various growth factors that are encrypted in the ECM and/or modification of growth factor production, receptor expression and/or alterations in the intracellular mitogenic signals have also been reported to contribute to this excessive smooth muscle migration, proliferation and survival. Inhibition of various RTK signalling pathways by specific inhibitors, such as imatinib, gefitinib and dovitinib, have been shown to exert beneficial effects in animal models of PH [34, 39, 42, 43]. However, further efforts still need to be made in order to establish the long-term safety and efficacy of these anti-proliferative approaches in PAH and their potential additive benefit with other drugs. Recent investigations also suggest that a chronic shift in energy production from mitochondrial oxidative phosphorylation to glycolysis (the Warburg effect) of pulmonary vascular cells is present and may participate in the pathogenesis [44–46]. Mechanistic studies focusing on cell metabolism and its interface with the genetic basis of PAH and inflammation are needed for a better appreciation of its role in the promotion of SMC proliferation and survival and to the disease progression.

45.2.3 Perivascular Inflammatory Cell Accumulation

In the past two decades, understanding of inflammation associated to PAH has moved from a common histopathological curiosity to a key pathomechanism that could be detrimental both in terms of disease susceptibility and development of pulmonary vascular remodelling. Histopathologically, pulmonary vascular lesions occurring in patients with PAH as well as in animal models of PH are characterised by varying degrees of perivascular inflammatory infiltrates, comprising of T and B lymphocytes, macrophages, DCs and mast cells. Recently, correlations were found between the average perivascular inflammation score and the intima plus media and adventitia thickness or mPAP, supporting a role of perivascular inflammation in the processes of pulmonary vascular remodelling [47]. In addition, inflammation

precedes pulmonary vascular remodelling in animal models of PH, strongly supporting the notion that increased perivascular immune cell infiltration around lung vessels plays a key role in PAH development and progression [25]. As previously discussed, circulating levels of certain cytokines and chemokines are abnormally elevated and can directly control cell proliferation, migration and differentiation of pulmonary vascular cells.

There seems to be a particular role for IL-6 in the pathogenesis of PAH. Delivery of recombinant IL-6 protein in rodents is sufficient to cause pulmonary vascular remodelling and PH or to exaggerate the pulmonary hypertensive response to chronic hypoxia [48, 49]. Furthermore, IL-6-overexpressing mice spontaneously develop PH and pulmonary vascular remodelling, whereas IL-6 knockout mice are more resistant to the development of PH induced by chronic hypoxia [50, 51]. Recent data from our group demonstrated that the overabundance of macrophage migration inhibitory factor (MIF) plays a pivotal role in the pathogenesis of PAH. MIF is a critical upstream inflammatory mediator with pleiotropic actions partly explained by its binding to the extracellular domain of the endothelial CD74. In endothelial cells, activation of the CD74 can lead to activation of Src-family kinase and MAPK/ERK, PI3K/Akt and nuclear factor-kappa B (NF-κB) pathways and to apoptotic resistance by increasing the anti-apoptotic factors BCL2 and BCL-xL and by inhibiting p53 (submitted data). In addition, MIF can bind to C-X-C chemokine receptor type 2 (CXCR2) and type 4 (CXCR4), lead to the proliferation of pulmonary artery smooth muscle cells and contribute to hypoxic PH [52–54]. While this body of knowledge provides a preliminary understanding, it also highlights subtleties and complexities that require further investigation to determine whether anti-inflammatory strategies will be useful in PAH treatment in the future.

45.2.4 Impaired Pulmonary Angiogenesis

Multiple lines of evidence suggest that angiogenesis is clearly disturbed in experimental and human PAH with loss and progressive obliteration of precapillary arteries leading to a pattern of vascular rarefaction (“dead-tree” picture). However, high levels of different angiogenic factors including FGF-2 and VEGF are present in patients with iPAH, strongly supporting the notion that this phenomenon is probably due to signalling defects in the endothelium in PAH. Cool et al. demonstrated exuberant expression of the VEGF receptor KDR, coupled with a reduced expression of p27/kip1 (a cell cycle inhibitory protein) in the pulmonary ECs of plexiform lesions [55]. Since increased pericyte coverage in iPAH has been recently reported, another explanation might be related to abnormal pericyte recruitment or to intrinsic abnormalities in pulmonary pericytes in PAH [36]. A greater understanding of the role of pulmonary pericytes in vascular homeostasis and remodelling is needed.

45.2.5 In Situ Thrombosis

PAH pathological specimens often display thrombotic lesions in the absence of clinical or pathological evidence of pulmonary embolism, suggesting an in situ clotting phenomenon [56, 57]. In addition, PH is associated with a hypercoagulable phenotype that includes vascular upregulation of tissue factor and an increase in circulating levels of von Willebrand factor or plasma fibrinopeptide A [58–60].

45.3 Development of Right Heart Failure

Despite its meagre ability to respond to a rapid increase in pressure, the RV is usually able to adapt to a gradually increasing afterload by augmenting its contractility and wall thickness. The one metric which best describes RV adaptation in PAH is ventriculo-arterial coupling, which takes into account both contractility and afterload. When the increased afterload is matched by an adaptive increase in RV contractility and mass, the RV is said to be coupled to the pulmonary arterial circulation [61]. However, in the majority of patients with PAH, the severity and chronicity of the afterload increase ultimately overwhelm the increases in RV mass and contractility. The final course of PAH is therefore characterised by RV dilatation and failure, and eventually death (see Fig. 45.1). It has been speculated that, as in LV failure, neurohormonal activation may be central in the transition from RV adaptation to RV failure [63]. Indeed, sympathetic nervous system activity is increased in PAH patients, which finding has prognostic significance [64]. Chapters 5 and 6 explain more about the involvement of sympathetic and parasympathetic nervous systems in heart failure. Likewise, an increased renin–angiotensin–aldosterone system (RAAS) activity (described in Chap. 35) reflects PAH disease severity [65].

A typical feature of RV failure is the prolongation of the systolic contraction time in comparison to the left ventricular contraction time, leading to a leftward shift of the septum at the end of RV contraction (during which time the LV is already in its relaxing phase) and impaired LV filling [66]. In addition to a systolic functional impairment, RV failure is characterised by diastolic dysfunction, which probably comes about through a combination of intrinsic stiffness and fibrotic replacement of RV cardiomyocytes [67, 68]. The transition from RV adaptation to RV failure is further characterised by reduced myocardial perfusion, which may not only reflect reduced coronary perfusion due to, e.g. systemic hypotension, but also an impairment in angiogenesis relative to the degree of hypertrophy [69, 70]. Metabolic remodelling is another recently highlighted characteristic of RV failure and includes a decreased uptake of fatty acids and an increased generation of ATPs through glycolysis rather than through glucose oxidation [71, 72].

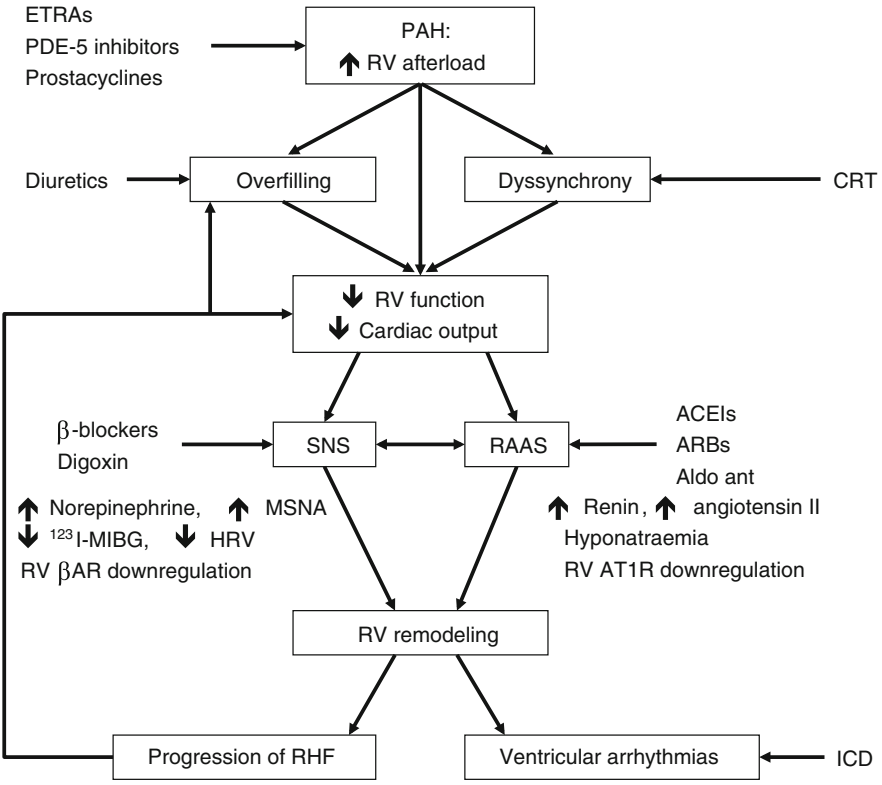

Fig. 45.1 Schematic overview of hypothetical pathophysiological mechanisms in PAH-related right heart failure, showing the multiple interactions between mechanical events (pressure overload, dilatation), electrophysiological changes (dyssynchrony, arrhythmias) and neurohormonal activation (Reproduced with permission from Ref. [62]). *RV* right ventricular, *ETRAs* endothelin receptor antagonists, *PDE-5* phosphodiesterase-5, *CRT* cardiac resynchronisation therapy, *SNS* sympathetic nervous system, *RAAS* renin–angiotensin–aldosterone system, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *MSNA* muscle sympathetic nervous activity, *HRV* heart rate variability, *βAR* cardiomyocyte β_1-adrenergic receptor, *AT1R* cardiomyocyte angiotensin type 1 receptor, *Aldo ant* aldosterone antagonist, *RHF* right heart failure, *ICD* implantable cardioverter defibrillator

45.4 Specific Drug Therapy

To facilitate a treatment plan, it is important to rule out all the possible underlying causes that could induce and cause progression of PAH. In addition to treating the underlying cause, when such a treatment is not available in the cases of idiopathic and heritable PAH, there are PAH-specific approved drugs which aim to dilate pulmonary vessels. In vitro and animal studies suggest that these drugs also have inhibitory effects on vascular remodelling [73]. Long-term treatment in patients has not led to a demonstrable regression of vascular remodelling [47]. Novel therapies in

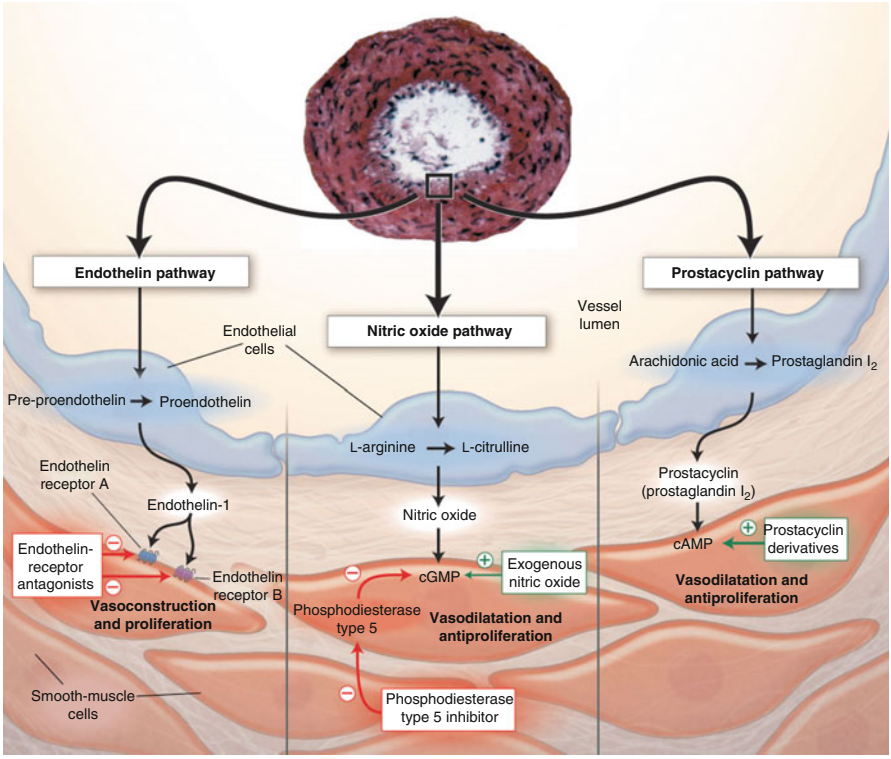

Fig. 45.2 The pathways involved in contraction and proliferation of pulmonary arterial smooth muscle cells and the endothelium. The four biggest groups of drugs available for PAH that target these pathways are endothelin receptor antagonists, nitric oxide, phosphodiesterase type 5 inhibitor and prostacyclin derivatives (Reproduced with permission from Ref. [75])

development (discussed later) show promising results with regard to inhibition of cell proliferation and inducing apoptosis, thereby limiting the progressive changes in morphometry [74].

45.4.1 Drugs Targeting the Pulmonary Vasculature

The currently available drugs for PAH treatment mainly target vasoconstriction via three biochemical pathways: ET-1, NO and PGI2 (Fig. 45.2) (see also Chap. 59) [76]. Experimentally, these therapies have some anti-proliferative effects [77, 78]. Table 45.3 shows FDA-approved therapeutics intervening in these three major pathways.

Table 45.3 FDA-approved drug therapies in PAH tested in randomised clinical trials

Drug	Study + reference	Improvement of					Serious adverse effects
		6MWD/exercise capacity	Haemodynamics	FC	Survival	Time to clinical worsening	
CCB[a]							
Amlodipine, diltiazem, nifedipine	Rich [77], Sitbon [79]	+	+	+	+		Systemic hypotension, bradycardia, oedema, headache, nausea
NO/cGMP							
Riociguat	PATENT [80]	+	+	+		+	Hypotension, syncope
Sildenafil	SUPER-1 [81], Sastry [82], Singh [83], PACES [84], Iversen [85]	+	+	+			Headache, flushing, epistaxis
Tadalafil	PHIRST [86, 87]	+	+			+	Headache, flushing, epistaxis
PGI2							
Beraprost	ALPHABET [88], Barst [89]	+[b]					Headache, flushing, jaw pain, diarrhoea, approved in Japan/South Korea
Epoprostenol	Rubin [90], Barst [91]	+	+		+		Local site infection, catheter obstruction and sepsis (pump related)
Iloprost (inhal)	AIR [92], STEP[c] [93], COMBI[c] [94]	+	+	+		+	Flushing, jaw pain
Treprostinil	Simonneau (s.c.) [95] TRIUMPH (inh.) [96], Freedom C1, C2 and M (oral) [97–99]	+[d]	+				Infusion site pain

(continued)

Table 45.3 (continued)

Drug	Study + reference	Improvement of					Serious adverse effects
		6MWD/exercise capacity	Haemodynamics	FC	Survival	Time to clinical worsening	
ET-1							
Ambrisentan	ARIES-1, ARIES-2 [100]	+		+		+	Peripheral oedema
Bosentan	Study-351 [101, 102], BREATHE-1 [103], BREATHE-2 [104], EARLY [105]	+	+	+		+	
Macitentan	SERAPHIN [106]	+			+		
Combination							
Initial	Galie [107]	+	+				
Sequential	BREATHE-2 [104], Kemp [108], AMBITION (NCT01178073)	+	+				

Modified after Galiè et al. [109] with regard to improvement in 6MWD/exercise capacity, haemodynamics, functional class, survival, time to clinical worsening and the most prominent adverse effects observed

[a]If prescribed after positive acute vasodilator test

[b]Temporal effect of 3–6 months

[c]Conflicting results with AIR study

[d]Not significantly different in Freedom C1 and C2

45.4.1.1 Calcium Channel Blockers

Intracellular calcium levels are elevated in pulmonary arterial SMCs of PAH patients, leading to contraction of the muscular layer in the vessels. Less than 10 % of the patients with iPAH respond to an acute vasodilator, like inhaled NO or iloprost. This small group harbours patients who obtain improvement of symptoms after treatment with calcium channel blockers such as long-acting nifedipine, diltiazem or amlodipine (Chap. 37). The patients who respond to long-term calcium channel blocker therapy exhibit a more pronounced reduction in mPAP, reaching an absolute mPAP of 33 ± 8 mmHg with acute vasodilator testing. As a result, the consensus definition of a response is now defined as a fall in mPAP of $\geq$10 mmHg, to an mPAP $\leq$40 mmHg, with an unchanged or increased cardiac output. Patients with iPAH who meet these criteria may be treated with calcium channel blockers [79, 110]. Owing to potential negative inotropic effects, verapamil should be avoided [111]. If the patient does not respond well to the calcium channel blockers (CCB), medication directing the NO, PGI2 or ET-1 pathway should be added or replace the current treatment [77].

45.4.1.2 Nitric Oxide Pathway

NO produced in ECs is translocated to the SMCs to bind to soluble guanylyl cyclase (sGC). This process leads to activation of cyclic guanosine monophosphate (cGMP), which has a strong vasodilatory and a mild anti-proliferative effect on the pulmonary vessels. In PAH, NO production is decreased, with a consequential decrease in cGMP levels resulting in vasoconstriction. Phosphodiesterase type 5 (PDE-5) inhibitors antagonise cGMP degradation by inhibiting PDE-5 and thereby increase cGMP availability. Tadalafil and sildenafil, also prescribed for erectile dysfunction, are effective PDE-5 inhibitors in PAH. The latter, a potent and highly specific PDE-5 inhibitor, was shown to improve exercise capacity, FC and haemodynamics in PAH in the Sildenafil Use in Pulmonary Hypertension (SUPER) trial [81]. Because the effectiveness of a PDE-5 inhibitor is determined by the amount of NO available, the new drugs developed are higher in the NO–sGC–cGMP chain. Riociguat is a new drug that increases sGC activity and thereby accelerates cGMP production. This balances the NO pathway, with vasodilatory and anti-proliferative effects as a consequence.

45.4.1.3 Prostacyclin Pathway

PGI2, produced by ECs, has antithrombotic, anti-proliferative, anti-mitogenic, immunomodulatory and vasodilating effects (Chap. 31). PGI2 and its downstream targets are downregulated in PAH patients. Drugs directed on this shortage are prostacyclin analogues and prostacyclin receptor agonists, the latter group including selexipag, which is currently tested for effectiveness in PAH. The first specific

drug for PAH was the prostanoid epoprostenol, which has to be administered (in a formulation, Flolan) continuously via a central venous catheter because of its short half-life (<5 min). Recently, a more stable form of epoprostenol, Veletri, is available and is more patient compliant [112]. Epoprostenol is the only treatment that has shown a reduction in mortality in a randomised controlled trial [91, 109]. Treprostinil, another prostacyclin analogue, is more stable and has a longer half-life (4 h) than epoprostenol and can be administered subcutaneously, intravenously (i.v.), orally and by inhalation. The FDA approved subcutaneous treprostinil in 2002 for use in FC II, III, and IV PAH. The possibilities of subcutaneous implantation of an i.v. pump system are now being researched to avoid limitations of an external pump system, as risk of infections, catheter-related embolism and thrombosis [113]. Iloprost, a chemically stable prostacyclin analogue, can also be administered by inhalation. Beraprost, an orally active prostacyclin analogue with a short half-life of 35–40 min only, is currently approved for PAH in Japan and South Korea.

45.4.1.4 Endothelin Pathway

ET-1 binds to the ET-A receptors located on vascular SMCs and exerts vasoconstrictive and proliferative effects (Chap. 31). Binding of ET-1 to ET-B receptors on ECs and SMCs antagonises vasodilation by NO and prostacyclin. Although assumed that ET-A selective inhibitors (bosentan) would be more effective in PAH treatment, there is no evidence that those treatments are more effective than nonselective (ambrisentan, macitentan) endothelin receptor antagonist (ERAs). It is important to monitor liver functions monthly when ERA treatment is prescribed, because this group of drugs can induce liver toxicity. Haemoglobin and haematocrit levels should also be monitored on a quarterly basis. The potential side effect of lower extremity oedema, particularly within the first several weeks after initiation of therapy, may need to be treated with diuretics. Sitaxentan, a nonselective ERA, has been withdrawn from the market due to two cases of fatal liver injury [2, 109].

45.4.1.5 Combination Therapy (Initial, Sequential)

When the results of monotherapy are not satisfying, combination therapy is usually started (sequential combination therapy). In patients who have been receiving monotherapy, combination therapy appears to be moderately more effective than continuation of monotherapy with regard to 6 minute walk distance (6MWD), with a magnitude of effect that is approximately equal to the estimated minimal important difference for PAH of 33 m. Several clinical trials of combination therapy, targeting two or more pathways, have also shown clinical benefit when used as upfront combination therapy [109]. The results from the recent AMBITION study still have to be published, but this randomised, double-blind, multicentre

study with initial combination therapy with ambrisentan and tadalafil in NYHA classes II and III PAH patients showed a delayed time to hospitalisation by 63 % (NCT01178073).

45.4.1.6 Transplantation

All of the drugs mentioned above are able to lower pulmonary vascular resistance to some extent, but long-term outcomes of PAH patients remain uncertain. Single-lung, double-lung and heart–lung transplantations can improve the patient's condition. Lung transplantation is generally reserved for those failing the best available medical therapy. It is shown that RV function can recover fast after lung transplantation, even in severe conditions preoperatively [114, 115]. Median survival of iPAH patients is 5.2 years after lung transplantation [116]. Combined heart and lung transplantation is generally reserved for those with complex congenital heart disease.

45.4.1.7 Additional Advice and Treatment Options

The PAH treatment guideline of the European Society of Cardiology gives general advice with regard to daily living and exercise. Physical activity should be encouraged with exercise rehabilitation, as long as it does not lead to severe breathlessness. Exercise training improves endothelial dysfunction, exercise capacity and quality of life [117]. Pregnancy is associated with a mortality rate of 30–60 % and should therefore be avoided [118, 119]. Psychosocial support is important since many PAH patients suffer from anxiety and depression [120]. Infection prevention could be considered, because PAH patients are prone to pneumonia and is the cause of death in 7 % of the patients [2].

Besides PAH-specific drugs, oral anticoagulants can be part of the PAH treatment plan. Patients suffering from right heart failure with fluid retention benefit from diuretic treatment. Oxygen supplementation should be considered for PAH in NYHA FC III and IV during long flights [2]. Although there is no proof for long-term effects, oxygen administration can lower the PVR in PAH patients, which may be beneficial. Ambulatory additional oxygen could improve symptoms and help with desaturation during exercise.

Atrial Septostomy: Atrial septostomy involves the creation of a right-to-left interatrial shunt to increase cardiac output, which, despite reduction in systemic arterial oxygen saturation, may increase systemic oxygen transport, thus reducing the signs and symptoms of right heart failure. Where advanced medical therapies are available, atrial septostomy is used as a palliative measure or a bridge to lung transplantation in appropriately selected patients with refractory right heart failure or syncope/near syncope despite therapy. In regions of the world without access to current medical therapies, atrial septostomy is sometimes used as a primary therapy [109, 117].

45.4.1.8 Future Therapeutic Options

As discussed before, perivascular inflammatory cell accumulation is frequently observed in all forms of PAH. Preclinical studies show beneficial effects in preventing and sometimes even reversing PH symptoms with treatments targeting the immunity. FK506 (calcineurin inhibitor) and anakinra (IL-1 receptor antagonist) are investigated in ongoing clinical trials after promising results in the preclinical setting [24]. In addition, a randomised clinical trial testing the safety and efficacy of the monoclonal antibody anti-CD20, a B-lymphocyte protein, is in phase 2 studies in patients with PAH with systemic sclerosis (NCT01086540).

Tyrosine kinase inhibitors (TKI) as imatinib, sorafenib and nilotinib showed encouraging results in preclinical studies with regard to vascular and cardiac function, with improvement of functional parameters such as exercise capacity. Unfortunately, these compounds are also associated with serious adverse events and raise safety concerns that limit their use in PAH. Indeed, several lines of evidence suggested that most of these molecules may induce cardiotoxicity [121].

Recent pharmacological studies suggest that activation of RhoA/ROCK signalling system is an important event in the pathogenesis of PH. In vivo, beneficial effects of treatment with Rho kinase inhibitor fasudil have been demonstrated in several animal models of PH [122–129]. In addition, the beneficial effect of sildenafil on PH is mediated, at least in part, by the inhibition of the RhoA/Rho kinase pathway [130]. Serotonylation of RhoA by intracellular type 2 transglutaminase (TG2), leading to constitutive RhoA activation, is also proposed as a possible risk factor of pulmonary vascular remodelling in PH [128, 131]. Similarly, findings from another recent study from Wei et al. indicate increased serotonylation of fibronectin in human and experimental PH [132].

Discovery of the mutations in the BMP/Smad signalling pathway has led to a new range of therapeutic targets in PAH treatment. In fact, restoration of the BMPR2 is a promising therapeutic strategy. A high-throughput screening on 3,756 drugs approved by the FDA has led to the identification of FK506 (tacrolimus) as an activator of this pathway in vitro. FK506 was subsequently shown to be effective in reducing the experimental PH induced in rodents [133], but as mentioned above, these effects may also have been the result of immune modulation.

45.4.2 Drugs Targeting the Heart

It is important to improve right ventricle function, because patients with persistent low RV ejection fraction despite effective vasodilator treatment have worse prognosis [134]. Digoxin increases myocardial contractility but does not show beneficial short-term effects in PAH treatment [135]. Beta-adrenoreceptor blockers are currently contraindicated in the treatment of PAH because there is a risk of lowering cardiac output and reducing myocardial contractility. However, reduced myocardial

oxygen consumption could also have beneficial effects on the heart and they could also help prevent arrhythmias. After positive results in experimental studies, the effectiveness and patient safety of carvedilol and bisoprolol are now being studied [136–138]. In addition, the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists remains debatable. Drugs targeting reactive oxygen species (ROS) are also possible therapeutics in PAH since they reduce damage to the RV and thereby prevent reduction of RV contractility. Both are being preclinically studied.

45.5 Concluding Remarks

PAH is a devastating disease characterised by sustained remodelling of the lung vasculature leading to increased vascular resistance. The adaptive response of the RV to the increased load critically determines clinical outcome. Pulmonary vasodilators have been the cornerstone of PAH therapy and induce calcium channel blockers and more than ten different drugs that modulate nitric oxide, prostacyclin and endothelin pathways. Although the use of these drugs has resulted in improved outcomes for patients, there is an urgent need for new therapies that reverse pulmonary vascular remodelling or directly target the heart, thereby improving right heart function and survival.

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Part VI
Cardiac Arrhythmias

Chapter 46
Cardiac Arrhythmias: Introduction, Electrophysiology of the Heart, Action Potential and Membrane Currents

Norbert Jost, Danina M. Muntean, and Torsten Christ

Abstract Myocytes represent the functional unit of cardiac muscle; nonetheless, the heart behaves more or less like an electrical syncytium, whose global activity depends on low resistance coupling between the myocytes. The term "more or less" is used here intentionally to imply that while the activity intrinsic to individual myocytes is affected by coupling, its features remain recognizable within the context of the whole heart and are important to determine its function. Electrical changes within the myocytes play an important role to initiate the cardiac contraction. This chapter addresses: (a) the electrical activity of individual myocytes, namely, the resting membrane potentials and action potentials; (b) the way action potentials are conducted throughout the heart to initiate coordinated contraction of the entire heart; and (c) the transmembrane ionic currents underlying cardiac action potential.

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Keywords Cardiac membrane potential • Action potential • Electrophysiology • Transmembrane ion channels • Atrial fibrillation • AV node • Potassium current • Calcium current • Cardiac conduction

Abbreviations

AF	Atrial fibrillation
APD	Action potential duration
AVN	Atrioventricular node
cAMP	Cyclic adenosine monophosphate
E_K, E_{Na}	Equilibrium potential for K^+ or Na^+, respectively
E_M	Resting membrane potential
HVA and LVA	High- and low-voltage-activated calcium channels, respectively
I_{CaL}	L-type calcium current
I_K	Delayed rectifier potassium current
$I_{K(ACh)}$	Acetylcholine-sensitive potassium current
I_{K1}	Inward rectifier potassium current
I_{KATP}	ATP-sensitive potassium current
I_{Kr}	Rapid component of the delayed rectifier potassium current
I_{Ks}	Slow component of the delayed rectifier potassium current
I_{Kur}	Ultrarapid component of the delayed rectifier potassium current
I_{Na}	Fast sodium current
I_{NaL}	Late sodium current
I_{NCX}	Na^+/Ca^{2+} exchanger current
I_{to}	Transient outward potassium current
KV	Voltage-gated K^+ channels
LQT3	Long QT3 syndrome
mRNA	Messenger RNA
Na/K pump	Sodium-potassium pump
NaV	Voltage-gated Na^+ channels
NCX	Sodium-calcium exchanger current
SAN	Sinoatrial node
V_m	Membrane potential

46.1 Introduction

The heartbeat arises from organized flow of ionic currents through ion-specific channels in the cell membrane, through the myoplasm and gap junctions that connect cells and through the extracellular space. The action potential formation results from the opening and closing (gating mechanism) of several inward and outward ion channels, which are largely expressed within the sarcolemma of cardiomyocytes. Ion channels possess distinct genetic, molecular, pharmacologic and gating properties, while exhibiting heterogeneous expression levels within different cardiac

regions. By gating, ion channels permit ion currents across the sarcolemma, thereby creating the different repetitive phases of the action potential, which will be discussed later in detail (e.g. resting phase → depolarization → repolarization circles). The importance of ion channels in maintaining normal heart rhythm is reflected by the increased incidence of arrhythmias in inherited diseases that are associated to several mutations in genes encoding cardiac ion channels or pumps/exchangers or their accessory proteins and in acquired diseases that are associated with changes in ion channel expression levels or gating properties (e.g. different forms of electrical, structural or contractile remodelling linked to congestive heart failure, dilated cardiomyopathy, permanent forms of atrial fibrillation, etc.). To understand the functioning of the transmembrane ion currents and their contribution to the cardiac action potential, it is important to understand the biophysics of the biological cell membranes, including the ion transports, membrane and Nernst potentials as well.

46.2 Cell Membrane Potentials and Electrical Activity in the Heart: Conduction System and Cardiac Action Potential

Cardiac cells, similar with the majority of the living cells from the body, have an electrical potential across the cell membrane. This potential can be investigated by inserting a microelectrode into the cell and to determine the electrical potential in millivolts (mV) inside the cell relative to the outside of the cell. By convention, the outside of the cell is considered 0 mV. If measurements are taken with a resting ventricular myocyte, a membrane potential of about −90 mV will be recorded. This resting membrane potential (E_M) is determined by the concentrations of positively and negatively charged ions across the cell membrane, the relative permeability of the cell membrane to these ions and the ionic pumps that transport ions across the cell membrane.

46.2.1 Equilibrium Potentials

Of several others ions present inside and outside of cells, the concentrations of Na^+, K^+, Cl^- and Ca^{2+} are most important in determining the membrane potential across the cell membrane. Table 46.1 shows typical concentrations of these ions. Among these ions, K^+ is the most important in determining the resting membrane potential. In a cardiac cell, the concentration of K^+ is relatively high inside (about

Table 46.1 Ion concentrations inside and outside of resting myocytes

Ion	Inside (mM)	Outside (mM)
Na^+	20	145
K^+	150	4
Ca^{2+}	0.0001	2.5
Cl^-	25	140

140–150 mM), while it is significantly lower outside (4–4.5 mM) the cell. Therefore, a strong chemical gradient (concentration difference) exists for K^+ that facilitates the ion diffusion out of the cell. The opposite situation is found for Na^+; its chemical gradient favours an inward diffusion. The concentration differences across the cell membrane for these and other ions are determined by the activity of energy-dependent ionic pumps and the presence of impermeable, negatively charged proteins within the cell that affect the passive distribution of cations and anions. These concentrations are approximations and are used to illustrate the concepts of chemical gradients and resting membrane potential.

To understand how concentration gradients of ions across a cell membrane affect membrane potential, consider a cell in which K^+ is the only ion other than the large negatively charged proteins inside of the cell. In this cell, K^+ diffuses down its chemical gradient out of the cell because its concentration is much higher inside than outside the cell. As K^+ diffuses out of the cell, it leaves behind negatively charged proteins, thereby creating a separation of charge and a potential difference across the membrane (leaving it negative inside the cell).

The membrane potential that is necessary to oppose the movement of K^+ down its concentration gradient is termed the equilibrium potential for K^+ (E_K) and is expressed by the Nernst potential. The Nernst potential for K^+ at 37 °C is as follows:

$$E_K = -61 \cdot \log \frac{\left[K^+\right]_i}{\left[K^+\right]_o} = -96mV$$

where the potassium concentration inside $[K^+]_i = 150$ mM, and the potassium concentration outside $[K^+]_o = 4$ mM. The –61 is derived from RT/zF, in which R is the universal gas constant, z is the number of ion charges (z = 1 for K^+; z = 2 for divalent ions such as Ca^{2+}), F is Faraday's constant and T is absolute temperature (°K). The equilibrium potential is the potential difference across the membrane required to maintain the concentration gradient across the membrane. In other words, the equilibrium potential for K^+ represents the electrical potential necessary to keep K^+ from diffusing down its chemical gradient and out of the cell. An increase in the outside K^+ concentration will reduce the chemical gradient for diffusion out of the cell, i.e. the membrane potential required to maintain electrochemical equilibrium would be less negative according to the Nernst equation. The E_M for a ventricular myocyte is about –90 mV, which is very close to the equilibrium potential for K^+. Because the equilibrium potential for K^+ is –96 mV and the resting membrane potential is –90 mV, a net driving force (net electrochemical force) acts on the K^+, causing it to diffuse out of the cell. In the case of K^+, this net electrochemical driving force is the E_M (–90 mV) minus the E_K (–96 mV), resulting in +6 mV. Because the resting cell has a finite permeability to K^+ and a small net outward driving force is acting on K^+, K^+ slowly leaks outward from the cell.

The sodium ions play a major role in determining the membrane potential. Because the Na concentration is higher outside the cell, this ion would diffuse down its chemical gradient into the cell. To prevent this inward flux of Na, a large positive charge is needed inside the cell (relative to the outside) to balance out the chemical diffusion forces. This potential is called the equilibrium potential for Na^+ (E_{Na}) and is calculated using the Nernst equation, as follows:

$$E_{Na} = -61 \cdot \log \frac{\left[Na^+\right]_i}{\left[Na^+\right]_o} = +52mV$$

where the sodium concentration inside $[Na^+]_i = 20$ mM, and the sodium concentration outside $[Na^+]_o = 145$ mM. The calculated equilibrium potential for sodium indicates that to balance the inward diffusion of Na^+ at these intracellular and extracellular concentrations, the cell interior has to be +52 mV to prevent Na^+ from diffusing into the cell.

46.2.2 The Cardiac Conduction System

The conducting system of the heart consists of group of several cardiac muscle cells and conducting fibres, which are specialized for initiating impulses and conducting them rapidly through the heart (Fig. 46.1). They initiate the normal cardiac cycle and coordinate the contractions of cardiac chambers, first contract both atria, then the ventricles. The conducting system provides the heart its automatic rhythmic beat. For the heart to pump efficiently and the systemic and pulmonary circulations to operate in synchrony, the events in the cardiac cycle must be coordinated. The cardiac impulse originates in the sinoatrial node (SA node), located in the right atrium, which is activated first followed by the left atrium. The general direction of the atrial activation is inferiorly, to the left, and posteriorly. This causes the atria to contract and pump blood from the atria to the ventricles; it is recorded on an EKG as a P wave (Fig. 46.1). The atrial impulse is delayed in the atrioventricular node (AV node) to allow the ventricular chambers to fill and is then conducted rapidly through the ventricles (the bundle of His, the right and left bundles and the Purkinje fibres). This causes the ventricles to pump blood out of the heart and to the body; it is recorded on an EKG as a QRS complex. Recovery following the cardiac cycle, or repolarization, follows. This is recorded as a T wave on an EKG. On the microscopic level, the wave of depolarization propagates to adjacent cells via gap junctions located on the intercalated disc. The heart is a functional syncytium (not to be confused with a true "syncytium" in which all the cells are fused together, sharing the same plasma membrane as in skeletal muscle). In a functional syncytium, electrical impulses propagate freely between cells in every direction, so that the myocardium functions as a single contractile unit. This property allows rapid, synchronous depolarization of the myocardium. While advantageous under normal circumstances, this property can be detrimental, as it has potential to allow the propagation of incorrect electrical signals. These gap junctions can close to isolate damaged or dying tissue, as in a myocardial infarction.

46.2.3 The Cardiac Action Potential

The normal mechanical (pump) function of the mammalian heart depends on proper electrical function [1, 2], as reflected in the successive activation of cells in specialized, "pacemaker" regions of the heart and the propagation of activity

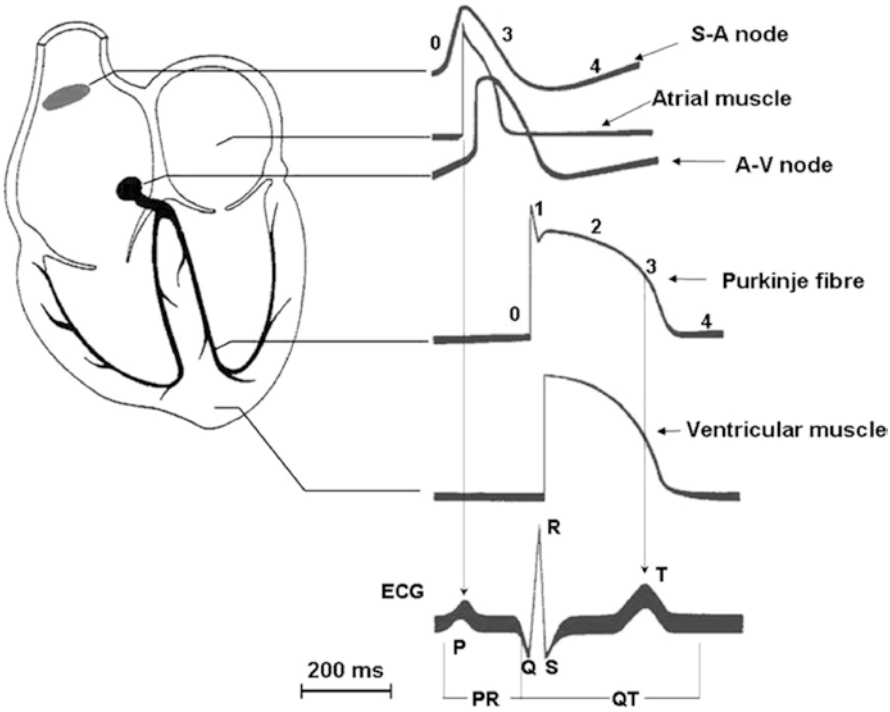

Fig. 46.1 Electrical activity in the myocardium. Schematic representation of a human heart with illustration of typical action potential (*AP*) waveforms recorded in different regions and their contribution to surface electrocardiogram

through the ventricles. Myocardial electrical activity is attributed to the generation of action potentials (AP) in individual cardiac cells, and the normal coordinated electrical functioning of the whole heart is readily detected in surface electrocardiograms (Fig. 46.1). Propagation of the electrical activity and coordination of the electromechanical functioning of the ventricles strongly depend on cellular electrical coupling mediated by gap junctions [3]. The generation of myocardial action potentials reflects the consecutive activation and inactivation of ion channels that conduct depolarizing, inward (Na^+ and Ca^{2+}), and repolarizing, outward (K^+), currents. The waveforms of action potentials in different regions of the heart are different reflecting to differences in the expression and/or the properties of the underlying ion channels. These differences contribute to the normal unidirectional propagation of excitation through the myocardium and to the generation of normal cardiac rhythms [4–6].

The cardiac electrical cycle has been divided in to five “phases”, four of them describing the AP contour and one the diastolic interval (Figs. 46.1 and 46.2). Phase 0 refers to the autoregenerative depolarization, which occurs when the excitation threshold is exceeded. Phase 0 is supported by activation of two inward

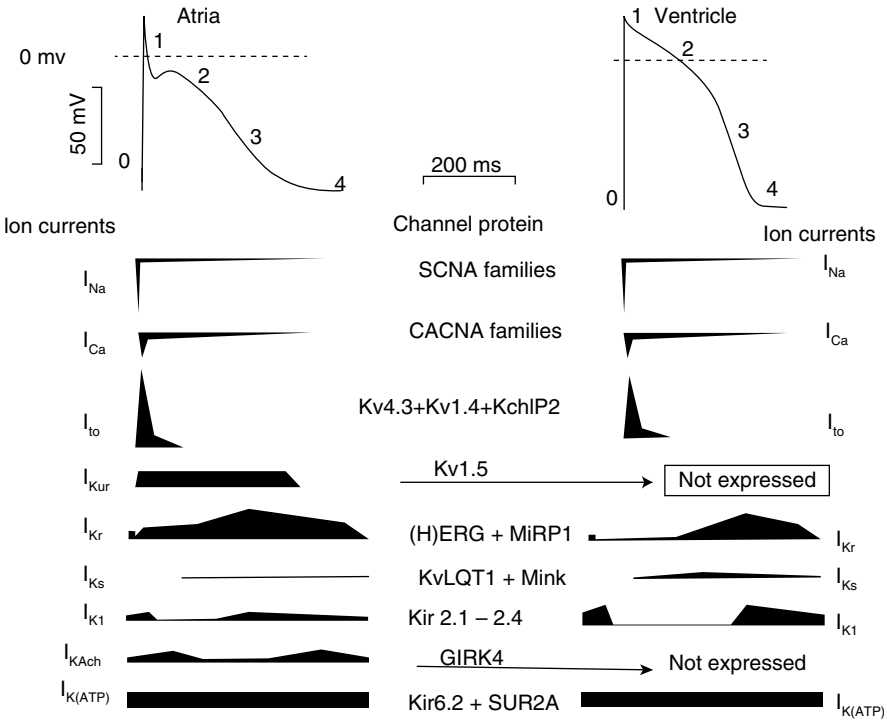

Fig. 46.2 Phases of a typical atrial and ventricular APs and underlying currents. The numbers refer to the five phases of the action potential. In each current profile, the horizontal line represents the zero-current level; inward currents are below the line, and outward currents are pointing upward

(depolarizing) currents, I_{Na} and I_{CaL}. Membrane depolarization will quickly activate these channels and, with a delay of several milliseconds for I_{Na} and of tens of milliseconds for I_{CaL}, inactivates them. Thus, membrane depolarization provides both the triggering and breaking mechanisms for the autoregenerative depolarization. Although short lived, I_{Na} is large and provides most of the charge influx required for AP propagation (see below). I_{CaL} has a small component with fast activation/inactivation (I_{CaT}) and a larger one with slower kinetics (I_{CaL}). I_{CaL} mediates most of Ca^{2+} influx required to trigger myocyte contraction and may support propagation under conditions in which I_{Na} is not expressed or functional (e.g. in the SA node). Phase 0 depolarization also activates K^+ currents, which contribute to termination of this phase and to subsequent repolarization. Among these, the transient outward current (I_{to}) is fast enough to limit the depolarization rate during phase 0.

Phase 1 is the initial phase of repolarization, mainly supported by $I_{to,f}$ (the Ca independent I_{to} fast component – see Sect. 46.3.3.1 for details), a potassium current that, similarly to I_{Na}, is activated and quickly inactivated by depolarization. Thus, $I_{to,f}$ supports fast repolarization.

Phase 2, also named "plateau", is the slow repolarization phase, which accounts for the peculiar configuration of the cardiac AP. The net transmembrane current flowing during phase 2 is small and it results from the algebraic summation of inward and outward components. The outward one (promoting repolarization) mainly consists of depolarization-activated K^+ currents collectively named "delayed rectifiers" (I_K). I_K is actually the sum of rapid (I_{Kr}) and slow (I_{Ks}) components (and ultrarapid in atria, I_{Kur}), carried by separate channels with different properties and pharmacology [7]. The inward phase 2 currents (opposing repolarization) are mostly carried by "window" components of I_{Na} and especially of I_{CaL}, which flow when membrane potential (V_m) is such that the activated state of these channels is not yet completely offset by the inactivation process. This inward calcium movement is through long-lasting (L-type) calcium channels that open when the membrane potential depolarizes to about −40 mV. L-type calcium channels are the major calcium channels in cardiac and vascular smooth muscles. They are opened by membrane depolarization (they are voltage operated) and remain open for a relatively long duration consequently causing the relative long plateau phase of AP (corresponding to the long ST segment of the ECG). The current generated by operation of the Na^+/Ca^{2+} exchanger (I_{NCX}) can variably contribute to phase 2, according to the magnitude and course of the cytosolic Ca^{2+} transient and to the subsarcolemmal Na^+ levels.

Phase 3 is the terminal phase of repolarization, which differs from phase 2 for its faster repolarization rate. Phase 3 is dominated by I_{Kr} and I_{K1}, both characterized by a kinetic property, named "inward rectification" [8, 9], suitable to support autoregenerative processes [10]. Initiation of phase 3 is probably supported by I_{Kr}, with a threshold determined by the balance between its onset and waning of phase 2 inward currents. I_{K1} takes over during the final part of phase 3 and effectively "clamps" membrane potential back to its diastolic value [11].

Phase 4 describes membrane potential during diastole. In myocytes expressing a robust I_{K1} (e.g. atrial and ventricular myocytes), V_m is stabilized at a value close to the current reversal, and a significant current source is required to re-excite the cell. Under such conditions, even small inward currents may cause progressive depolarization, eventually leading to re-excitation (automatic behaviour) [12]. Besides the time-dependent currents, specific for each AP phase, time-independent (or "background") currents may also contribute to the whole AP course. These mainly include the Na^+/K^+ pump current (I_{NaK}) and the Na^+/Ca^{2+} exchanger current (I_{NCX}). Direction and magnitude of these currents during the various AP phases will be determined essentially by their electromotive force.

46.3 Transmembrane Ion Channels in the Heart

46.3.1 Voltage-Gated Na^+ (NaV) Currents

Voltage-gated cardiac Na^+ (NaV) channels open extremely rapidly (within 3 ms) on membrane depolarization and, in principle, determine alone the rapidly rising phases of the action potentials recorded in mammalian ventricular and atrial

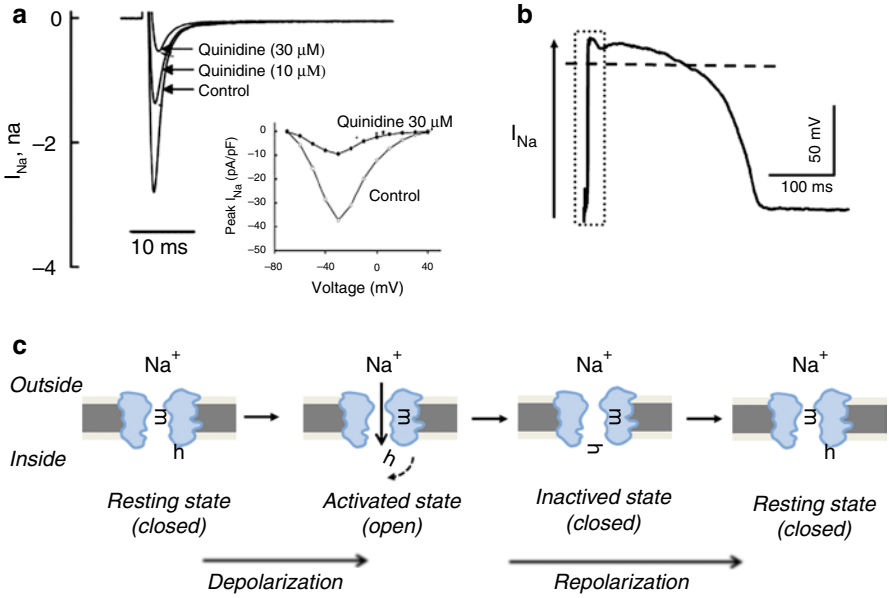

Fig. 46.3 The voltage-gated fast sodium channel (I_{Na}). (**a**) Original I_{Na} trace recorded in rabbit ventricular myocytes (Adapted from [16] with permission). The original recording shows representative recordings of peak I_{Na} from a single cell in the absence (control) and the presence of 10 and 30 μM/L quinidine (a typical Class IA, i.e. a known sodium channel blocker, antiarrhythmic drug). Inset shows current–voltage curves in the absence (*open circles*) and the presence (*solid circles*) of 30 μM/L quinidine. (**b**) The schematic contribution of I_{Na} to the phase 0 (depolarization) on the action potential shape. (**c**) The biophysical double-gating model of the sodium channel. Sodium channel has two gates, one activating gate (m) and one inactivating gate (h). In the resting (closed) state, the m-gates (activation gates) are closed, although the h-gates (inactivation gates) are open in order to wait activating pulse to open the channel. Rapid depolarization to threshold opens the m-gates (voltage activated), thereby opening the channel and enabling sodium to enter the cell. Shortly thereafter, as the cell begins to repolarize, the h-gates close and the channel becomes inactivated. Towards the end of repolarization, the m-gates again close, and the h-gates open. This brings the channel back to its resting state. Summarizing, the channel can be activated only after reaching again the resting phase (i.e. the activating gate must first close, and the inactivated gate must reopen). This phenomenon represents the subcellular basis of the refractoriness of the heart, i.e. the heart cannot be tetanized

myocytes and in cardiac Purkinje fibres [13, 14]. Although the properties of the NaV channels expressed in different cardiac cells are alike, the biophysical and pharmacological properties of these channels are quite different from NaV channels expressed in other excitable cells (neurons or skeletal muscle). Cardiac NaV channels, for example, are remarkably insensitive to the NaV channel toxin tetrodotoxin (TTX). On membrane depolarization, cardiac NaV channels activate and inactivate very rapidly [15]. Figure 46.3 shows typical representative recordings from a single cell of I_{Na} in control and during superfusion with 10 and 30 μmol/L quinidine, a well-known sodium channel blocker Class IA antiarrhythmic drug [16]. The threshold for NaV channel activation is negative (approximately −55 mV), and the

activation of these channels is strongly voltage dependent. Importantly, the inactivation is also voltage dependent and is so fast that cardiac NaV channels can undergo voltage-dependent inactivation without ever opening.

At values corresponding to the action potential plateau in ventricular myocytes, present estimates are that 99 % of the NaV channels are already in an inactivated, nonconducting state [17]. There is, therefore, a finite, albeit small (1 %), probability of NaV channels being opened at potentials corresponding to the action potential plateau [17]. This slow component of NaV channel inactivation called late Na current (I_{NaL}) has indeed been described in normal human ventricular myocytes [18].

The probability of NaV channel opening at depolarized potentials (i.e. during phase 2) is determined by the overlap of the curves describing the voltage dependences of channel activation and inactivation. Consistent with these predictions, electrophysiological studies reveal the presence of a sustained component of inward NaV current, i.e. a "persistent" NaV current, during prolonged membrane depolarizations, which was named "window" current. Although the "window" current is relatively small in comparison with the magnitude of the I_{Na} current, this current may contribute to action potential durations [19]. It has been reported that the expression level of the persistent NaV current component is different in various regions of the ventricles, differences that could contribute to the observed regional heterogeneities in ventricular action potential durations [20]. The impact of alterations in the "persistent" NaV channel window current on cardiac rhythms has now been unequivocally demonstrated with the identification of mutations in the gene, SCN5A, encoding the TTX-insensitive cardiac NaV channels in patients with an inherited form of long QT syndrome, LQT3 [21]. Several SCN5A mutations in different affected individuals/families have been identified and linked to Brugada syndrome and to conduction defects, in addition to LQT3 [22, 23] (Chaps. 49 and 52).

46.3.2 Voltage-Gated Ca^{2+} (CaV) Currents

In contrast to skeletal muscle, it has long been recognized that Ca^{2+} entry from the extracellular space is required for excitation–contraction coupling in the mammalian myocardium [2, 24]. Several studies reported late that a "slow inward" (in comparison with NaV channel) current is carried by Ca^{2+} through a membrane conductance distinct from the Na^+ movement [25]. Further studies characterized the time- and voltage-dependent properties of voltage-gated cardiac Ca^{2+} (CaV) currents in multicellular preparations and, later in isolated single cardiac cells as well [26, 27].

Based on differences in the thresholds for channel activation, two different types of CaV currents/channels were reported to be present in chick and rat sensory neurons [28, 29]. These channels were termed high-voltage-activated (HVA) and low-voltage-activated (LVA) CaV channels, respectively. In the heart, HVA and LVA CaV channels were first described in isolated canine atrial cells [30]. LVA CaV channels, also referred to as T-type Ca^{2+} channels [31], activate at relatively hyperpolarized membrane potentials, to about −50 mV, and these channels activate and inactivate rapidly [28, 29]. On the contrary, HVA CaV channels (L type) open on

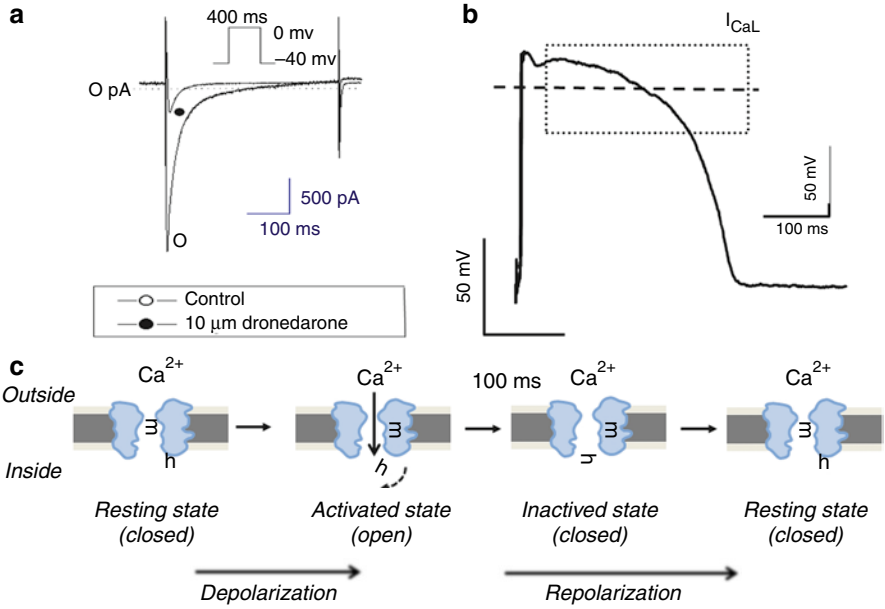

Fig. 46.4 The voltage-gated L-type calcium channel (I_{CaL}). (**a**) Original I_{CaL} trace recorded in dog ventricular myocytes (Modified from [32] with permission). The original recording shows representative recordings of I_{CaL} from a single cell in the absence (control) and the presence of 10 µM/L dronedarone (known as iodine free "amiodarone" a typical multichannel antiarrhythmic drug, which is similar to amiodarone and a strong I_{CaL} channel blocker). (**b**) The schematic contribution of I_{CaL} to the phase 2 (depolarization) on the action potential shape. Lower panels (**c**) The biophysical double-gating model of the calcium channel. Calcium channels, like sodium channel, have two gates, one activating gate (m) and one inactivating gate (h). In the resting phase (*left panel*), m-gate is closed, while h-gate is open waiting for the activating pulse to open the channel. When membrane reaches the activating voltage threshold, m-gate opens facilitating the entrance of the Ca^{2+} ion from the extracellular space into the cell (2nd panel). The resulting inward current is extremely fast activating (within 1–3 s, see panel **a**, *left*). The inactivating gate (h) fast closes (3rd panel) causing the relative fast inactivation (to about 50–150 ms) of the I_{CaL} current. This medium fast-inactivating calcium current is responsible for the relative long plateau phase of the AP shape. The double-gated cardiac calcium channel has the intrinsic properties that it cannot be reactivated again from the inactive state to open the channel. The channel can be activated only after reaching the resting phase (4th *right panel*) (i.e. the activating m-gate must first close and h the inactivated gate must reopen)

depolarization to more positive membrane potentials (approximately −20 mV) and inactivate over a longer time scale (several tens of milliseconds to seconds). Under physiological conditions, with Ca^{2+} as the charge carrier, HVA channels in most cells inactivate in <100 ms at depolarized voltages [30]. Figure 46.4 shows typical representative recordings from a dog ventricular single cell of I_{CaL} in control and during superfusion with 10 µM/L dronedarone, an antiarrhythmic drug known to possess strong I_{CaL} channel blocker effect [32].

In the mammalian heart, L-type CaV channel currents appear to be ubiquitously expressed. Apparently, there are no interspecies and transregional differences in the properties, and the densities of L-type CaV channel currents occur, suggesting simi-

lar molecular compositions of the underlying channel. Since the opening of cardiac L-type CaV channels in response to membrane depolarization is delayed relative to the NaV channels, I_{CaL} contributes little to phase 0 depolarization in Purkinje, atrial and ventricular cells (Figs. 46.1 and 46.2). The opening of L-type CaV channels and the Ca^{2+} entry through these channels are responsible for the action potential plateau (phase 2), which is particularly prominent in ventricular and Purkinje cells.

In addition, Ca^{2+} influx through the L-type CaV channels triggers Ca^{2+} release from intracellular Ca^{2+} stores and underlies excitation–contraction coupling in the working (ventricular) myocardium [1, 2, 33]. L-type CaV channels are also expressed in other heart regions as SAN and AVN cells, where they play an important role in action potential generation and automaticity regulation too [34]. Cardiac L-type CaV channels undergo rapid voltage- and Ca^{2+}-dependent inactivation [35], processes that will also influence the action potential waveforms (Fig. 46.2) by interfering the duration of the plateau (phase 2) and the time course of action potential repolarization.

46.3.3 Voltage-Gated K^+ Channels

Voltage-gated K^+ (KV) channels are the primary determinants of action potential repolarization in the mammalian myocardium. There is considerable electrophysiological and functional cardiac KV channel diversity as compared with cardiac NaV and CaV channels [36]. Based primarily on differences in time- and voltage-dependent properties and pharmacological sensitivities [6, 36], two large classes of repolarizing cardiac KV currents have been distinguished: transient outward K^+ currents (I_{to}) and delayed, outwardly rectifying K^+ currents (I_K). I_{to} currents activate and inactivate rapidly on membrane depolarizations to potentials positive to approximately −30 mV and underlie the early phase (phase 1) of repolarization (notch) in ventricular and atrial cells (Fig. 46.2). The cardiac delayed rectifiers (I_K) activate at relative similar membrane potentials, however, having variable kinetics. I_K currents determine the latter phase (phase 3) of repolarization back to the diastolic potential. Multiple types of myocardial I_{to} and I_K channels were identified in various species. The distinct time- and voltage-dependent properties and differences in the densities and the biophysical properties of these channels contribute to variations in the waveforms of action potentials recorded in different cardiac cell types [4, 36] (see also Chaps. 49, 50 and 52).

46.3.3.1 Transient Outward KV Currents

Although cardiac transient outward currents were first described in sheep Purkinje fibres and thought to reflect Cl^- conductance [37], subsequent work demonstrated the presence of two transient outward currents with distinct properties, and they were referred to as I_{to1} and I_{to2} [38]. Pharmacological studies revealed that the K^+ selective I_{to1} is blocked by high concentration of 4-aminopyridine (3–5 mM 4-AP) and is not affected by changes in extracellular Ca^{2+}, whereas I_{to2} cannot be blocked by 4-AP and is Ca^{2+} dependent [38].

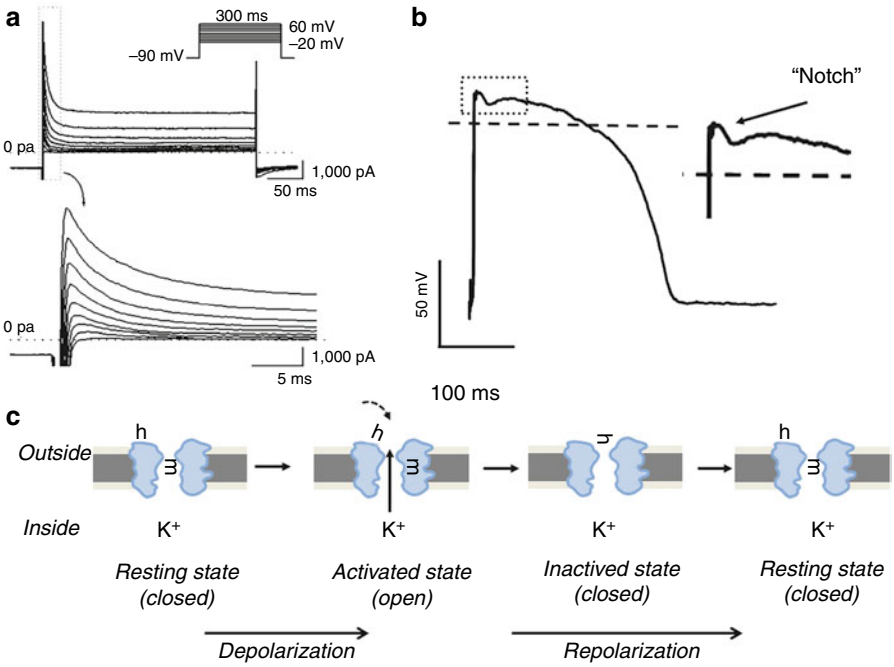

Fig. 46.5 The transient outward K^+ channel (I_{tof}). (**a**) Original I_{tof} trace recorded in dog ventricular myocytes (This panel is modified from [42] with permission). I_{to} current was activated by 300 ms long depolarizing voltage pulses (inset top panel shows applied voltage pulse), while *bottom panel* shows the magnified I_{to} current recorded under the first 20 s long depolarizing pulse (corresponding with the magnification of I_{to} marked by the *dashed-line rectangle* on the *top panel*). (**b**) The schematic contribution of $I_{to,f}$ to the phase 1 (early repolarization, the notch phase of the AP) on the action potential shape. (**c**) The biophysical double-gating model of the transient outward channel. Like fast sodium (see Fig. 46.3) and inward calcium (see Fig. 46.4) channels, I_{to} channels have two gates, one activating gate (m) and one inactivating gate (h). In the resting phase (*left panel*) m-gate is closed, while h-gate is open waiting the activating pulse to open the channel. When membrane potential reaches the activating voltage threshold, m-gate opens facilitating the exit of the K^+ ion from the intracellular space to the extracellular space (2nd panel). The resulting outward current is extremely fast activating (within 1–3 s, see panel **a**, *left*). The inactivating gate (h) fast closes (3rd panel) causing the relative fast inactivation (to about 50–150 ms) of the I_{to} current. The double-gated cardiac I_{to} channel has the intrinsic properties that it cannot be reactivated again from the inactive state. The channel can be activated only after reaching again the resting phase (4th panel) (i.e. the activating gate must first close, and the inactivated gate must reopen)

In further studies, it was shown that the Ca^{2+}-dependent I_{to2} in Purkinje fibres and ventricular cells is a Cl^- channel (Ca^{2+}-activated chloride channel) [39]. The transient outward K^+ currents, referred to variably by different laboratories as I_{to}, or I_{to1} [40], have now been described in many cardiac cell types and in most species [41]. Comparison of the detailed biophysical properties of the transient outward K^+ currents described in various cell types and species, however, suggested that there are two types of transient outward K^+ currents (Fig. 46.5) [42]. This hypothesis is supported by several electrophysiological and pharmacological studies. In adult mouse and rat ventricular myocytes, for example, two transient K^+ currents, termed $I_{to,fast}$

($I_{to,f}$) and $I_{to,slow}$ ($I_{to,s}$), have been distinguished [43]. On membrane depolarization, mouse ventricular $I_{to,f}$ channels activate and inactivate rapidly, and on membrane repolarization, these ($I_{to,f}$) channels recover rapidly from steady-state inactivation. Similar to $I_{to,f}$, mouse ventricular $I_{to,s}$ channels activate and inactivate rapidly. Although the properties of the transient K^+ currents in different cell types and species are similar and are amenable to classification as either $I_{to,f}$ or $I_{to,s}$, there are large cell type and interspecies variations in the detailed biophysical properties of the ($I_{to,f}$ and $I_{to,s}$) currents [41]. These observations suggest that there may well be subtle, albeit potentially important, cell type- and/or species-dependent molecular heterogeneity among $I_{to,f}$ and $I_{to,s}$ channels in different cell types and/or in different species.

Although originally identified in Purkinje fibres, $I_{to,f}$ is a prominent repolarizing current in atrial and ventricular myocytes in the other species including humans [44–46]. In humans and other larger mammals (as dog), $I_{to,f}$ underlies the early phase (phase 1, notch) of repolarization in ventricular and atrial cells (Fig. 46.5) and likely also contributes to determining the plateau (phase 2) [32, 41, 47, 48]. Recent studies reported that the transient outward potassium current $I_{to,f}$ may influence not only indirectly by modulating the plateau duration but also directly the phase 3 of the ventricular repolarization in dog and human hearts [32, 49]. However, there are exceptions. In guinea pig ventricular cells, for example, $I_{to,f}$ has not been detected except when extracellular Ca^{2+} is removed [50]. These channels are absent in rabbit atrial and ventricular cells [46]. Nevertheless, there are transient KV currents in rabbit myocytes (typically referred to as transient inward current I_t), which inactivate slowly and recover from (steady state) inactivation very slowly, whose properties more closely resemble mouse ventricular $I_{to,s}$ than $I_{to,f}$ and reflect possible different molecular structure background.

Transient KV currents classified as $I_{to,f}$ have also been shown to be expressed in (rabbit) SAN cells, although, similar to NaV currents, $I_{to,f}$ densities vary markedly among SAN cells. In addition, when expressed, $I_{to,f}$ appears to play a role in shaping action potential waveforms and in regulating automaticity in SAN cells [51]. Cells isolated from the (rabbit) AVN also express $I_{to,f}$, and detailed kinetic analysis of the currents reveals the presence of two components with distinct rates of inactivation and recovery [52]. It is unclear whether these findings reflect differences in the kinetic properties of a single type of $I_{to,f}$ channel or if two distinct types of I_{to} channels are expressed in (rabbit) AVN cells.

46.3.3.2 Delayed Rectifier KV Currents

The delayed rectifier potassium current (I_K) is a major outward current responsible for ventricular muscle action potential repolarization [53]. This current was first described in 1969 by Noble and Tsien using the two-microelectrode voltage-clamp technique in sheep cardiac Purkinje fibre strands [54]. Since its discovery, it has been examined in single isolated myocytes obtained from various regions of the heart in several mammalian species [7, 55, 56]. In most species, I_K can be separated

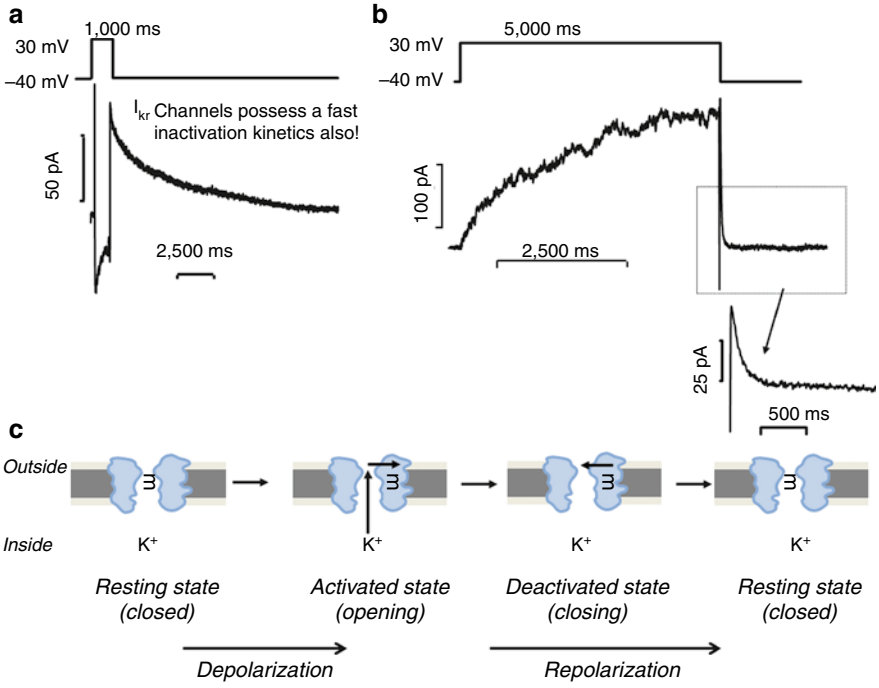

Fig. 46.6 The fast and the slow components of the delayed rectifier K^+ channel (I_{Kr} and I_{Ks}). Upper panels. Original I_{Kr} (**a**) and I_{Ks} (**b**) traces recorded in human ventricular myocytes (Modified from [58, 59] with permission). I_{Kr} and I_{Ks} currents were activated using test pulses of 1,000 ms (I_{Kr}) or 5,000 ms (I_{Ks}) in duration to 20 mV from the holding potential of −40 mV. The decaying tail current at −40 mV after the test pulse was assessed as I_{Kr} and I_{Ks} tail currents. (**c**) The biophysical single-gating model of the delayed rectifier potassium channels. I_K channels unlike the previously presented I_{Na}, I_{Ca} and I_{to} channels (see Fig. 46.3, 46.4 and 46.5, respectively) have only one channel gate, which in resting state is closed (*left panel*). When cells are depolarized, the channel activates (2nd panel). In I_{Kr} channels, this activation is fast, while in I_{Ks} channels it is relatively slow. When cells are repolarized, the channels are closed (3rd and 4th panels). I_{Ks} channels are not inactivating, thereby the closing mechanism is called deactivation. Previously it was thought that I_{Kr} behaves a similar way that I_{Ks} having one gate-based activating and deactivating kinetics, until Spector et al. [60] reported that I_{Kr} channels have in fact double-gating mechanism like I_{to} channels. I_{Kr} channels inactivate having extremely fast inactivation kinetics; however, this inactivation displays a voltage-dependent behaviour. At positive membrane potential, the inactivation is blocked, while when membrane potential repolarizes and becomes more negative; the inactivation blocking effect disappears, and channels deactivate with a relative slow kinetics

into rapid (I_{Kr}) and slow (I_{Ks}) components (Fig. 46.6) that differ from one another in terms of their sensitivity to drugs, rectification characteristics and kinetic properties [55, 57–59].

Although I_{Kr} activates rapidly, inactivates very rapidly and thereby displays marked inward rectification, no inward rectification is evident for the slowly activating I_{Ks} [60]. In cardiac ventricular myocytes isolated from healthy human donor

hearts, I_{Kr} activated fast and deactivated slowly and biexponentially ($\tau_1 \approx 600$ ms and $\tau_2 \approx 6{,}700$ ms) [61], while I_{Ks} exhibited slow- and voltage-independent activation at more positive than 0 mV ($\tau \approx 900$ ms) and had fast and monoexponential deactivation kinetics [58, 59]. This deactivation was voltage dependent, being fast at more negative (at −50 mV, $\tau \approx 90$ ms) and slow at more positive voltages (at 0 mV, $\tau \approx 350$ ms) [59]. In dog cardiac ventricular cells, I_{Kr} activated fast and deactivated slowly and biexponentially ($\tau_1 \approx 360$ ms and $\tau_2 \approx 3{,}300$ ms), while I_{Ks} activated slowly ($\tau \approx 800$ ms) at voltage more positive than 0 mV and deactivated rapidly and monoexponentially ($\tau \approx 150$ ms) [55, 62]. In the guinea pig, where it was first described, I_{Ks} activated very slowly, not saturating even after 5–7 s at +50 mV, and deactivated slowly, within 500–1,000 ms [63]. Initially, it was not observed in the rabbit, but later studies revealed a large and consistent I_{Ks} in the rabbit ventricle [56, 64]. Considering the kinetic properties, the human cardiac slow delayed rectifier potassium current best resembles those measured in the dog [55, 62] and rabbit [56, 64] ventricle but significantly differs from those found in the guinea pig heart [57]. I_{Ks} was augmented with an increase in sympathetic tone as a result of elevation in intracellular cAMP levels [58, 65].

In canine [66] and human [67] atrial myocytes, a novel, very rapidly activating, and largely non-inactivating, outward KV current, now typically referred to as I_{Kur} [66], has been described. In most species, I_{Kur} is not detected in ventricular cells. It is likely that the expression and the properties of I_{Kur}, together with $I_{to,f}$, contribute to the more rapid repolarization evident in atrial, as compared to ventricular, myocytes (Figs. 46.1 and 46.2). This suggests that I_{Kur} channels might represent a therapeutic target for the treatment of atrial arrhythmias without undesirable effects on impulse propagation, ventricular functioning or cardiac output [68]. However, Wettwer et al. [69] reported that I_{Kur}-blockade may either prolong or shorten atrial APD depending on the disease status of the atria, which questioned the selective I_{Kur}-blockade to atrial specific antiarrhythmic potential [69] (Chap. 50).

46.3.3.3 Inward Rectifier Potassium Currents

In addition to the depolarization-activated KV currents, inwardly rectifying K^+ (Kir) currents, through I_{K1} channels, also contribute to myocardial action potential repolarization, particularly in ventricular cells [71]. As the "inward rectifier" terminology implies, Kir channels carry inward K^+ currents rather than outward K^+ currents [71]. Nevertheless, it is the outward K^+ currents through these channels that are important physiologically because myocardial membrane potentials never reach values more negative than the K^+ reversal potential (approximately −90 mV).

At the macroscopic level, I_{K1} channels have been characterized in human guinea pig and rabbit atrial and ventricular myocytes and in rabbit SAN cells [11, 71, 72]. The properties of the I_{K1} channels in each of these preparations are similar in that all are K^+ selective, blocked by extracellular Ba^{2+} and intracellular Cs^+ and strongly inwardly rectifying [72]. The strong inward rectification evident in cardiac I_{K1} channels is attributed to block by intracellular Mg^{2+}, Ca^{2+} and polyamines [9, 73, 74].

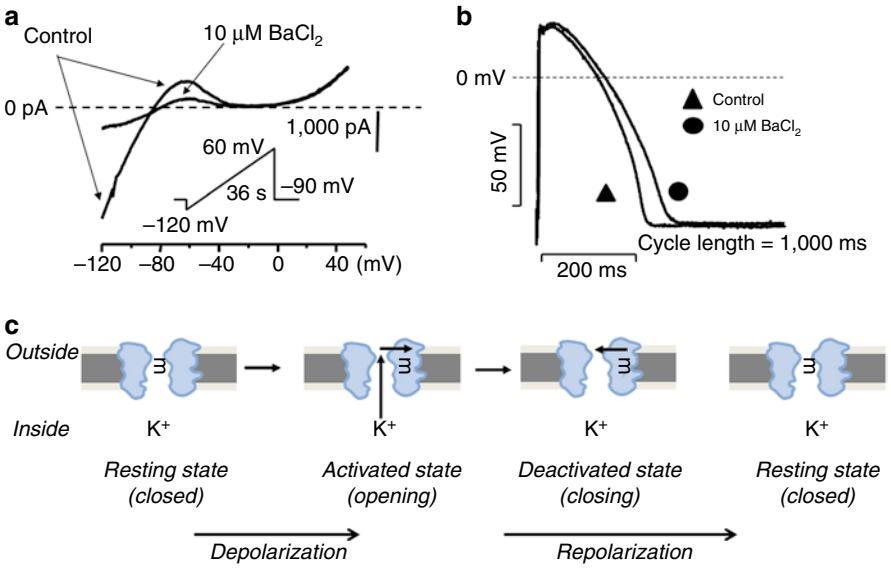

Fig. 46.7 The inward rectifier potassium channel (I_{K1}). (**a**) Original I_{K1} recording in a dog ventricular myocyte in the absence (control) and the presence of 10 μM/L $BaCl_2$ (a typical I_{K1} channel inhibitor). (**b**) The effect of selective I_{K1} channel blockade by $BaCl_2$ on the action potential recorded in dog right ventricular preparation (Both two panels are adapted from [75] with permission). (**c**) The biophysical single-gating model of the inward rectifier potassium channel. I_{K1} channels like I_{Ks} channels have only one channel gate, which is closed in the resting state. When cells are depolarized, the channel is activated, and later when the membrane is repolarized, the extremely slow deactivation of the channel occurs

The expression of I_{K1} is clearly reflected in the negative slope region (between approximately −50 and −10 mV) of the (total steady state) myocyte conductance-voltage relation, which is prominent in ventricular myocytes and smaller in atrial cells [72]. The fact that the strongly inwardly rectifying I_{K1} channels conduct at negative membrane potentials suggests that these channels play a primary role in establishing the resting membrane potentials of Purkinje fibres, as well as of atrial and ventricular myocytes. Direct experimental support for this hypothesis was provided with the demonstration that ventricular membrane potentials are depolarized in the presence of large concentration of Ba^{2+} [70], which blocks I_{K1} channels. In addition, action potentials are prolonged, and phase 3 repolarization is slowed in the presence of extracellular Ba^{2+} (Fig. 46.7), suggesting that I_{K1} channels also contribute to repolarization [75] and especially of repolarization reserve and arrhythmogenesis [58, 77], particularly in the ventricular myocardium (Chap. 48). Similar to the KV channels, I_{K1} densities and the detailed biophysical properties of the currents vary in different myocardial cell types. In the human heart, for example, I_{K1} density is more than twofold higher in ventricular, than in atrial, cells [77]. A recent study reported that ventricular I_{K1} current density in human is significantly lower than in dog; therefore, selective blockade of I_{K1} lengthens ventricular APD less in human

than in dog [76]. However, this behaviour indirectly causes a more less pronounced I_{Kr}-blockade-induced APD lengthening in the dog than in human ventricle; therefore, any I_{Kr} block drug effect tested in dogs can be underestimated when it is extrapolated to humans [76].

Another important and special ligand-gated cardiac Kir channel type is the acetylcholine-sensitive potassium channel $I_{K(ACh)}$, which is gated through a G protein-coupled mechanism mediated by muscarinic acetylcholine receptor activation [78]. Physiologically, $I_{K(ACh)}$ channels are activated by the binding of G protein subunits in response to the acetylcholine released on vagal stimulation [68]. Although $I_{K(ACh)}$ channels are expressed in AVN, SAN, atrial and Purkinje cells and are activated by acetylcholine released on vagal stimulation, these channels are not thought to contribute appreciably to action potential repolarization under normal physiological conditions. Consistent with this hypothesis, targeted deletion of one of the Kir-encoding $I_{K(ACh)}$ channels, Kir3.4, does not measurably affect resting heart rates. Interestingly, atrial fibrillation (AF) is not evident in Kir3.4 null mice exposed to the acetylcholine receptor agonist carbachol, suggesting that activation of $I_{K(ACh)}$ channels is involved in the cholinergic induction of atrial fibrillation [79]. Similar to I_{Kur}, $I_{K(ACh)}$ is also an atrial-specific channel. Thus, it is interesting whether selective $I_{K(ACh)}$-blockade causes repolarization lengthening effect and be a basis for developing new antiarrhythmic drugs for treating chronic AF (cAF). In the study of Dobrev et al. [80], $I_{K(ACh)}$ channels in cAF are constitutively active without any direct ligand stimulation. This observation suggests that selective $I_{K(ACh)}$-blockade may be a target for developing new antiarrhythmic drugs for treating cAF. Several pharmacological studies have supported this hypothesis [81].

46.3.3.4 ATP-Sensitive Potassium Currents

The existence of K^+ channels which could be blocked by internal ATP in cardiac muscle was suggested a long time ago [82], but direct demonstration of the presence was possible only later with the aid of voltage-clamp techniques. The ATP-sensitive potassium current (I_{KATP}) channels are inhibited by intracellular ATP, which are activated by nucleotide diphosphates, thus providing a link between cellular metabolism and membrane potential [83]. The current is time independent and is activated when intracellular ATP concentration decreases below 1 mM. The reversal potential of I_{KATP} (reported to be at −85 mV) is close to the K^+ equilibrium potential [84], suggesting K^+ as the major ion carrier. The current can be activated by several vasodilators such as cromakalim (Fig. 46.8a), pinacidil (Fig. 46.8b) and nicorandil and is blocked by Ba^{2+}, Cs^+, tetraethylammonium and tedisamil (Fig. 46.8a, b) [41, 85, 86]. However, under normal conditions, the current is completely blocked by physiological intracellular ATP level. In the ventricular myocardium, the opening of I_{KATP} channels is thought to be important under conditions of metabolic stress, as occurs during ischaemia or hypoxia, and to result in shortening action potential durations and minimizing K^+ efflux [83]. Activation of I_{KATP} contributes to the repolarization and shortening of refractoriness in hypoxic/ischaemic conditions, which may cause life-threatening

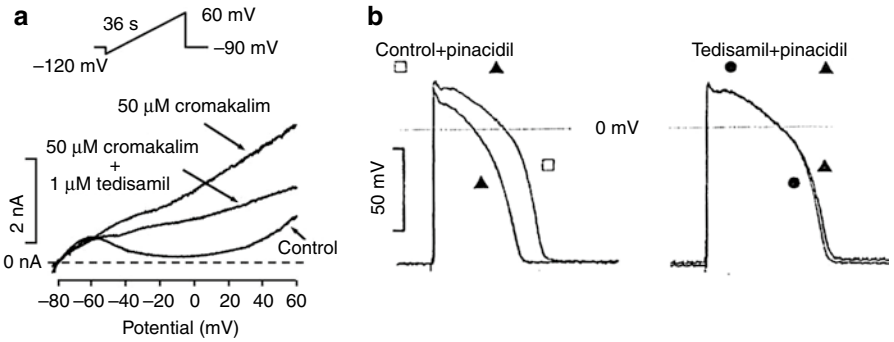

Fig. 46.8 The ATP-sensitive potassium channel (I_{KATP}). (**a**) Original I_{KATP} recordings in a rabbit ventricular myocyte under control conditions, after opening of the I_{KATP} channels with 50 μM cromakalim and after application of 1 μM tedisamil (an investigational antiarrhythmic drug having multichannel blocker profile) in the continuous presence of cromakalim. (**b**) The effect of 1 μM tedisamil on the pinacidil (10 μM) induced APD shortening in dog ventricular muscle fibres (All panels modified from [41] with permission)

cardiac arrhythmias. Drugs that inhibit I_{KATP} can prevent or lessen the hypoxia/ischaemia-induced shortening of repolarization and refractoriness and may protect from dangerous arrhythmias. On the other hand, however, growing evidence suggests that shortening of the APD can protect the myocardium from calcium overload, thus providing significant cardioprotection during acute ischaemia [87]. Although I_{KATP} channels appear to be distributed uniformly in the RV and LV and through the thickness of the ventricular wall, these channels are expressed at much higher density than other sarcolemmal K^+ channels, suggesting that action potentials could be shortened markedly when only very small numbers of I_{KATP} channels are activated.

Table 46.2 summarizes the description of the ionic currents operating in cardiac muscle.

46.3.3.5 Background Potassium Channels

A small and time-independent potassium conductance has been described in guinea pig cardiac myocytes [88]. None of the cloned 6Tm–1P or 2Tm–1P channels encode such current, but several recently cloned tandem-pore subunits (4Tm–2P) encode currents with this "leak" current behaviour, e.g. the fairly ubiquitous TWIK subunit (*Tandem of P-domains in a Weakly Inward rectifying K^+ channel*) [89]. Presence of TWIK mRNA was found in large amount in human atrial and ventricular preparations [90]; however, the properties of the current formed by these channels are still poorly understood. A related subunit TASK (*TWIK-related acid-sensitive K^+ channel*) is also highly expressed in the heart [91]. The channel is sensitive to pH variations in the physiological range and contains a C-terminal PDZ-binding motif. This relatively new family is rapidly expanding and subunits responsible for the cardiac background potassium channel (I_{Kp}) component yet to be established.

Table 46.2 Summary of the ionic currents operating in cardiac muscle, their physiological roles and pharmacologic modulation

Current	Region	Activated by	Blocked by	Main charge carrier	Effect
Fast inward sodium current (I_{Na})	A, V, AVN and Purkinje	Depolarization beyond −60 mV	TTX and local anaesthetics	Na^+	Rapid depolarization (phase 0), and maintenance of plateau (phase 2)
Inward calcium currents					
L-type I_{Ca}	A,V, SAN, AVN and Purkinje	Depolarization beyond −30 mV	Cd^{2+}, Mn^{2+} and organic Ca channel blockers	Ca^{2+}	Depolarization, maintenance of plateau (phase 2) and calcium-induced calcium release
T type I_{Ca}	A, SAN and AVN	Depolarization beyond −60 mV	Mibefradil, amiloride and flunarizine	Ca^{2+}	Depolarization and automaticity
Transient outward currents					
$I_{to,f}$	A, V, SAN, AVN and Purkinje	Depolarization beyond −20 mV	4 Aminopyridine (4-AP) and Heteropoda toxin	K^+	Rapid repolarization (phase 1)
$I_{to,s}$	A, V	Depolarization and intracellular Ca^{2+}	Intracellular EGTA and anion channel blockers (SITS, DIDS)	Cl^-	Early repolarization (notch, phase 1)
Delayed rectifier potassium currents					
I_{Kr}	A,V, SAN, AVN and Purkinje	Depolarization beyond −20 mV and I_{Kr} activators (NS3623, NS1643)	Class IA and III antiarrhythmic drugs (quinidine, dofetilide, E-4031, d-sotalol)	K^+	Termination of repolarization (phase 3)
I_{Ks}	A,V, SAN, AVN and Purkinje	Depolarization beyond 0 mV and sympathetic activation	L-735,821, HMR-1556 and chromanol 293B	K^+	Termination of repolarization (phase 3)

I_{Kur}	A	Depolarization beyond −30 mV	Low concentration (50 μM) 4-AP and AVE0118	K^+	Modulation of plateau (phase 2) and termination of repolarization (phase 3)
Inward rectifier potassium currents					
I_{K1}	A,V, AVN and Purkinje	Depolarization	Ba^{2+} and indapamide	K^+	Reduction of membrane conductance during plateau (phase 2), termination of repolarization (phase 3) and restoring of the resting membrane potential (phase 4)
I_{KACh}	A, SAN and AVN	Depolarization and stimulation of muscarinic receptor (carbachol)	Tertiapin and Ba^{2+}	K^+	Shortening of repolarization, decreases resting membrane potential (phase 4)
I_{Kp}	A, V and undefined in other regions	Depolarization	Unknown	K^+	Decreases membrane potential
ATP-sensitive potassium current					
I_{KATP}	A and V	Depolarization and decrease of intracellular ATP and vasodilator agents (cromakalim, pinacidil, nicorandil)	Glibenclamide	K^+	Shortening of repolarization during hypoxia

A atria, *V* ventricle, *SAN* sinoatrial node, *AVN* atrioventricular node; SITS (4-acetamido-4-isothiocyanatostilbene-2,2-disulfonic acid); DIDS (4,4′-Diisothiocyanato-2,2′-stilbenedisulfonic acid disodium salt); E-4031 (IUPAC name: (1-[2-(6-methyl-2-pyridyl)ethyl]-4-(4-methylsulfonyl-aminobenzoyl) piperidine); L-735821 (IUPAC name: (E)-3-(2,4-dichlorophenyl)-N-[(3R)-1-methyl-2-oxo-5-phenyl-3H-1,4-benzodiazepin-3-yl]prop-2-enamide); HMR-1556 (IUPAC name: N-[(3R,4S)-3-hydroxy-2,2-dimethyl-6-(4,4,4-trifluorobutoxy)chroman-4-yl]-N-methylethanesulfonamide); chromanol-293B (IUPAC name: trans-N-[6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl]-N-methyl-ethanesulfonamide); AVE0118 (IUPAC name: 2′-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2carboxylic acid (2-pyridin-3-yl-ethyl)-amide

46.4 Concluding Remarks

This chapter has focused on ion channels that contribute to AP formation in normal hearts in physiological conditions. However, several ion channels play only a role in pathophysiological conditions related to different cardiac diseases or during early development. Several studies have indicated that ion channels function properly only in the presence of various exogenous and/or endogenous regulatory molecules; moreover, next to several identified gene mutations and polymorphisms, ion channel expression is strongly influenced by molecular variants (genes and/or small noncoding RNAs and microRNAs). The investigations of these effects on channel expression near electrophysiological properties of the transmembrane ionic currents are of importance, because: (1) exploring their function may provide novel mechanistic insights into the pathophysiology of several specific cardiac diseases and (2) the investigation of the transmembrane ion current at organ, cellular and subcellular levels may identify new and more specific targets to treat arrhythmias, which will provide a more potent effect without proarrhythmic side effects that are present with the currently used antiarrhythmic drugs.

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Chapter 47
Pathophysiology of Cardiac Arrhythmias: Arrhythmogenesis and Types of Arrhythmias

Peter P. Karpawich

Abstract As a pumping organ with an intrinsic electrical system, the heart is unique. For most individuals, it remains efficient for decades. However, as a pump, it can fail. Often the failure is due to inherent or acquired problems with the electrical system. Failure of maintenance of normal sinus rhythm often results in adverse or no heart rhythm, a term referred to as "arrhythmias." These can result in the heart rate being too fast ("tachy-") or too slow ("brady-") and alter blood flow resulting in patient morbidities and mortalities. Arrhythmias can occur anywhere in the heart and may not always be caused by any adverse lifestyle events such as coronary disease. Certain inherited congenital heart defects can cause abnormalities within the developing electrical system that can appear even before birth. Alternatively, the simple process of normal aging can adversely affect the heart's ability to maintain normal rhythms. Once initiated, arrhythmias can be sustained by the normal anatomical variations of cardiac structures. There are three common arrhythmia etiologies: "automaticity" "reentry," and "triggered." Automaticity results from alterations of the basic cellular ion exchange mechanism which is depicted as a distinct electrical pattern, the action potential. Once an electrical impulse is initiated, it typically propagates cell to cell in a relatively uninterrupted fashion. However, if an obstruction (valves, veins) or postinfarction scar tissue occurs, the impulse can circle around the obstruction, creating a reentrant pathway. In rare instances, drugs or disease states can alter cell action potentials, triggering abnormal impulse initiation. This chapter will address all of these issues.

Keywords Arrhythmias • Tachycardia • Bradycardia • Reentry • Automaticity • Congenital heart

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47.1 Introduction

Although perhaps somewhat of a misnomer, the term cardiac "arrhythmias" ("a" = absence of) is typically used whenever there is any alteration of normal electrical activity (rhythm) of the heart, not necessarily that there is no heart rhythm. An equally descriptive term of "dysrhythmias" ("dys" = abnormal) is also found in the literature. Both terms describe the clinical presentation of abnormal cardiac electrical impulse formation or impulse conduction through cardiac muscle. These can result in either too slow ("brady") or too fast ("tachy") heart rhythms. Of note, the heart is not alone in this property. Similar impulse alterations can also occur in the brain, the other primary "electrical" organ of the body. Although those brain arrhythmias are called seizures, the etiologies are comparable. As a result, pharmacotherapies can overlap.

Arrhythmias can occur at any age from the developing fetus through adulthood. Developmental alterations of the cardiac conduction tissue, genetically inherited changes of myocardial cellular ion membrane properties, and associated structural congenital heart anatomical defects can all play a role (Chap. 59). Add the normal aging process; sequelae of lifestyle habits; as well as associated metabolic disorders, systemic hypertension with resultant cardiac muscle hypertrophy, and coronary artery disease with diminished regional muscle perfusion; and an otherwise normal heart can express electrical abnormalities. However, in deference to adult-onset ischemic cardiac issues, abnormal heart rhythms occurring in young children can spontaneously disappear as the child grows. Both atrial and ventricular arrhythmias occur in the young although atrial rhythm abnormalities far exceed those of the ventricle. In the adult, atrial arrhythmias may occur solely on the basis of age, while ventricular origins are often associated with coronary blood flow alterations.

The purpose of this chapter is to inform individuals in the pharmaceutical, biomedical, as well as other health care professionals with an understanding of the "why" of arrhythmias; "what," if any, are the predisposing factors, either structural or chemical; and the "where" in the heart they may be located. An understanding of these concepts can aid in continued future applications of selective interventions to either control or eliminate these abnormalities which, in themselves, often lead to patient morbidity and/or mortality.

47.2 Cardiac Electrical Development Predisposing to Arrhythmias

Intrinsically, in the development of the human heart, there exists the predisposition for arrhythmias based solely on anatomy and how that affects electrical impulse transmission, irrespective of any future ischemic cellular changes. In addition, anatomical congenital heart disease, such as septal defects or valve abnormalities, can cause alterations in the normal cardiac electrical system, predisposing to brady- or

tachyarrhythmias. Any surgical repairs of these congenital defects can leave behind scars and fibrotic changes which also will predispose to eventual arrhythmias, even decades later [1, 2] (Chap. 59).

The embryogenic human heart forms as a tube and begins spontaneous peristaltic muscle contractions at approximately 23 days of gestation. The eventual specialized atrioventricular (AV) conduction system, which develops from differentiated myocytes along the coronary artery system, forms later through 6 weeks of gestation. In the majority of instances, the right coronary artery will supply blood to the sinus and AV nodes. In the region of the developing atrium near the superior vena cava-atrial junction, specialized cells form into the horseshoe-shaped sinus node at variable locations with the central area typically evolving into cells exhibiting pacemaker action potential impulse initiation. This is discussed below. Taillike projections extend into the lateral aspect of the developing atrium toward the appendage. The periphery of these tails commonly also exhibits pacemaker activity extending electrically active cell connections along the atrial wall. This anatomical arrangement can create a focus for atrial arrhythmias [3, 4]. In comparison to the developing ventricles, the atria do not contain any specialized electrical conducting tissue, per se. Although there are alignments of muscle fibers that facilitate the electrical propagation from the sinus to AV nodes (Wenckebach, Thorel) as well as right to left atrium (Bachmann), the spread of electrical impulses activity can be compared to a wave. This concept will play an important role in the initiation and propagation of such arrhythmias as atrial flutter [5].

The anatomy of the atria itself also plays a role in arrhythmias [6]. The endocardial surfaces are not smooth. As a result of embryologic connections of venous structures into the developing right and left sides, as well as anatomical landmarks permitting preferential flow patterns of placental blood, the endocardial surface is marked by irregularities, valves, openings, and ridges. Heart tissue itself is not a histologic syncytium but rather comprised of individual membrane-bound myocytes of various alignments, connected by discrete junctions. The term "cardiac anisotropy" has been applied to define these properties, all of which alter electrical flow [7]. To better understand this concept, envision standing on a beach and watching waves coming to shore. Typically, the waves are sequential, at regular intervals, and parallel. The waves die out after hitting the shore, and another follows. Now add rocks, piers, and docks and watch how the waveforms react as they bounce off these obstacles. The regular flow patterns are disrupted, and propagation is altered, resulting in waves coming back on themselves, creating a more chaotic wave distribution. If waves circle around an obstacle, they will eventually end back where they started and "reenter" the initial pathway. This constitutes the basic of many arrhythmias and helps to comprehend how, for example, atrial flutter can start and be self-sustaining. This concept will be discussed below.

As mentioned above, the initial cardiac tube has direct muscle connections between the developing atria and ventricles. With eventual AV valve formation, these direct muscle connections become disrupted. Electrical propagation is then relegated to the developing AV node and bundle of His conduction pathways, creating a single atrial-ventricular electrical conduction pathway

(atrioventricular junction). This has distinct survival advantages since the specialized AV conduction system has an inherent property (decremental conduction) that slows impulse propagation from atrium to the ventricle (seen as the PR interval on a surface ECG). The ventricle is then protected from rapid and potentially fatal atrial arrhythmias (Chaps. 46 and 50).

However, in a subset of individuals, these primitive direct muscle connections remain, ostensibly bypassing the specialized conduction tissue and causing early ventricular electrical activation at the region where the fibers intersect with the ventricle. Persistence of these connections results in various "preexcitation" syndromes, such as Wolff-Parkinson-White [8, 9]. Since these muscle fibers lack the inherent capacity to slow impulses coming from the atrium, any atrial tachycardia (such as flutter) can propagate rapidly to the ventricle potentially causing sudden death. Also, instead of a single connection pathway, electrical impulses can travel along two: down one, up the other, and back down again. A reentrant circuit is created.

In the region of the apex of the anatomical triangle of Koch of the right atrium, electrophysiologic tissues, derived from cells in the sinus venous walls and atrioventricular canal regions, coalesce into a compact structure, the AV node. It varies in size, may be in the right atrial septum, across the central fibrous body, or entrapped in the tricuspid valve annulus. Rarely, it can extend leftward and even be located close to the base of the aortic valve. It is a heterogeneous structure consisting of diffuse anatomical myocellular arrangements. As an analogy, if a hairnet is pulled at one corner, the weblike strands coalesce into a more compact alignment. Previous histological studies have demonstrated comparable cellular arrangements in the para-AV node region [10]. However, as the fibers align, the muscle's intrinsic electrical conduction properties can be altered, resulting in gap junctions with "slow" and "fast" conducting fibers exhibiting different refractory periods, allowing electrical impulses to travel between fibers. Although not necessarily associated with sudden death, these changes do permit reentrant arrhythmias associated with patient morbidities [11].

The diffuse cellular configurations at the entrance into AV node organize into a more longitudinal pattern which becomes the penetrating portion of the bundle of His. This enters into the central fibrous body and, at the crest of the interventricular septum, branches into right and left bundles. On the right, it continues along the moderator band. On the left, it rapidly spreads into a more diffuse Purkinje arrangement. In addition to structural anatomical differences between the left and right ventricles, with the left architecture more amenable to supporting higher pressures, this electrical conduction distribution pattern supports the importance of the systemic left over that of the pulmonic right ventricle. The longer course of the right bundle places that structure at increased risk for damage. This is especially true in congenital heart defects.

Any congenital anatomical defect involving the AV canal or septum can cause intrinsic errors of electrical system development as the evolving conduction tissue responds to these structural anatomical anomalies. For example, a persistent opening in the region of septum, such as seen with an AV canal or ventricular septal defect, can cause a deviation of the electrical conduction tissue away from its normal septal course, resulting in abnormal ventricular activation sequences. Intrinsic bundle branch block patterns, any degree of AV conduction delay including complete

heart block, as well as an altered QRS frontal plane axis as seen on a surface ECG may, therefore, be the result of embryologic development and not necessarily always related to acquired or ischemic heart disease. This is an important concept in the evolving field of adult congenital heart disease [12, 13].

47.3 Electrical Impulse Initiation

The basic premise behind cardiac tissue electrical impulse initiation is the inherent ability of cells to generate an action potential (AP), either intrinsically as in the sinus or AV nodes, or in muscle cells in response to an appropriate stimulus, a concept termed "excitability." As originally described in the 1950s in regard to nerve cells, and applicable to cardiac cells, electrolyte concentration differences associated with the continuous influx and efflux of sodium (Na^{++}), potassium (K^{+}), calcium (Ca^{++}), and chloride (Cl^{-}) ions between the interior and exterior of cells create a transmembrane electrical gradient, with an intracellular side typically −80 to −90 mV among cardiac muscle cells and −60 mV in nodal cells, with respect to the extracellular side. Potassium is the primary intra- and sodium the primary extracellular ion [14]. The typical muscle AP pattern consists of five phases of membrane ion exchange (0–4) while sinus and AV nodal cells exhibit only three (0,3,4) starting with a rapid Na^{++} (muscle) or slow Ca^{++} (nodal) influx which alters the transmembrane electrical gradient, concluding with membrane restabilization back to baseline in muscle but undergoing spontaneous depolarization back up to threshold levels in nodal cells (Fig. 47.1). This spontaneous diastolic depolarization of nodal cells maintains normal heart rates. On a surface ECG, the QRS-T components reflect these phases of the AP (Fig. 47.2) (Chap. 46).

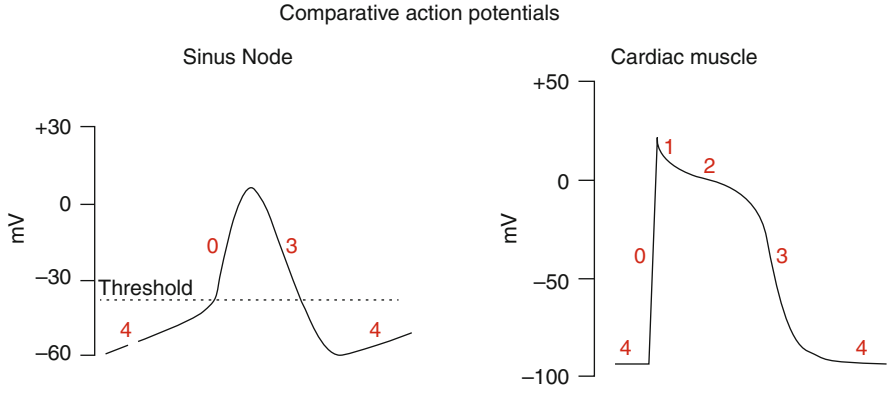

Fig. 47.1 The difference between nodal (Ca^{++}) and muscle (Na^{++}) action potentials is illustrated. Compared with sodium channels of muscle, nodal calcium channel APs have a less negative resting membrane potential, slower upstroke, absence of phases 1 and 2. These cells inherently undergo spontaneous depolarization (automaticity) as seen by the upstroke of phase 4. Once the membrane potential reaches the threshold level, a new impulse is created

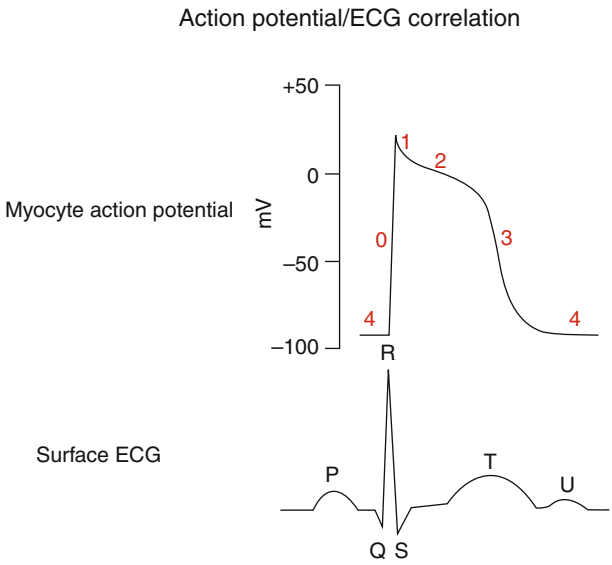

Fig. 47.2 Cardiac muscle action potential with a comparable surface ECG tracing. As illustrated, AP phases are indicated (0–4) and reflect ion exchange concentrations. The ventricular QRS-T of the ECG reflects the intracellular ion flux: QR = phase 0–1, while ST-T = phases 2–3. For this reason, changes in cardiac cellular metabolism, associated with arrhythmias, will often result in ECG changes such as T wave inversion or ST elevations as a marker of intracellular abnormalities

The spontaneous membrane electrical depolarization activity, or automaticity, of nodal cells permits these cells to generate action potentials at a constant rate and act as "pacemakers," regulating cardiac rhythm. Based on ion channel recovery duration, cells may or may not be able to propagate another AP at any given time interval, a term referred to as "refractoriness." This property becomes important in the propagation of arrhythmias once they are initiated, and this forms a major focus in pharmacotherapeutic control of arrhythmias. The interdigitating configuration of cardiac cells permits this integrated electrical activity to spread throughout the heart, thus permitting overall muscle contraction. Detailed descriptions of these intra- and intercellular processes can be found elsewhere in numerous reports, and microelectrode voltage-clamp studies and are beyond the scope of this chapter [15]. However, a basic understanding of the normal action potential helps to put some arrhythmias into perspective since any alteration in AP duration, amplitude, or configuration can be the focus for abnormalities of cardiac rhythm (Chap. 46).

47.4 Altered Action Potentials Causing Arrhythmias

As mentioned above, any alterations of normal cardiac cellular action potentials either by disease, ischemia, inherited genetic conditions, cellular chemical composition, drugs, or even simply aging, can be arrhythmogenic. The sinus node becomes less efficient with age, resulting in loss of its "pacemaker" capabilities, causing slower intrinsic heart rates in the elderly but an increase in abnormal escape rhythms

due to this lack of rate control. The term "sick sinus syndrome" has been applied to symptomatic arrhythmias associated with sinus bradycardia, sinus arrest, or alternating brady- and tachyarrhythmias. Since sinus nodal control of heart rate begins to decrease after the age of 55 years, the intrinsic ability of heart muscle to generate electrical activity acts against the individual with a reported nearly 25 % lifetime risk of developing atrial fibrillation based on the aging process alone [16]. Any patient with repaired congenital heart, or anyone who has been on cardiopulmonary bypass, can have resultant sinus node damage by virtue of superior vena cava cannulation or sutures. In addition, certain congenital heart defects, such as atrial septal defects, may intrinsically have abnormal sinus node function [17].

Electrolyte abnormalities can affect APs causing atrial and ventricular arrhythmias. Sodium ion overload can occur in the heart tissue resulting in Na-Ca exchange abnormalities, as seen in arrhythmias associated with tissue reperfusion following periods of ischemia. Cardiac muscle acid-base balance can also alter APs. Although a decrease in tissue pH values raises intracellular Na^{++} and alters contractions by an increase in Ca^{++} release, a severe decrease to pH 6.7 or less can be associated with Ca^{++} overload arrhythmias [18]. Abnormalities of the inward potassium channel (I_{Ks}), as seen with such inherited genetic conditions such as the long QT syndrome (LQT1), cause AP duration prolongation resulting in membrane instability and a predisposition to often fatal ventricular arrhythmias (polymorphic ventricular tachycardia or *torsade de pointe*) (Chap. 49). The APs of normal muscle cells, following any metabolic insult such as ischemic injury, can be altered, permitting spontaneous initiation of depolarization. Diseased atrial muscle fibers as well as Purkinje cells can exhibit chronic depolarizations independent of any extracellular activity. Premature atrial contractions (PACs), premature ventricular contractions (PVCs), ectopic atrial tachycardia (EAT/AET), or junctional ectopic tachycardia (JET) can be the result of these adverse membrane changes. Ischemic cells lose potassium causing an increase in extracellular K^+ concentrations, which, in turn, alter transmembrane ion ratios, which adversely alter APs [19]. Calcium plays a role in delayed afterdepolarizations contributing to arrhythmias. The normally quiescent membrane ion activity during phase 4 of cardiac muscle APs can become unstable, permitting an increased inward current sufficient enough to trigger a new action potential (early afterdepolarization) and propagate what is referred to as "triggered arrhythmias." These cellular changes can often be detected by concomitant changes in the S-T, T, and T-U wave patterns seen on the surface ECG (Chap. 48).

Pharmacologic agents, including antiarrhythmic drugs can be proarrhythmic by virtue of adverse action potential effects such as an increasing AP duration or depressing sinus or atrioventricular node activity which can allow for ectopic escape rhythms. Bradycardia contributes to *torsade de pointe*, while an increase in heart rate can provoke ventricular tachycardia/fibrillation. Drugs or electrolyte abnormalities (hypokalemia) that cause the AP duration to increase have been implicated in fatal arrhythmias. Excellent reviews of pharmacologic agents provoking arrhythmias can be found elsewhere [20, 21] and in Chap. 48. However, a brief listing includes antiarrhythmics (sotalol, ibutilide, and amiodarone), antibiotics (erythromycin and trimethoprin-sulfa), antihistamines (terodiline), and antiseizure

agents (thioridazine and tricyclics). In addition, other drugs (psychotropic agents, antifungal agents, chemicals (organophosphates)), as well as liquid protein diets can adversely alter cardiac cell action potentials and provoke arrhythmias.

47.5 Reentrant Arrhythmias

As introduced above, cardiac electrical wave propagation tends to flow relatively smoothly. However, if a wave is blocked in one direction but permitted to reroute and return to the original site of excitation, a revolving pattern of wave propagation ensues: "reentry," "circus movement." This concept was first described in the early twentieth century [22]. This circular impulse activity can occur anywhere in the heart in which there is an impediment to electrical propagation (ischemic, anatomical, or mechanical) and is responsible for most of the important clinical tachyarrhythmias. Among these are atrioventricular reentrant tachycardia (AVRT), atrioventricular nodal tachycardia (AVNRT), atrial flutter/fibrillation, and ventricular tachycardia/fibrillation.

Initiation of a reentrant tachycardia is dependent on several factors: (1) the existence of at least two intersecting pathways or limbs (often referred to as α and β) that create a loop for the wave to travel, (2) the wave propagation must be blocked in one of the limbs of the loop and be allowed to travel down the other limb, and (3) the conduction properties of the tissue creating the loop (speed and refractoriness) must be such that the wave can continue to circle around the loop (Fig. 47.3). Although a patient may be susceptible to having a reentrant tachycardia, intrinsic tissue proper-

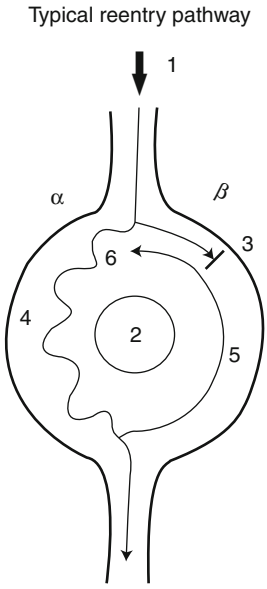

Fig. 47.3 Tissue properties that allow for a reentrant pathway to occur: *1* entering impulse, *2* obstacle (anatomy, scar, ischemic tissue, etc.), *3* impulse blocked in one limb of the loop, *4* impulse propagates with slow conduction down the other limb, *5* impulse enters up the original blocked limb in a retrograde fashion, and *6* impulse "reenters" the original limb

ties dictate when such an occurrence will happen. For example, a patient with Wolff-Parkinson-White syndrome with accessory atrioventricular pathways that form an anatomical loop with the normal AV node, may exhibit tachyarrhythmias only intermittently. Necessary conditions, often provoked by transient electrical alterations, such as premature atrial or ventricular complexes, need to occur to initiate such an arrhythmia. These reentrant circuits typically do not occur among individuals with completely normal hearts, which is why not everyone complains of abnormal tachycardias. However, even normal hearts can be made abnormal by factors that change myocellular properties.

47.6 Types of Arrhythmias

The pathogenesis of the various arrhythmias has been mentioned above. As a quick review, the following should be useful in the understanding of the diverse topic of abnormal heart rhythms. It is important to remember that any region of the heart can be associated with electrical abnormalities.

Sinus Arrhythmia: This is more of a misnomer than anything. Heart rate variability is normal. Typically, this is due to autonomic tone and not an abnormality, per se. The normal heart rate fluctuates, often in response to physiologic changes in the body. Normal heart rate range values for patient ages are readily available elsewhere.

Sinus Bradycardia: This is a normal sinus rhythm but too slow for a given age. This can be due to autonomic tone, drugs, age, or sinus node damage. This may require a pacemaker if there are clinical symptoms.

Sinus Tachycardia: This is a normal sinus rhythm but too fast for a given age. This can be due to autonomic tone, drugs, metabolic conditions (fever, thyroid, adrenal gland), age, or sinus node damage. This may require pharmacologic agents to control. Rarely, the sinus node itself can have a reentrant tachycardia circuit (*sick sinus syndrome*) that can be amenable to ablation techniques.

Sinus Arrest/Pause: Normally, the sinus node rate fluctuates. However, due to sinus node or para-nodal tissue issues, long pauses between sinus complexes can occur. Often, these are a numerical variable of the heart rate. If symptoms develop, pacemaker therapy may be required.

Atrial Arrhythmia: Any abnormality of heart rhythm arising from the atria. By definition, normal sinus arrhythmia can be considered an atrial arrhythmia. However, the term is more appropriately used to categorize such heart rhythm abnormalities as *premature atrial complexes*, *ectopic atrial tachycardias*, reentrant atrial muscle tachycardias such as *flutter/intra-atrial reentrant tachycardia* (*IART*), or chaotic electrical muscle activity, and *atrial fibrillation*. Etiologies include normal variations as well as intrinsic heart muscle damage/disease. All three categories (automaticity, reentry, and triggered) can be causative. Single atrial complexes can be normal and seldom require any intervention, especially in infants. All others can be amenable to catheter ablation and/or pharmacologic intervention depending on clinical issues.

Atrial Paroxysmal Tachycardias: These are rapid atrial heart rates that come and go. These are often due to reentrant mechanisms (discussed above) associated with Wolff-Parkinson-White or other preexcitation syndromes causing *atrioventricular reciprocating tachycardia* (*AVRT*), or related to intrinsic AV nodal and paranodal tissue configurations causing *atrioventricular nodal tachycardia* (*AVNRT*). These can be amenable to ablation or pharmacologic therapy.

Ventricular Arrhythmias: Comparable to abnormalities of heart rhythm arising from the atria, the ventricles can also be the source for arrhythmias. However, these typically are more clinically significant since they can be associated with higher patient mortalities. Again, most are related to rapid reentrant mechanisms (*ventricular tachycardia*) which, however, can degenerate into uncontrolled rhythms (*ventricular fibrillation*, *torsade de pointes*) as a prodrome to sudden death. Etiologies include inherited cardiac muscle disease (*hypertrophic cardiomyopathy*), inherited cardiac electrical disease (*long QT syndrome*), and ischemic heart muscle due to coronary disease, surgical scars, and drugs. Single premature complexes (*PVCs*) can be related to all of the above etiologies or can be normal, especially in adolescents (*benign ectopy of adolescents*). Clinical correlation is mandatory in all situations.

Heart Block: As discussed above, congenital developmental abnormalities of cardiac structures, ischemic muscle damage, drugs, disease, or surgical scars can adversely affect the developing electrical conduction system. Delays in impulse propagation through the atrioventricular conduction system can result in slow conduction (*first-degree AV block*) detected by a prolongation of the PR interval on the resting EKG, intermittent conduction (*second-degree AV block*), or no conduction (*third-degree* (*complete*) *AV block*). Impulse delay further in the ventricles can result in either a *right or left bundle branch block*. In the former conditions affecting the AV node, symptoms of bradycardia, including *Stokes-Adams* attacks, may require pacemaker therapy. In the latter ventricular conditions, ventricles are depolarized abnormally resulting in ventricle contractility issues.

47.7 Concluding Remarks

As an electrical organ, the heart initiates and sustains impulse formation and propagation. Typically, it functions appropriately. However, normal anatomical configurations, congenital defects of development as well as the basic cellular matrix predispose all hearts, even among individuals with no prior history of cardiac disease, to a susceptibility to arrhythmias. Add ischemic cellular changes associated with lifestyle, other disease states, and aging, and this susceptibility increases. This chapter has discussed etiologies, locations, and some clinical correlations of the various types of cardiac rhythm abnormalities to which anyone in the health care field will be exposed. An understanding of normal anatomy or congenitally defective or inherited cardiac conditions as well as altered disease states, as they

predispose and contribute to cardiac arrhythmogenesis, enables future study into how to effectively treat and potentially prevent associated morbidities and mortalities associated with adverse heart rhythms.

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Chapter 48
Proarrhythmic Effects of Antiarrhythmic and Non-antiarrhythmic Drugs

J. William Schleifer and Komandoor Srivathsan

Abstract Many drugs, including both antiarrhythmic and non-antiarrhythmic medications, affect the ion channels and receptors of the heart with the potential to produce a proarrhythmic action. The proarrhythmic action of these drugs is influenced by electrolyte disturbances, hemodynamic abnormalities, and conditions affecting the metabolism and excretion of the medication. This chapter will discuss the mechanisms of proarrhythmic states commonly encountered, illustrate characteristic scenarios, and explain treatment strategies for medication-induced proarrhythmic states. As it is often difficult clinically to differentiate between arrhythmias occurring at therapeutic medication concentrations and those occurring at toxic levels, the treatment of antiarrhythmic toxicity is also discussed.

Keywords Antiarrhythmic • Digoxin • Potassium channel • Sodium channel • Toxicology

48.1 Introduction

An estimated 300,000 people in the United States die annually from sudden cardiac death [1]. Some of these deaths are primary electrical disorders and some ventricular arrhythmias secondary to underlying cardiac dysfunction, but a disturbingly large number are either exacerbated or directly caused by drugs. It is impossible to know the exact number of deaths secondary to medication-induced arrhythmias; however, because of the potentially preventable nature of medication-induced arrhythmias, it is an important subject of research.

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Proarrhythmia is the property of a medication to make the heart more susceptible to electrical disturbance. Narrowly defined, proarrhythmia is a medication-induced change in the depolarization or repolarization phase of membrane action potential within the cardiac myocytes that results in either a new arrhythmia or aggravation of an existing arrhythmia at nontoxic plasma concentrations of the medication [2]. Clinically, there is often no clear way of knowing whether a patient's plasma concentration of a particular medication is at a therapeutic or toxic level. Two common scenarios illustrate how difficult it can be to differentiate between toxic and therapeutic drug levels: (1) patients with an unstable arrhythmia who are unable to provide a history and (2) patients maintaining stable doses of medications in the setting of a disturbance in renal function, volume status, electrolytes, or other drugs. Very few serum drug levels are available rapidly enough to be immediately useful, and in the context of unstable life-threatening arrhythmias, treatment must be initiated prior to obtaining these diagnostic test results.

Drug-induced proarrhythmias are important for several reasons. First, because of the Hippocratic responsibility to "first do no harm," physicians should avoid prescribing drugs that are likely to cause life-threatening dysrhythmias. The unanswerable question is what risk of arrhythmia is too high. Multiple drugs have been taken off the market because of their risk for arrhythmias. Other drugs have tight restrictions regarding initiation and monitoring. Many other drugs with lower risk of proarrhythmia are frequently prescribed without obtaining a baseline ECG. Many of these drugs are prescribed for otherwise healthy people, and preventable deaths in this population are particularly tragic. Policy development and system-based practices to promote medication safety are important but beyond the scope of this chapter.

Secondly, drugs may uncover abnormalities in cardiac conduction. This fact has led to the development of pharmacologic challenge tests to diagnose some conditions. However, the therapeutic implications of a pharmacologically induced arrhythmia are unclear. Implantable cardioverter-defibrillator (ICD) may be considered in patients with pharmacologically uncovered Brugada syndrome (a hereditary sodium channelopathy originally described in 1992 by Pedro and Josep Brugada); ICD implantation is generally not indicated for other medication-induced ventricular arrhythmia. Pacemaker implantation is not recommended for medication-induced bradycardia and atrioventricular (AV) block, because such are considered reversible conditions. However, these bradyarrhythmias may reflect underlying conduction system disease. There are no unique abnormalities on an ECG that prove that a dysrhythmia is medication induced, and so the ECG must be interpreted in the light of the clinical situation. If the dysrhythmias recur after the ostensible culprit medication has been discontinued, additional treatment will be required.

Thirdly, arrhythmias induced by drugs are often an indication of toxicity. Arrhythmias are always an indication for aggressive treatment, and when medication overdoses are suspected, a toxic medication effect should be assumed. Therefore, in addition to describing mechanisms of drug-induced proarrhythmia, this chapter will also discuss briefly the appropriate management of patients with these arrhythmias. These patients often are critically ill, and they are at high risk for sudden deterioration. Care for these patients should be coordinated between cardiologists, intensivists, pharmacists, and toxicologists, in addition to other specialties as needed.

Finally, the development of a medication-related arrhythmia represents a crisis point in the long-term management of patients. The culprit medication may be difficult to positively identify, or may be essential to the ongoing treatment of the patient. Discontinuation of the culprit medication may be easily recommended in theory, but in clinical practice, the patient's condition may require continuation of the medication with adjustment of other drugs and frequent monitoring to safely continue use.

48.2 The Proarrhythmic Potential of Pharmacotherapeutics

While some drugs have characteristic proarrhythmic effects, many classes of medications overlap to varying degrees. Therefore, the subsequent sections will discuss not only the broad spectrum of proarrhythmic effects but also specific types of proarrhythmia. Many drugs have more than one proarrhythmic effect.

48.2.1 Diversity of Proarrhythmic Potential

Many drugs affect the cardiac ion channels and receptors, with the potential to produce a proarrhythmic state. While drugs classified as "antiarrhythmics" also have significant proarrhythmic potential, many other drugs whose primary targets are not the cardiovascular system also have proarrhythmic action. There is significant variety in the proarrhythmic potential of particular drugs. Some drugs are proarrhythmic only at high doses or only if taken with other drugs or only in the context of electrolyte disturbances, while other drugs are potentially proarrhythmic at any dose, in a dose-independent fashion. Some drugs rarely cause arrhythmias, while others commonly do. Additionally, the severity of the arrhythmias ranges from asymptomatic occasional atrial and ventricular premature complexes (APCs and VPCs) to life-threatening polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).

48.2.2 General Mechanisms of Proarrhythmia

The mechanisms of proarrhythmia can be classified based on how they affect the action potential. These mechanisms are illustrated in Fig. 48.1.

- Enhanced automaticity, affecting phase 4 (supraventricular tachycardias, atrial fibrillation, APCs, VPCs, and ventricular arrhythmias)
- Suppressed automaticity, affecting phase 4 (bradyarrhythmias)
- Blocked or slowed conduction in phase 0 (bradyarrhythmias and tachyarrhythmias with widening of the QRS)
- Changes in depolarization and repolarization between the epicardium and endocardium causing arrhythmias in phase 2 (Brugada syndrome)

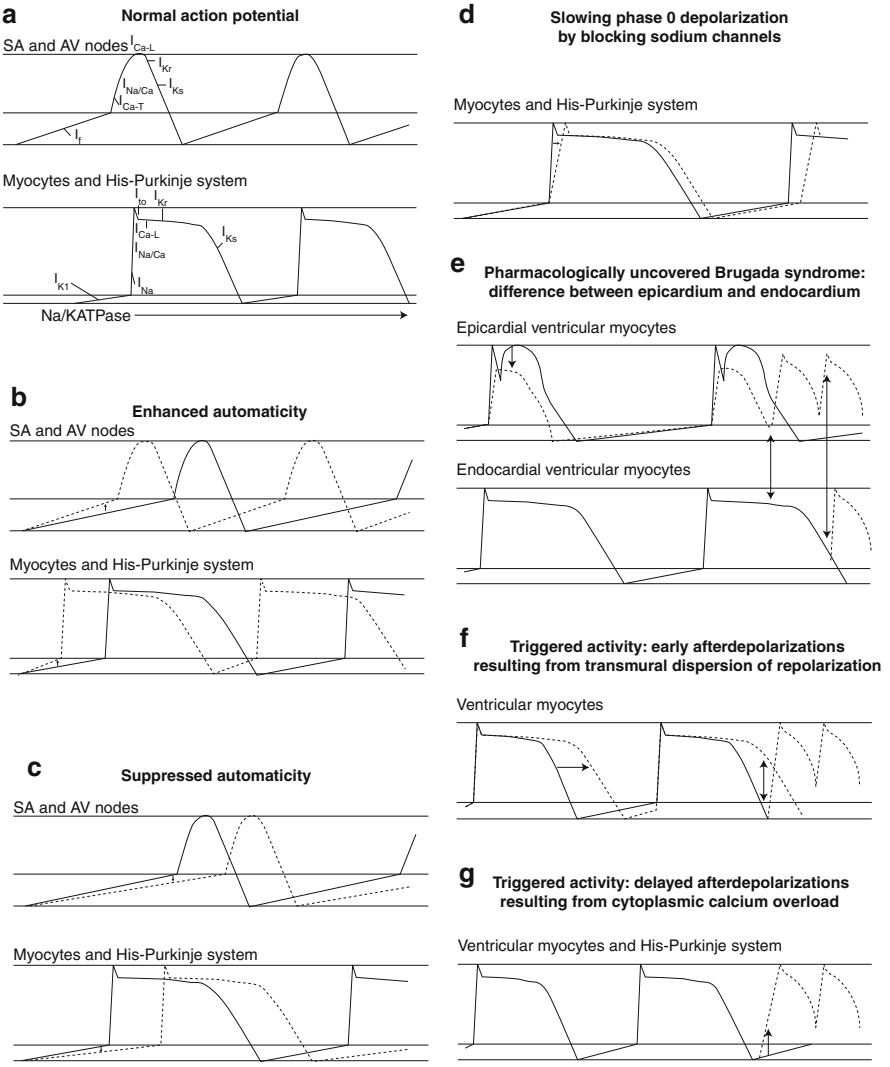

Fig. 48.1 Mechanisms of proarrhythmia in comparison with normal cardiac action potentials illustrated, with alterations in the cardiac action potential noted by a dotted line. (**a**) Normal cardiac action potential, with the primary contributing ion currents noted; (**b**) enhanced automaticity predominantly decreases the duration of phase 4; (**c**) suppressed automaticity prolongs phase 4; (**d**) sodium channel blockade slows phase 0 depolarization and thus slows conduction rate; (**e**) pharmacologically uncovered Brugada syndrome involves a difference in depolarization and repolarization characteristics between the epicardium and endocardium, leading to spontaneous depolarizations during phase 2; (**f**) transmural dispersion of repolarization manifesting on the ECG as QT prolongation can lead to early afterdepolarizations during phase 3 and torsade de pointes; (**g**) calcium overload in the cytosol, predominantly as a result of digoxin toxicity, leads to spontaneous depolarizations during phase 4. Abbreviations: $I_{Ca\text{-}L}$ L-type calcium channel current, $I_{Ca\text{-}T}$ T-type calcium channel current, I_f hyperpolarizing sodium current, I_{K1} inward rectifier potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Na} fast inward sodium current, I_{to} transient outward potassium current, I_{K1} inward rectifier potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Na} fast inward sodium current, $I_{Na/Ca}$ sodium/calcium exchanger, I_{to} transient outward potassium current, *Na/K ATPase* sodium/potassium adenosine triphosphatase

- Altered repolarization, resulting in transmural dispersion of repolarization in phase 3 triggering early afterdepolarizations (prolonged QTc, torsade des pointes, and VF) (Chap. 49)
- Altered calcium cycling resulting in intracellular calcium overload, triggering delayed afterdepolarizations in phase 4 (atrial fibrillation, ventricular arrhythmias, and digoxin-specific arrhythmias)

48.3 Specific Proarrhythmic Mechanisms Illustrated

48.3.1 Enhanced Automaticity

Automaticity may be enhanced by increased sympathetic stimulation or parasympathetic withdrawal. This can allow an ectopic focus to become the dominant source of the heart rhythm. The result is sinus tachycardia if the sinoatrial (SA) node is stimulated the most; atrial tachycardia or premature atrial contractions if atrial tissue is affected more; accelerated junctional rhythm if the atrioventricular (AV) node's rate of excitability exceeds the sinoatrial node rate; and ventricular tachycardia, premature ventricular contractions, or accelerated idioventricular rhythm if the ventricle is the predominant site of enhanced automaticity.

Because of the complex regulatory mechanisms affecting heart rate and contractility, there are multiple ways that drugs can increase automaticity by acting through β-adrenergic receptors, L-type calcium channels, cyclic adenosine monophosphate (cAMP), sodium channels, potassium channels, and adenosine receptors. Cytosol calcium concentration is vitally related to sinus node rate, myocardial contractility, and excitability. The cytosolic and extracellular calcium concentrations are modulated through the sodium/calcium exchanger and the sodium/potassium ATPase. Cytosolic calcium is also cycled between the sarcoplasmic reticulum via the ryanodine receptor, and this is modulated by calmodulin, calsequestrin, and the sarcoplasmic reticulum energy-requiring calcium pump (SERCA) (Chap. 4). The cytosolic phosphorylation and activation of these calcium-cycling proteins not only is regulated by cAMP (generated by the G-protein coupled β-adrenergic receptor) but also by the phosphatidylinositol 3-kinase pathway activated by insulin.

Because of the complexity of the pathways involved, many different types of drugs have a similar impact in contractility. Sympathomimetics increase intracellular cAMP by activating the G_s-coupled beta adrenergic receptor (Chap. 5). Milrinone as a phosphodiesterase inhibitor prevents the breakdown of cAMP. Calcium and digoxin both increase calcium in the cytosol, increasing both contractility and the potential for excitability. Methylxanthines such as caffeine inactivate the inhibitory effect of adenosine on the adenosine-sensitive potassium channels (I_{Kado}) in the atria and the adenosine A1 receptors that are also coupled to cAMP. Atropine counteracts the inhibitory effect of the parasympathetic nervous system by blocking muscarinic M2 receptors.

Most arrhythmias that result from these drugs are benign and self-limited. These include sinus tachycardias and atrial tachycardias, common in patients with pulmonary diseases not only on account of the interrelation between the heart and lungs but also because of the frequent requirement for beta-agonists and methylxanthines

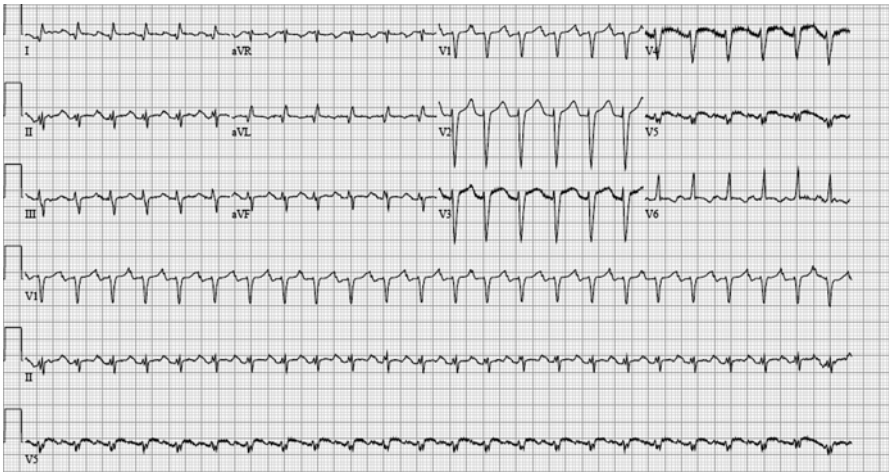

Fig. 48.2 A 60-year-old man with no prior history of arrhythmias, admitted with acute decompensated heart failure, was initiated on a beta-agonist, dobutamine. Although his hemodynamics improved, he had frequent PACs which stimulated runs of a narrow-complex tachycardia that terminated with adenosine. These episodes subsided with discontinuation of the beta-agonist

[3, 4]. Right ventricular outflow tract ventricular tachycardia is triggered by catecholamines and cAMP and may also occur in response to beta agonists.

To counteract the effects of these drugs, particularly in overdose situations, it is more effective to address the dysrhythmias by inhibiting a different part of the regulatory cycle than the one currently affected by the medication. Therefore, in tachycardias from beta-agonists, non-dihydropyridine calcium channel blockers are useful, as well as adenosine for acute dysrhythmias. The dihydropyridine calcium channel blockers act primarily peripherally resulting in a reflex sympathetic activation that counteracts any inhibition of cardiac cells; therefore, dihydropyridine calcium channel blockers would not be useful in patients with excessive sympathetic stimulation [5]. Beta-blockers are helpful in treating tachycardias resulting from thyroid hormone derivatives and methylxanthine overdose, but in cocaine intoxication, they can cause hypertensive crisis by leaving the patient with unopposed alpha receptor activation. Cocaine and other sympathomimetics that act centrally as well as peripherally are best initially treated with centrally acting drugs such as benzodiazepines. Peripherally acting sympathomimetics such as dopamine and dobutamine are short acting, but since they are typically used in hemodynamically compromised patients, it is often necessary to continue these drugs and use amiodarone to suppress arrhythmias. Enhanced automaticity is illustrated in Figs. 48.2 and 48.3.

48.3.2 Suppressed Automaticity

In patients receiving beta-adrenergic antagonists (class II antiarrhythmics) or calcium channel blockers (class IV antiarrhythmics), the calcium current causing the slow action potential is suppressed in the sinoatrial and atrioventricular nodes.

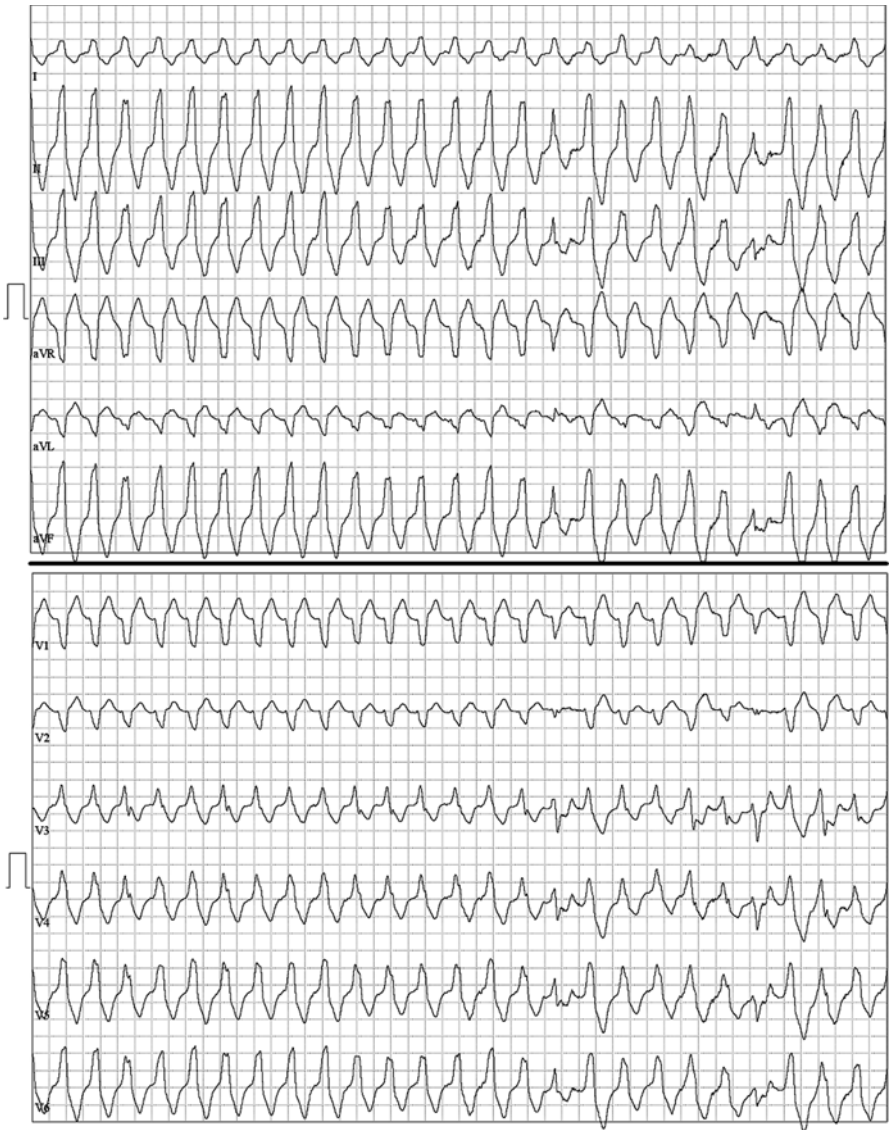

Fig. 48.3 A 59-year-old man with no prior history of arrhythmias presented for preoperative stress testing. During treadmill stress testing, he developed frequent ectopy and monomorphic ventricular tachycardia, thought to be an outflow tract ventricular tachycardia. The tachycardia has features of a catecholamine-driven ventricular tachycardia that was entirely suppressed by beta-blockade

Patients receiving high doses of these drugs frequently demonstrate sinus bradycardia or AV blocks, most commonly first-degree or second-degree Mobitz type 1 [6]. Automaticity may also be suppressed by increasing parasympathetic tone, such as with reversible acetylcholinesterase inhibitors such as donepezil and galantamine, which are commonly found to cause bradycardia (Chap. 6). Clonidine centrally inhibits the sympathetic nervous system and increases the parasympathetic tone as

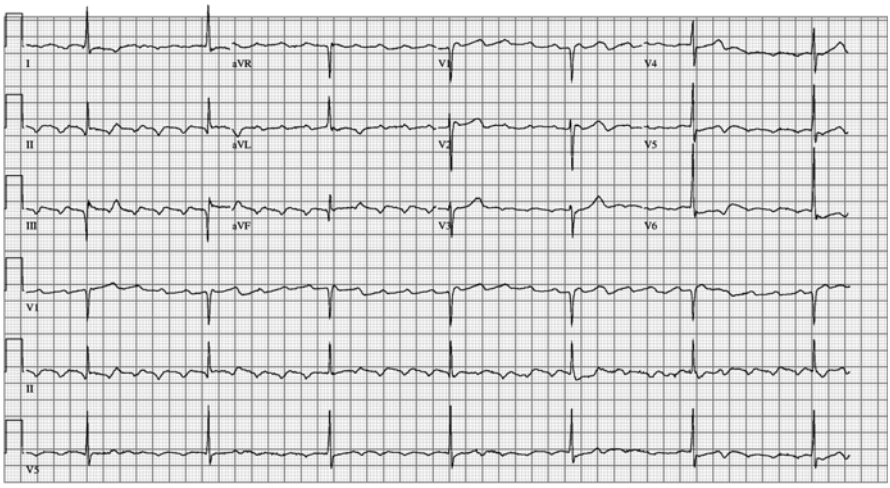

Fig. 48.4 An 80-year-old man with chronic atrial flutter accidentally took two diltiazem extended release tablets instead of his usual single 360-mg daily tablet. He was admitted with lightheadedness and atrial flutter with a ventricular rate of 30–40 beats per minute. His symptoms and bradycardia resolved with treatment with calcium, time, and bed rest

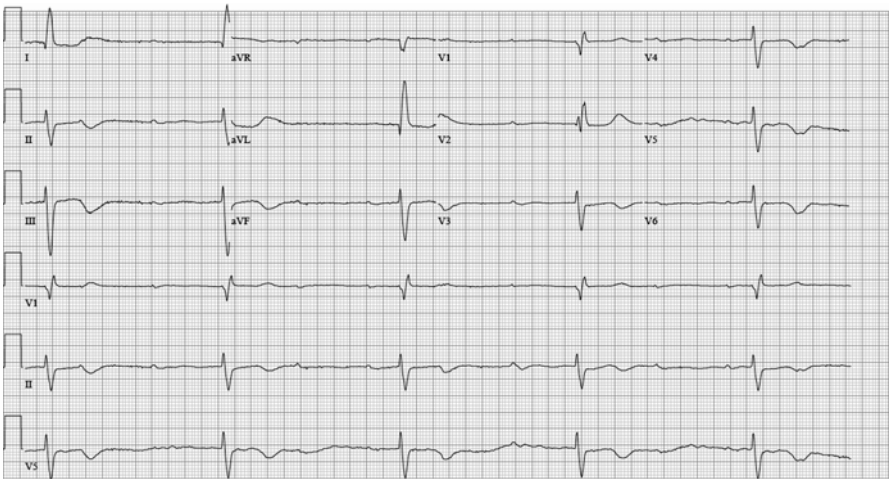

Fig. 48.5 An 82-year-old patient developed acute renal insufficiency while continuing her maintenance atenolol. She had symptomatic bradycardia with hypotension that responded to boluses of glucagon. She ultimately required dual-chamber permanent pacemaker placement as she continued to have intermittent AV block

an alpha-2 agonist and is also associated with bradyarrhythmias (Chap. 39). Figures 48.4 and 48.5 demonstrate a pharmacologic suppression of automaticity.

Arrhythmias increase in severity as the amount of calcium channel blocker or beta-blocker ingested increases. An investigation of poison control records

demonstrated that unintentional ingestion of small doses of additional medication is frequently asymptomatic [7]. Most asymptomatic patients can be managed as an outpatient if they are not markedly bradycardic. Patients that ingest more than one cardiac drug have the greatest risk of morbidity and mortality from beta-blocker overdose [8]. Calcium channel blocker and beta-blocker overdose together are particularly problematic, because not only do they profoundly slow the heart rate, they also can profoundly suppress contractility, causing cardiogenic shock. Both aspects must be aggressively addressed to effectively treat calcium channel blocker or beta-blocker overdose. Temporary pacing alone does not improve contractility. Therefore, pharmacologic intervention to counteract the effect of the calcium channel blocker or beta-blocker is required.

Calcium infusion is a logical treatment for calcium channel blocker overdose that also benefits patients who overdose on beta-blockers. Interestingly, it leads to improvements only in the mechanical contractility and not the electrical abnormalities [9]. Glucagon is a hormone secreted by the pancreas to stimulate gluconeogenesis in times of hypoglycemia; it acts through a different receptor coupled to the G_s protein that activates protein kinase A to increase cAMP in the cells independent of the beta-adrenergic receptor. It is effective for calcium channel blocker and beta-blocker overdose, and a clinical effect is rapidly seen with its use. It primarily results in an increased heart rate and increased cardiac output and has little effect on blood pressure. It frequently causes GI distress, however, and tachyphylaxis prevents its long-term use. There have been no randomized studies of glucagon use in humans [10].

As noted above, calcium cycling in the cardiac myocytes is also regulated by phosphatidylinositol-3 kinase, which is activated by insulin and insulin-like growth factor. Using this pathway, insulin is an effective treatment for cardiogenic shock from calcium channel blocker and beta-blocker overdose. Insulin is not proarrhythmic and can allow rapid weaning of pressors by reversing the cardiogenic shock caused by the drugs [11]. Insulin is administered with sufficient glucose to prevent hypoglycemia and potassium to prevent hypokalemia and thus is called a "hyperinsulinemia/euglycemia" protocol [12]. Additionally, insulin and glucose ensure that nutrients are supplied to the myocardium. Hyperinsulinemia/euglycemia treatment is not associated with tachyphylaxis like glucagon is, and as long as patients are closely monitored, it is associated with a low risk of adverse effects [12]. Studies in pig models of beta-blocker toxicity actually show significantly better response with better survival when treated with hyperinsulinemia/euglycemia therapy compared to vasopressors such as epinephrine and vasopressin [13]. Clinically, calcium channel blocker and beta-blocker toxicity range from patients taking normal doses of their prescribed medication who develop some interfering disturbance, such as a patient on atenolol who develops renal failure, to massive ingestions as suicidal attempts. Specific therapy with calcium, glucagon, or hyperinsulinemia/euglycemia is required only if patients develop cardiogenic shock. In medically refractory cases of shock, mechanical hemodynamic support may be required. Figures 48.4 and 48.5 demonstrate significant changes in rhythm precipitated by small changes in medication dose (Fig. 48.4) or renal clearance (Fig. 48.5).

48.3.3 Slowing of Phase 0 Depolarization

The primary effect of sodium channel blockers is to slow the initial phase 0 depolarization of the cardiomyocyte. Because these fast sodium channels are not present in the sinoatrial node and atrioventricular node, these drugs have minimal effect on the sinus rate. By slowing phase 0, each myocyte takes longer to depolarize. At high levels of sodium channel blockade, the QRS on the surface ECG can prolong noticeably. Sodium channel blockers, particularly those in Vaughan Williams classes IA (quinidine, procainamide, and disopyramide) and IC (flecainide and propafenone), are felt to be toxic if the patient's QRS width has increased by >25 %. However, these drugs are proarrhythmic at any dose and should be used with caution. For example, patients on quinidine for atrial fibrillation had a higher mortality than patients with atrial fibrillation who did not take quinidine, without any notable QRS widening [14]. Additionally, class IC antiarrhythmics were associated with increased mortality in patients with prior myocardial infarction in the Cardiac Arrhythmia Suppression Trials, despite monitoring for drug toxicity [15–17].

Class IA and class IC antiarrhythmics bind to sodium channels in their active state. The more frequently the sodium channels are in their active state, the more effect the antiarrhythmic has on the channels. This property is called the use dependence phenomenon. Consequently, at faster heart rates, the antiarrhythmic will have more effect, and the QRS will be wider. Thus, sometimes, exercise ECGs can be performed to monitor for excessive sodium channel blocker effect, to evaluate prolongation of the QRS with faster heart rates. Use dependence is illustrated in Fig. 48.6. Because of extreme QRS widening from use dependence, differentiating ventricular tachycardia from supraventricular tachycardia with aberrant conduction may be difficult, if not impossible, in sodium channel blocker toxicity states, as shown in Fig. 48.7. The algorithms used to differentiate ventricular tachycardia from supraventricular tachycardia on surface ECG were all developed with patients who were on potentially confounding antiarrhythmics excluded. Therefore, there is no validated approach in these patients to diagnose VT.

The safest approach is to assume that whatever the rhythm is, in the setting of antiarrhythmic toxicity, it is potentially more unstable than it would be otherwise. Therefore, even in hemodynamically stable patients, urgent sedation followed by synchronized direct current cardioversion is the treatment of choice. Beta-blockade will help with preventing tachycardia and blocking catecholamines, preventing to a large degree the recurrence of proarrhythmia [18]. Theoretically, a different sodium channel blocker, lidocaine, could be used for VT in this situation, but it is preferential to avoid having multiple concurrent antiarrhythmics if possible, to minimize proarrhythmia. Intravenous sodium bicarbonate is useful in overcoming the sodium blockade both by raising the sodium concentration slightly and raising the pH slightly to reduce the sodium channel blocker's affinity for the sodium channel. Sodium bicarbonate actually prolongs urinary excretion of sodium channel blockers such as flecainide, but in toxicity situations, it is more important to disrupt the affinity between the flecainide and the sodium channel than to expedite its excretion from the body. A similar strategy is used in treating tricyclic antidepressant toxicity.

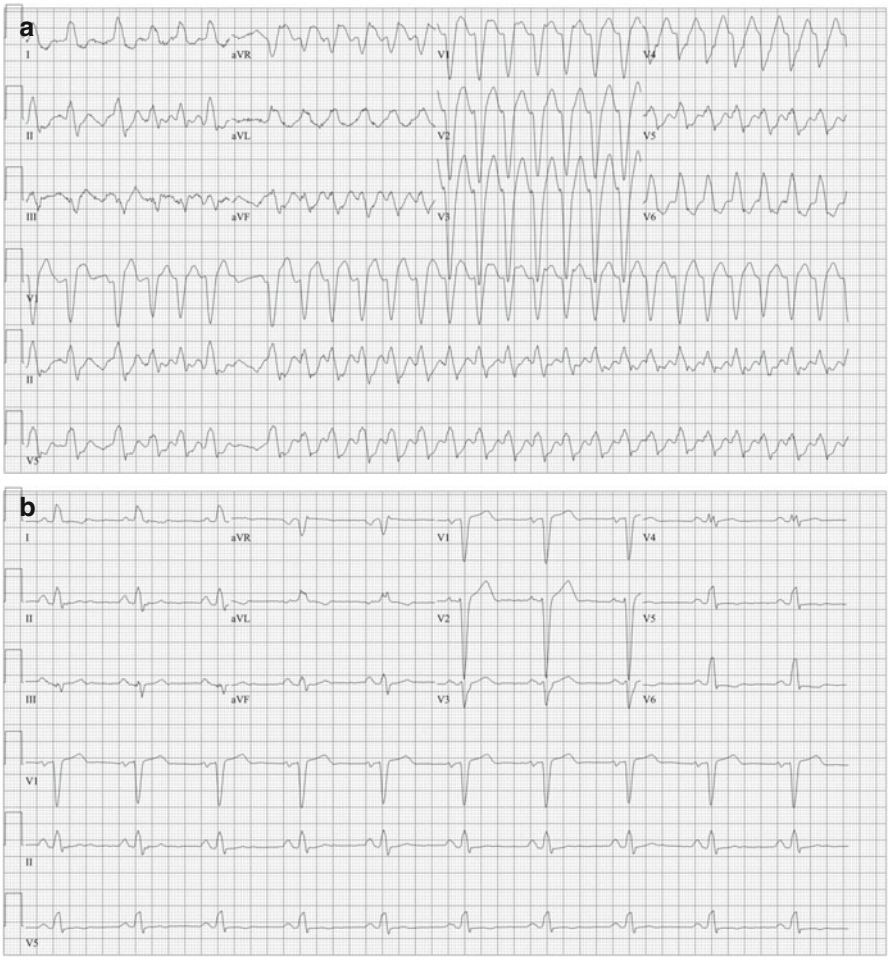

Fig. 48.6 A 78-year-old woman with atrial fibrillation and atrial flutter treated with flecainide and metoprolol presented with palpitations and a wide-complex irregular tachycardia (**a**). She underwent cardioversion as her underlying rhythm was determined to be atrial flutter with rapid, variable ventricular conduction. With a slower heart rate, her QRS became significantly narrower (**b**)

48.3.4 Atrial Flutter with 1:1 Conduction

Atrial fibrillation and atrial flutter are frequently alternating arrhythmias within the same patient (see also Chap. 50). Patients with atrial flutter have a >50 % risk of developing atrial fibrillation in 10 years [19], and patients with atrial fibrillation have a 30 % chance of developing atrial flutter. The development of atrial flutter becomes increasingly likely with treatment with a sodium channel blocker, which can organize the atrial arrhythmia into a macroreentrant circuit. Furthermore, the sodium channel blockade slows down the flutter cycle length from the typical

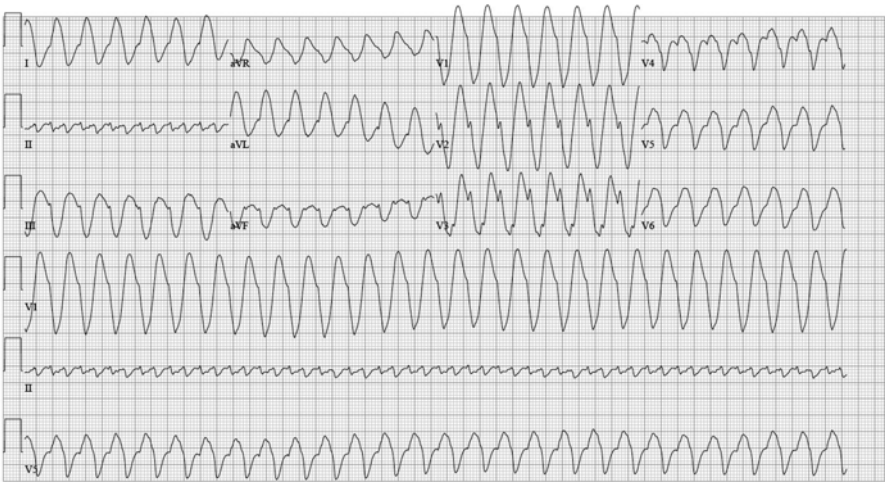

Fig. 48.7 Rapid tachyarrhythmias combined with the use dependency of flecainide can cause arrhythmias that are very difficult to differentiate between a supraventricular tachycardia with aberrancy and ventricular tachycardia. A 64-year-old man with paroxysmal atrial fibrillation treated with "pill-in-the-pocket" flecainide presented with chest pain and hemodynamic instability. He later reported that he took flecainide "whenever he felt bad" and had taken a total of 30 50-mg flecainide tablets over 4 days. His initial ECG meets published criteria for VT, particularly with regard to the width of the QRS complex; however, published criteria exclude QRS widening due to antiarrhythmic drugs. Lead II resembles typical atrial flutter, and it is impossible to differentiate with certainty whether this arrhythmia is ventricular tachycardia or 2:1 atrial flutter with marked QRS widening due to the use dependence phenomenon characterizing flecainide. He was cardioverted and treated with intravenous sodium bicarbonate. The following day, his QRS width had normalized

200–250 ms of typical flutter to a cycle length of 250–300 ms. Without the effects of antiarrhythmic therapy, the AV node only rarely can conduct atrial flutter faster than a 2:1 atrioventricular ratio. With sodium channel blockade, atrial flutter at slower atrial cycle length can conduct at a 1:1 ratio. This paradoxically increases the ventricular rate in patients with atrial flutter on sodium channel blockers, to the point of impending hemodynamic collapse.

One study of eight patients with 1:1 atrial flutter noted that the cycle length conducted 1:1 during flutter was significantly shorter than the shortest cycle length achievable when pacing patients during electrophysiology study [20]. This finding indicates that enhanced conduction across the AV node, most likely caused by sympathetic stimulation with catecholamines, enhances the conduction across the AV node. Despite its acute presentation, patients who develop 1:1 atrial flutter do not have a significantly worse prognosis compared to patients who do not develop this arrhythmia [21]. Therefore, sodium channel blockers should be combined with a chronic AV node-blocking medication such as a beta-blocker, diltiazem, verapamil, or digoxin. Despite this practice, 1:1 atrial flutter sometimes does occur in the setting of chronic therapy with AV node-blocking drugs. Because 1:1 atrial flutter can

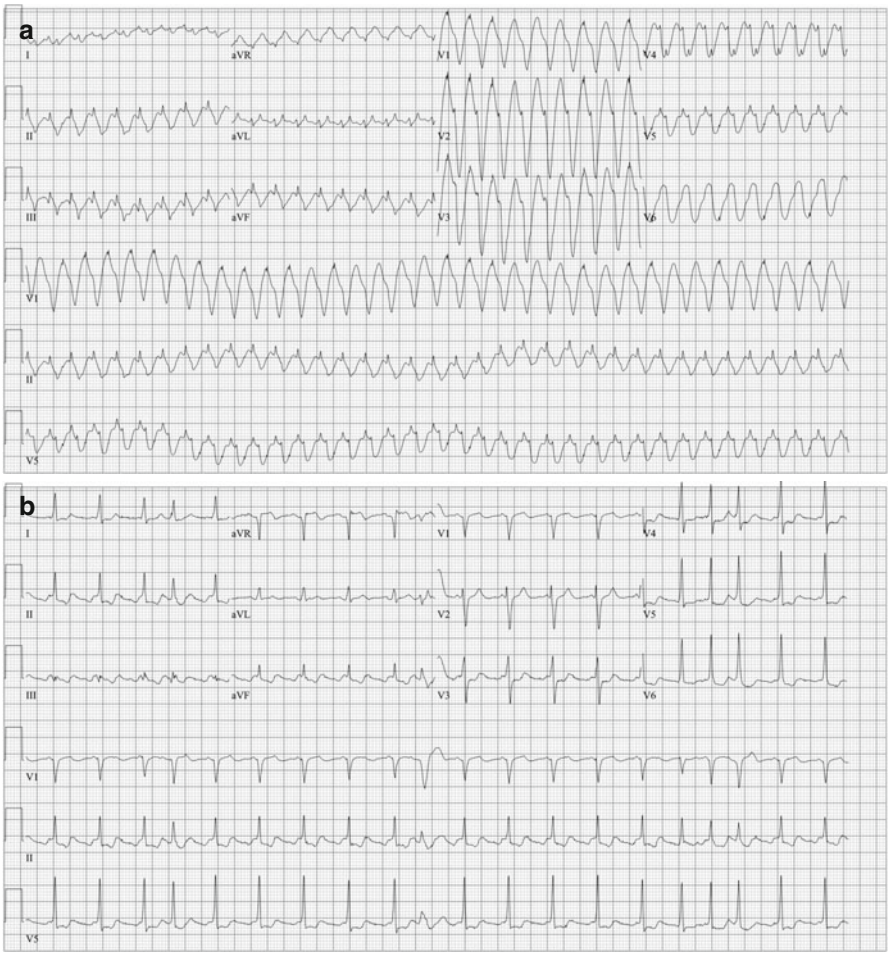

Fig. 48.8 A 60-year-old female with a history of atrial flutter was started on chronic metoprolol and "pill-in-the-pocket" flecainide. A subsequent physician discontinued the chronic metoprolol due to side effects. Later, when her palpitations recurred, she took flecainide without the metoprolol. Since she felt worse, she presented to the emergency department, where the following ECGs were obtained within 2 min of each other. Between ECG (**a**) and ECG (**b**), all the patient received was a single dose of benzodiazepine for sedation in preparation for cardioversion. Note that the R–R interval in ECG (**a**) is exactly the same as the flutter cycle length in ECG, 270 ms (**b**), proving that the wide complex tachycardia on ECG (**a**) is indeed atrial flutter with 1:1 atrioventricular conduction

occur at any dose of sodium channel-blocking medication, it does not definitively represent toxicity. It should be treated with AV node-blocking agents and synchronized cardioversion if the rhythm persists. Ultimately, atrial flutter ablation is indicated as a highly effective treatment for atrial flutter. Atrial flutter with 1:1 atrioventricular conduction is illustrated in Fig. 48.8.

Table 48.1 Drugs that can cause drug-induced Brugada pattern are organized by pharmacologic category [22]

Medication class	Examples
Antiarrhythmics, class IA	Procainamide, disopyramide, cibenzoline
Antiarrhythmics, class IC	Flecainide, propafenone, ajmaline, pilsicainide
Other antiarrhythmics	Amiodarone, propranolol, lidocaine
Anticonvulsants	Phenytoin, oxcarbazepine, carbamazepine, lamotrigine
Antidepressants	Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine, fluoxetine, fluvoxamine, maprotiline
Antipsychotics	Thioridazine, perphenazine, trifluoperazine, loxapine
Anesthetics	Bupivacaine, procaine, propofol, ketamine
Others	Lithium, acetylcholine, ethanol, cocaine, ergonovine, cannabis, tramadol

48.3.5 Drug-Induced Brugada Syndrome

The SCN5A sodium channel is defective in Brugada syndrome, a genetic condition that confers an increased risk of sudden cardiac death. The ECG in a patient with Brugada syndrome may have a normal ECG at baseline, and the pattern can be brought out by administering a sodium channel blocker (Fig. 48.9). Arrhythmias occur when abnormal depolarization and repolarization of the epicardium develop, allowing spontaneous depolarization of the epicardium during phase 2 of the cardiac cycle, sometimes called phase 2 reentry [22]. In fact, patients with a pharmacologically inducible Brugada type 1 pattern on their ECG are at a higher risk of ventricular arrhythmias [23]. ICD implantation is indicated in any patient with syncope, ventricular arrhythmias, or aborted cardiac arrest who has a pharmacologically inducible Brugada type 1 pattern on ECG (Chap. 53). On the other hand, a patient with a pharmacologically induced Brugada type 1 pattern with no symptoms concerning for malignant arrhythmias may be at an increased risk of ventricular arrhythmias [24], but management and risk stratification in this patient population is controversial. The management of a patient with an incidental finding of a Brugada pattern ECG in the context of sodium channel-blocking drugs predominantly involves discontinuation of the sodium channel blocker and education of the patient to avoid similar drugs (see www.brugadadrugs.org) [25, 26]. These drugs are listed in Table 48.1. The management of patients with electrical storm who have a medication-induced Brugada pattern is similar to those with Brugada syndrome [27].

48.3.6 QT Prolongation and Torsade de Pointes

Potassium channel blockers prolong phase 3 of cardiac repolarization primarily by affecting the rapid delayed internal rectifying potassium current (I_{Kr}). This current is mediated by the KCNH2 potassium channel encoded by the human ether-à-go-go-related gene. In addition to the Vaughan Williams class III antiarrhythmics,

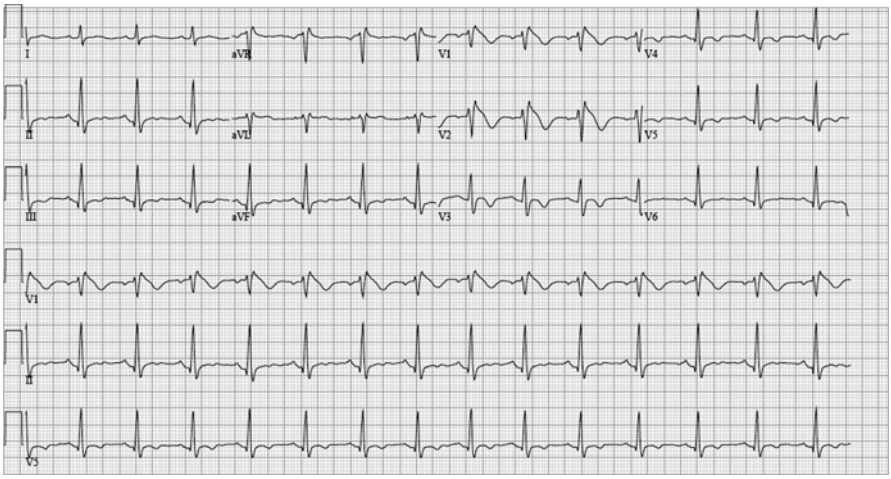

Fig. 48.9 A 44-year-old female with a history of bipolar disorder and post-traumatic stress disorder had been started on amitriptyline, bupropion, and lithium over the course of 18 months. She had a normal ECG prior to starting these drugs. She then presented with palpitations, and her ECG demonstrates a type I Brugada pattern, with coved ST segment elevation in leads V1 and V2, most likely related to the combination of amitriptyline and lithium, requiring these drugs to be discontinued

many other drugs affect this channel, prolonging repolarization. An updated list of these drugs is available on www.crediblemeds.org [26, 28]. These drugs prolong the action potential duration, which is measured as the QT interval. The drugs that prolong the QTc are listed in Table 48.2 (also see Chap. 49).

Because of the lusitropic response to sympathetic stimulation, the QT interval should decrease with an increase in heart rate. Numerous formulas have been developed to calculate a corrected QT interval (QTc), but none has proven superiority [29]. Current computerized ECG analysis programs use more complex linear regression functions. In patients with a prolonged QRS duration, the JT interval can be measured to more precisely measure the duration of repolarization; the JT interval comprises only the ST segment and the T wave duration [30]. Whether QT prolongation is secondary to gene mutations in ion channels affecting repolarization in long QT syndrome, or secondary to medication effects, there is a small but significant risk of torsade de pointes and VF. Torsade de pointes ("twisting around points") is a polymorphic VT of a fluctuating cycle length with a QTc >450 ms [31].

Proarrhythmia among the class III antiarrhythmics is heterogeneous. All class III antiarrhythmics prolong the QTc. Amiodarone rarely causes torsade de pointes despite marked prolongation of the QTc [32, 33], whereas dofetilide causes a dose-dependent increase in both the QTc and the risk of torsade de pointes [32, 34]. Torsade de pointes is initiated by an alternating long-short cycle sequence that likely exacerbates the transmural dispersion of repolarization [31]. Thus, portions of the myocardium depolarize with a VPC at the same time that other portions are still repolarizing. In addition to the effects of drugs, torsade de pointes frequently occurs

Table 48.2 Drugs that can prolong the QT interval are organized by pharmacologic category [25]

Medication class	Examples
Antiarrhythmic, class IA	Quinidine, procainamide, disopyramide
Antiarrhythmic, class III	Amiodarone, dronedarone, dofetilide, ibutilide, sotalol
Antiarrhythmic, other	Flecainide
Adrenergic agonists	Albuterol, levalbuterol, arformoterol, formoterol, isoproterenol, metaproterenol, salmeterol, terbutaline, ephedrine, pseudoephedrine, norepinephrine, epinephrine, phenylephrine, amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methamphetamine, methylphenidate, apomorphine, dopamine, dobutamine, cocaine, midodrine
Anesthetics and sedatives	Sevoflurane, chloral hydrate, dexmedetomidine
Antianginal	Ranolazine, bepridil, ivabradine
Antibiotic (fluoroquinolone)	Ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
Antibiotic (macrolide)	Erythromycin, clarithromycin, azithromycin, telithromycin
Antibiotic (other)	Metronidazole, trimethoprim-sulfamethoxazole, pentamidine, telavancin, bedaquiline
Anticonvulsant	Fosphenytoin, felbamate
Antidepressant	Trazodone, venlafazine, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, atomoxetine, amoxapine, mirtazapine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine
Antiemetic	Ondansetron, granisetron, dolasetron, domperidone, promethazine
Antifungal	Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
Antihistamine	Diphenhydramine, cisapride, famotidine
Antihypertensive	Isradipine, moexipril, hydroclorothiazide, furosemide, indapamide, nicardipine
Antimalarial	Chloroquine, quinine sulfate, halofantrine, dihydroartemisinin/piperaquine
Antineoplastic	Arsenic trioxide, anagrelide, bortezomib, bosutinib, crizotinib, dabrafenib, dasatinib, eribulin, lapatinib, pazopanib, nilotinib, sorafenib, sunitib, tamoxifen, vandetanib, vemurafenib, vorinostat
Antipsychotic	Haloperidol, pimozide, thioridazine, chlorpromazine, droperidol, amisulpride, aripiprazole, clozapine, iloperidone, olanzapine, paliperidone, quetiabine, risperidone, ziprazidone
Antispasmotic	Tizanidine, tolterodine, solifenacin
Antiviral	Amantadine, atazanavir, foscarnet, nelfinavir, rilpivirine, ritonavir, saquinavir, telaprevir
Appetite suppressant	Phentermine, fenfluramine, phenlpropanolamine, sibutramine
Men's health	Alfuzosin, vardenafil
Neurodegenerative disease agents	Galantamine, apomorphine, amantidine, tetrabenazine
Women's health	Mifepristone, oxytocin, toremifene, tamoxifen
Others	Tacrolimus, perflutren, pasireotide, fingolimod

in association with electrolyte abnormalities, notably, hypomagnesemia and hypokalemia. Torsade de pointes is more common in females than males [35], but pharmacogenomic investigations have been unable to identify any significant genetic predictors of this arrhythmia [36]. The high risk of torsade de pointes while initiating dofetilide has been mitigated successfully by the requirement of inpatient admission and prescriber safety training [34, 37]. Torsade de pointes in the setting of multiple interacting drugs is illustrated in Fig. 48.10.

Torsade de pointes is a frequent cause of drug discontinuation and withdrawal from the market [33], and two recent studies have quantified this risk with atypical antipsychotics (incidence rate ratio of 1.99, CI 1.68–2.34) [38] and the antibiotic azithromycin (hazard ratio 2.88, CI 1.79–4.63) [39]. Torsade de pointes can occur at therapeutic dose levels of most drugs listed in Table 48.2. Discontinuation of the culprit medication(s) as well as repletion of potassium and magnesium is required. The most effective treatment for torsade de pointes is pacing at a rate sufficient to suppress VPCs. This prevents the long-short initiating sequence from causing recurrent torsade de pointes [31]. Isoproterenol to increase the underlying heart rate may be effective, but it is not as effective as pacing.

48.3.7 Digoxin Toxicity

Digoxin, a drug frequently used for heart failure and rate control in atrial fibrillation, is notorious for causing arrhythmias related to calcium loading of the myocytes and thus is associated with its own unique ECG pattern. By inhibiting the sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) enzyme, digoxin increases the sodium gradient across the cell membrane, making the sodium/calcium exchanger more active. This shifts more calcium into the cytosol, creating the potential for calcium to trigger spontaneous depolarizations after the cell membrane has completely repolarized, called delayed afterdepolarizations. Extreme digoxin toxicity is also associated with hyperkalemia as potassium is not transported intracellularly. The hallmark is that atrial and ventricular myocytes will be increasingly excitable, because of increased calcium loading in the cytosol that makes cardiac myocytes more easily depolarized. Despite that increase in excitability, there is inhibition of the AV node because of the significant enhancement of vagal tone because digoxin enhances vagal release of acetylcholine. Thus, many different arrhythmias are possible in digoxin toxicity such as paroxysmal atrial tachycardias, bradyarrhythmias related to AV node block, and ventricular tachyarrhythmias including bidirectional VT, which is particularly specific for digoxin toxicity or another calcium overload condition, catecholaminergic polymorphic ventricular tachycardia. Digoxin also frequently causes repolarization abnormalities manifesting as a diffuse sloped ST segment that is likely related to alterations in the membrane potential during the plateau phase due to excessive extracellular potassium [40].

Digoxin overdoses and toxicities are treated with a monoclonal antibody. Figure 48.11 demonstrates a patient who ingested leaves containing an alkaloid

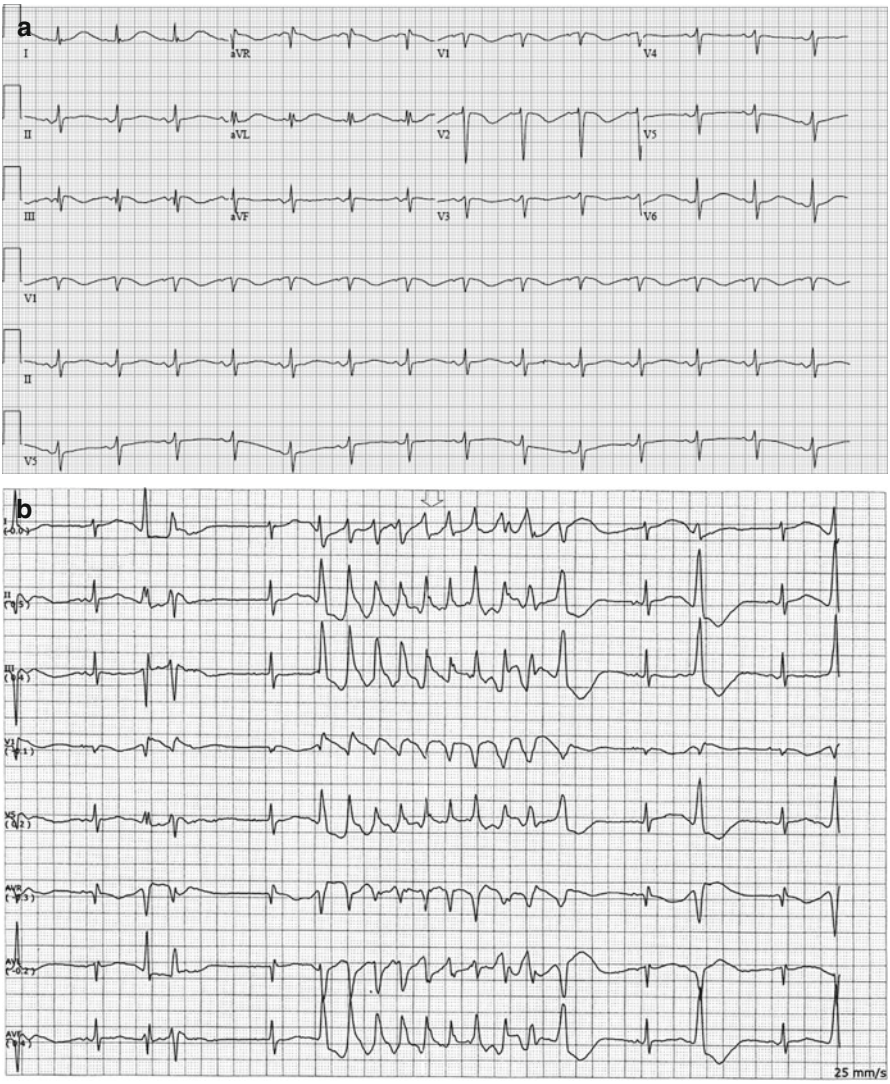

Fig. 48.10 An 80-year-old female with a prior stroke was admitted with dyspnea. Due to nausea and worsening pulmonary infiltrates, she was treated with levofloxacin for pneumonia and ondansetron for nausea in addition to her usual 60 mg of fluoxetine. Additionally, her serum potassium dropped to 3.4 mmol/dL. Likely, as a combination of these factors, her QT prolonged to 660 ms (upper limit of normal for females is 460 ms) (**a**). Later, she developed runs of polymorphic ventricular tachycardia consistent with torsade de pointes that were fortunately non-sustained (**b**). Her QTc markedly decreased with potassium and magnesium administration and discontinuation of her levofloxacin

resembling digoxin. That patient had a markedly positive digoxin level and was successfully treated with digoxin-specific antigen-binding fragments (Fab) of a digoxin-specific antibody. Of note, the total digoxin levels are unreliable in patients

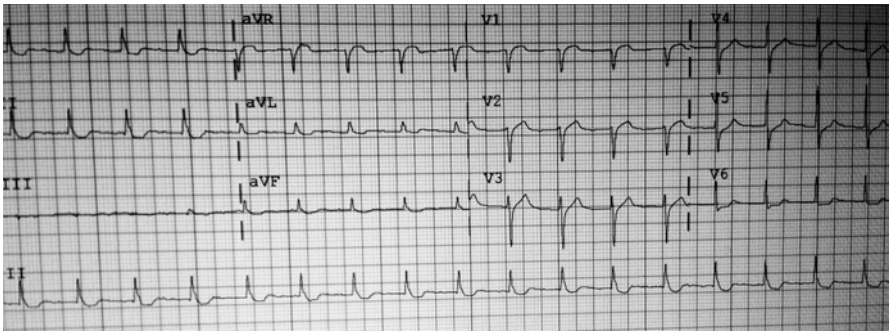

Fig. 48.11 A patient ingested oleander leaves in an attempt to commit suicide. These leaves contain a potent cardiac glycoside similar to digoxin with similar ECG manifestations [46]. This patient responded to treatment with digoxin-specific antigen-binding fragments (Fab)

receiving digoxin-specific Fab; the dose should be calculated based on the initial ingestion or the initial serum level [41].

Digoxin-specific Fab is absolutely required to treat any digoxin toxicity-provoked arrhythmia, a serum digoxin concentration >10 ng/mL, and an acute ingestion of 10 mg or more in an adult [42]. It is also required in any ingestion of a plant such as oleander that contains a toxin similar to digoxin [43]. Elevated digoxin levels in the setting of hyperkalemia are particularly dangerous, and digoxin-specific Fab is also indicated in this situation. Renal impairment reduces the excretion of digoxin, and so digoxin-specific Fab is also useful in this case. A cost-benefit analysis showed that treatment with digoxin-specific Fab is cost-effective for patients with a digoxin concentration >3.5 ng/mL and a creatinine clearance >21 mg/min [44]. Magnesium and potassium repletion are also important, even if serum values are normal [45]. An example of an intoxication requiring treatment with digoxin-specific Fab is shown in Fig. 48.11.

48.4 Other Conditions

48.4.1 Reentry Tachyarrhythmias

By themselves, drugs cannot cause a reentry tachycardia. However, many people have the potential to develop a reentry tachycardia without having a structurally abnormal heart. For example, cavotricuspid isthmus-dependent atrial flutter can occur without requiring any underlying pathology. Also, approximately half of people presenting with supraventricular tachycardia are found to have dual AV node physiology, most of whom have no structural cardiac abnormality. Therefore, by enhancing the automaticity of the atrium, a medication could cause APCs that then would precipitate these reentry tachycardias along existing substrates. Additionally, people with previously unknown accessory pathways may develop accessory pathway-mediated arrhythmias as an unintended consequence of drugs interfering

with the normal conduction through the AV node. In patients with underlying structural heart disease, the presence of scar will also provide the substrate for the development of atypical atrial flutter or monomorphic ventricular tachycardia. Structural heart disease, resulting in heterogeneous areas of scar in the myocardium, further increases the potential for developing reentry tachycardias. Zones of slow conduction around scar can allow unidirectional block that initiates the reentry circuit. Other drugs can make this unidirectional block more likely to occur (Chap. 47).

48.4.2 Indirect Proarrhythmia

Drugs which cause cardiotoxicity directly (anthracyclines and other chemotherapeutics) secondarily lead to a proarrhythmic state by leading to hemodynamic destabilization. Other drugs, such as diuretics, may secondarily cause a proarrhythmic state by causing imbalances in electrolytes. Still other drugs may interfere with the metabolism or excretion of another medication that itself is proarrhythmic and thus lead to a complex proarrhythmic state. Thus, it is important once the immediate management of the arrhythmia has commenced, and the most likely offending medication has hopefully been eliminated, that other contributing factors are identified and dealt with accordingly.

48.5 Toxicology of Medication-Induced Arrhythmias

The development of arrhythmias is usually an indication for emergent, aggressive pharmacotherapy to reverse the effects of the culprit medication. Airway protection is mandatory and support with mechanical ventilation may be required if the patient's mental status is impaired. Treatment with activated charcoal, commonly used in toxic ingestions, was shown in a randomized, controlled trial comparing multiple-dose and single-dose activated charcoal to be not significantly more beneficial than placebo [47]. Specific therapies related to either the ingestion of particular drugs or particular ECG manifestations are discussed in detail above and summarized in Table 48.3 below [48]. The medical management of patients following a massive toxic ingestion is often complex and requires multidisciplinary cooperation between cardiologists, intensivists, nephrologists, toxicologists, and poison control centers.

48.6 Concluding Remarks

It is too simplistic to say that *X* medication causes *Y* arrhythmia. The proarrhythmic potential of any medication is related to the underlying cardiac substrate, the dose of the medication, other drugs that may interact, and current status of electrolytes.

Table 48.3 Specific regimens to treat medication-induced arrhythmias are shown [45]. This list is by no means comprehensive, but selects more common scenarios that present to the cardiologist

Clinical syndrome	Manifestation	Treatment
Thyrotoxicosis	Atrial fibrillation is common; may be associated with heart failure	Propranolol Methimazole, if primary hyperthyroidism
Cocaine-induced arrhythmias	Sinus tachycardia, atrial tachycardia, or ventricular tachycardia; associated with hypertension	Benzodiazepines Sodium bicarbonate Lidocaine for VT to directly compete with cocaine
Methylxanthines and beta-agonist toxicity	Sinus, atrial, and supraventricular tachycardias Hypotension through beta-2 stimulation	Beta-blockers Diltiazem or verapamil Alpha agonists for hypotension
Beta-blocker or calcium channel blocker toxicity	Bradycardia with cardiogenic shock; extreme cardiogenic shock can lead to ventricular tachycardia from hemodynamic compromise	Calcium gluconate or chloride Glucagon 50 μg/kg bolus, then 2–5 mg/h drip Hyperinsulinemia/euglycemia: 1 unit/kg bolus insulin with 0.5 g/kg dextrose, followed by 0.5–1 unit/kg/h insulin drip with 0.5 g/kg/h dextrose infusion
Sodium channel blocker toxicity	Wide QRS, particularly at faster rates; difficult to distinguish VT from SVT	Sodium bicarbonate
Lidocaine or other local anesthetic toxicity	Delirium, altered perception, seizure, sinus arrest	Intravenous lipid emulsion, with dose depending on the toxic agent
Electrical storm with Brugada ECG	Coved ST-segment elevation on ECG in leads V1, V2, and sometimes V3 leading to VF	Isoproterenol beginning at 0.002 μg/kg/min, titrate up until ST segments normalize
1:1 atrial flutter	Narrow- or wide-complex tachycardia at the same rate as the flutter cycle length, frequently symptomatic with lightheadedness or syncope	Sedation and synchronized direct current cardioversion, with catheter ablation to prevent recurrence
Torsade de pointes	Prolonged QTc, long-short alternating cycle lengths; polymorphic VT and VF	Magnesium Pacing at an elevated heart rate Isoproterenol is less effective than pacing

(continued)

Table 48.3 (continued)

Clinical syndrome	Manifestation	Treatment
Digoxin toxicity	Increased excitability with AV node block is characteristic; ST-segment abnormalities; bidirectional VT is rare Nausea, abdominal pain, delirium, visual disturbances	Supplement potassium to >4 mg/dL and magnesium to >2 mg/dL Digoxin-specific Fab: multiply serum digoxin concentration by patient's weight in kilograms divided by 100 to calculate number of vials required

ECG electrocardiogram, *Fab* antigen-binding fragment, *SVT* supraventricular tachycardia, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Furthermore, it is still unknown what role genetic and protein characteristics have on individuals' risks for proarrhythmia [36, 49]. The types of proarrhythmias can be categorized based on the mechanism of action of particular drugs. Beta-agonists, phosphodiesterase inhibitors, other sympathomimetics, thyroxine analogs, methylxanthines, and cocaine all cause enhanced automaticity by different mechanisms and lead to sinus tachycardia, ectopy, atrial tachycardia, atrial fibrillation, and sometimes can precipitate ventricular arrhythmias. Beta-blockers and calcium channel blockers affect not only the sinus rate and AV node conduction but also suppress cardiac contractility. Medical treatment with calcium, glucagon, hyperinsulinemia/euglycemia, or mechanical hemodynamic support is required for patients with beta-blocker or calcium channel blocker overdose in cardiogenic shock. Sodium channel blockers can cause a wide array of proarrhythmic conditions from pharmacologically uncovered Brugada syndrome to atrial flutter with 1:1 conduction to wide complex tachycardia that cannot be determined whether it is VT or supraventricular tachycardia, with aberrant conduction due to use-dependent sodium channel blockade. A large number of cardiovascular and non-cardiovascular drugs affect cardiac potassium channels, in particular, the rapid delayed internal rectifying potassium current I_{Kr}. These drugs lead to prolongation of the QTc and torsade de pointes. Finally, digoxin causes many different types of arrhythmias due to cytoplasmic calcium overload; each arrhythmia is itself an indication for treatment of digoxin toxicity with digoxin-specific Fab.

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Chapter 49
Drug-Induced Prolongation of the QT Interval: Present and Future Challenges for Drug Discovery

Gary Gintant and Jean-Pierre Valentin

Abstract Delayed repolarization (manifest as prolongation of the QT interval) is a well-established surrogate marker for a rare but potentially lethal arrhythmia termed torsade de pointes (TdP). Numerous preclinical assays have been developed to detect liabilities associated with drug-induced delayed repolarization across multiple levels of integration (including subcellular, cellular, organ, whole animals) and species (including humans). Off-target effects of noncardiovascular drugs (e.g., terfenadine, cisapride) include block of I_{Kr} (also known as Kv11.1 or hERG), a repolarizing potassium current that plays a prominent role in ventricular repolarization. While contributing to the genesis of TdP, additional drug effects on other cardiac currents that modulate repolarization across different preclinical models must be considered when characterizing drug-induced delayed repolarization and translating proarrhythmic risk to humans. This chapter describes the basis for this important cardiovascular liability facing all small molecule drug candidates, various preclinical proarrhythmia models available to characterize proarrhythmic risk related to delayed repolarization, and evolving future approaches focused on cellular and subcellular mechanism-based in vitro and in silico evaluations of proarrhythmia.

Keywords Acquired long QT • Arrhythmia • hERG • QT interval • Repolarization • Torsade de pointes • Proarrhythmia

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Abbreviations

ADRs	Adverse drug reactions
AP	Action potential
APD	Action potential duration
AV	Atrioventricular
CiPA	Comprehensive in vitro proarrhythmia assay
C_{max}	Maximum plasma concentration
CVS	Cardiovascular
EADs	Early after depolarizations
ECG	Electrocardiogram
hERG	Human ether-a-go-go-related gene
IC_{50}	Concentration inhibiting 50 % of the response
ICH	International conference on harmonization
LQTS	Long QT syndrome
MAPD	Monophasic action potential duration
NCE	New chemical entity
PD	Pharmacodynamic
QTc	QT interval corrected for heart rate
TdP	Torsade de pointes
TDR	Transmural dispersion of repolarization
TQT	Clinical thorough QT study
TRiAD	Triangulation, reverse use dependence, instability, and action potential duration
VF	Ventricular fibrillation

49.1 Introduction: Drug-Induced QT Prolongation and Proarrhythmia in Context

Over the last decade, both preclinical and clinical safety have remained the major cause of drug attrition during clinical development and of drug withdrawal from the market, accounting for 35–40 % of all drug discontinuation [1, 2]. Adverse drug reactions (ADRs) in humans fall into five types (A–E), of which type A represents 75 % of all cases [1]. Type A ADRs are dose-dependent and predictable from primary, secondary, and safety pharmacology; indeed drug-induced QT interval prolongation and torsade de pointes (TdP)-type arrhythmia fall under this category. In a recent review of 154 drugs discontinued from clinical development for cardiovascular reasons, 4 % were due to prolonged QT or TdP, 23 % to non-QT type arrhythmia, and 73 % for "other" cardiovascular reasons [3]. The prominence of arrhythmias (approximately half of the 19 % reported by Valentin et al. [1]) echoes the continuing concern for drug-induced delayed repolarization and TdP arrhythmia. Figure 49.1 graphically compares reasons for drug withdrawals

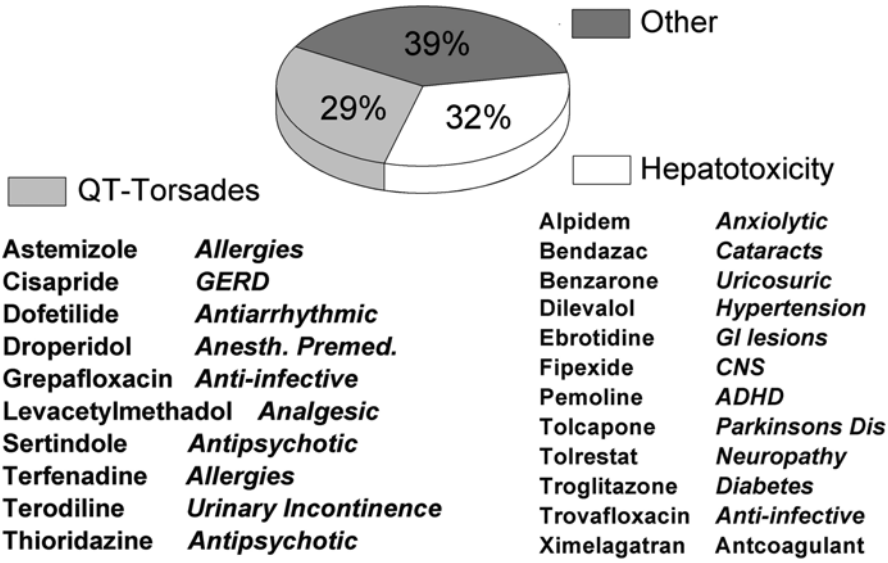

Fig. 49.1 Drugs withdrawn from market between 1990 and 2006 based on overall mechanism of toxicity. The category "QT-Torsades" represents QT interval prolongation and torsade de pointes, while the category "Other" includes aplastic anemia and convulsions. Hepatotoxicity following prolonged administration is listed under "Other" category (Data derived from Shah [4])

from various markets from 1990 to 2006, along with names and categories of drugs involved.

Drug-induced long QT syndrome (LQTS, also referred to as acquired long QT syndrome, aLQT) is characterized by QT interval prolongation and increased risk of TdP. In 1964, Selzer and Wray [5] reported QT prolongation and ventricular fibrillation (VF) in response to quinidine. Two years later, Dessertenne [6] described TdP, a polymorphic ventricular tachycardia where QRS complexes "twist" around the isoelectric line in a sinusoidal fashion. Symptoms of TdP include palpitations, syncope, and seizure-like convulsions. TdP is usually self-limited but may degenerate into ventricular fibrillation and sudden cardiac death. A variety of medications from multiple classes have been implicated in drug-induced LQTS and TdP ([7, 8], also see www.crediblemeds.org for an updated listing and also in Chap. 48).

Long QT syndromes linked to mutations of cardiac ion channels have also been identified [9]. Genetic linkage analysis of affected families with congenital LQTS has described several loci associated with LQTS, with most of the affected genes encoding for ion channels or subunits involved in ventricular repolarization (see [6]). The most frequent LQTS variants are loss-of-function mutations in the KCNQ1 (LQT1) and KCNH2 (LQTS2) genes encoding for the slow and rapid components of the delayed rectifier potassium channel currents I_{Ks} (Kv7.1) and I_{Kr} (KV.11.1, also referred to as hERG current). A gain-of-function mutation of the SCN5A gene encoding for the cardiac sodium channel current I_{Na} (Nav1.5) is associated with LQT3. Mutations in genes causing congenital LQTS have been found

in patients with drug-induced QT prolongation and ventricular arrhythmia. Congenital LQTS is an inherited disease usually occurring in structurally normal hearts. Beyond genetic evidence, pharmacological evidence exists linking those cardiac ion channels and TdP, and pharmacologic challenge has been used to identify forms of congenital LQTS (see also Chaps. 48 and 52). Most clinically relevant drug-related QT prolongation occurs via inhibition of I_{Kr}, a potassium current mediated in humans by the ion channel KCNH2 (KV11.1) encoded by the human ether-a-go-go-related gene (HERG), analogous to the genetic LQT2 form of the congenital disease (Fig. 49.2).

49.2 How Does Delayed Repolarization Predispose to TdP and Lead to Proarrhythmia?

Ventricular repolarization is a dynamic process representing a fine balance of inward (depolarizing) and outward (repolarizing) ionic currents. The net outward current that flows with each heartbeat ensures the orderly termination of each cardiac cycle appropriate to the heart rate, modulates cardiac refractoriness and excitability (by defining the time course of reactivation of sodium and calcium currents), as well as affects intracellular calcium handling and cardiac contractility. Drugs that delay repolarization may predispose the myocardium to interruptions in repolarization

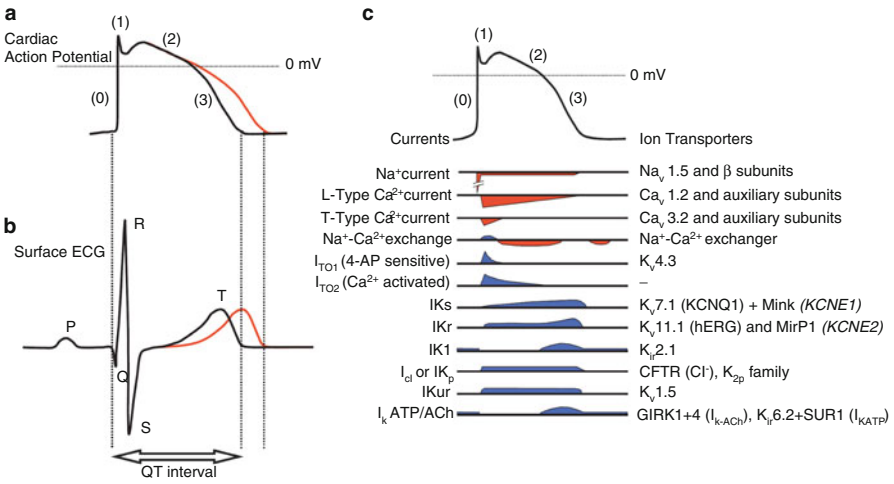

Fig. 49.2 Panels (**a**, **b**). Simplified relationship between prolongation of action potential duration and QT interval. Panel (**c**) illustrates contributions of multiple inward currents (*downward deflections*, *red*) and outward currents (*upward deflections*, *blue*) to electrogenesis of a generalized ventricular action potential. I_{Kr}/KV11.1 (hERG) and associated subunits MirP1) represent just one of multiple currents functioning during repolarization. I_{Kur} and $IK_{ATP/ACh}$ currents are more prominent in atria compared to ventricular myocytes (Adapted with permission from Abriel et al. [8])

termed "early after depolarizations" (EADs). EADs represent a form of abnormal electrical activity in which repolarization is interrupted by an inappropriate depolarization that arises during the action potential plateau (or later during the relative refractory period) but prior to full repolarization. EADs can, if of sufficient amplitude and timing, propagate within the ventricles (especially those in which repolarization may be more heterogeneous due to spatiotemporal differences in drug-induced delayed repolarization, creating a proarrhythmic substrate) to elicit premature ventricular excitation that elicit TdP.

It is generally accepted that most drugs that delay cardiac repolarization reduce the rapidly activating delayed rectifier current I_{Kr} encoded by hERG. A historical review of hERG current in cardiac safety studies can be found in Rampe and Brown [10]. Given the multiple components involved in initiating TdP, it is now recognized that drug-induced delayed repolarization is a surrogate marker of TdP proarrhythmia. Indeed, in most instances, drug-induced delayed repolarization simply leads to prolongation of ventricular repolarization (manifest as QT prolongation) that does not result in repolarization instability and triggered activity and is simply reversed upon drug removal. While it is generally accepted that prominent delayed repolarization leads to increased risk for TdP proarrhythmia, the extent of delayed repolarization necessary to elicit EADs or TdP is uncertain and is likely dependent on the presence of covert or overt heart disease and the presence or absence of known risk factors. Such factors include heart rate (bradycardia), electrolyte imbalances (hypokalemia, hypocalcemia, hypomagnesemia), age (older population), sex (female), disease conditions (congestive heart failure, left ventricular hypertrophy, liver function impairment), and congenital long QT syndrome. Many of these risk factors can be considered as reducing "repolarization reserve," a term that refers to the ability of the myocardium to repolarize in the setting of reduced outward current [11, 12]. Given the integrated response of multiple currents that define repolarization, reducing one outward current may modestly delay repolarization (but not lead to proarrhythmia) due to the remaining multiple currents that support repolarization. However, in the presence of risk factors that may reduce repolarization reserve, additional small reductions in net outward current may have more prominent effects on repolarization stability and predispose to TdP.

49.3 Further Consideration of Drug that Delay Cardiac Repolarization

Emerging data suggest that in most cases, the hERG/I_{Kr} and in vivo QT assays that form the core of the prevailing preclinical ICH S7B Guidance [10] detect drugs that prolong the QT interval in humans. However, there is a growing understanding of instances where "results among preclinical studies are inconsistent and/or results of clinical studies differ from those of preclinical studies" [13]. In these instances, "retrospective evaluation and follow-up preclinical studies can be used to

understand the basis for the discrepancies" [13]. Indeed, a comparison of the potency of hERG block of drugs also tested in clinical thorough QT studies revealed a surprising number of false-positive and false-negative findings [14]. Follow-up studies may include studies of drug metabolites and more comprehensive studies of drug effects on multiple cardiac currents (see the CiPA initiative, below). There are drugs (such as verapamil and phenobarbital) that do not prolong the QT interval even though free exposure levels encompass the inhibitory concentration range for prominent outward (repolarizing) I_{Kr} block. In such cases, the lack of concordance is most easily explained by postulating that block of outward (repolarizing) current is mitigated by concomitant block of inward (depolarizing) current during repolarization. Such complex, integrated effects have been called multichannel block [15] or mixed ion channel effects (MICE, [16]). One such candidate current is the L-type calcium current (Cav1.2) that provides depolarizing current that sustains the ventricular action potential (AP) plateau. One can see evidence of multichannel block by changes in the configuration of the AP plateau (representing the integrated activity of multiple ion channels), with calcium channel block reducing repolarization delays elicited by hERG channel block [15]. Alternatively, it is possible to separately evaluate drug effects on multiple cardiac currents (expressed in heterologous systems using higher-throughput automated patch systems; see [17, 18]) and integrate multiple effects using regression techniques [13] or computer reconstructions of ventricular electrical activity [19].

There are instances where a new chemical entity (NCE) is found to block I_{Kr} current and to prolong the QT interval in vivo at plasma concentrations much lower than those expected based on potency of hERG block. In such cases, myocardial drug accumulation may contribute to the reduced safety margin based on hERG IC_{50} values alone. There is good evidence that this is an issue for some antipsychotic compounds (e.g., risperidone and haloperidol [20]). This combined with the reported ability of hERG to "trap" compounds [17, 21], kinetic considerations that modulate the dynamic block and unblock of I_{Kr} [22], effects of plasma protein binding on drug availability, along with previously mentioned multichannel effects, may provide the basis for pharmacokinetic–pharmacodynamic mismatches that make the preclinical assessment risk of proarrhythmia difficult, even for hERG-selective compounds. In addition, there is evidence that some compounds indirectly reduce hERG current by reducing trafficking and/or expression of the channel protein to the sarcolemma with chronic exposure [20]. For such a mechanism, simple assays have be devised to measure the change in surface channel expression [23, 24]. Inhibition of hERG transcription, for example, by desethylamiodarone, a metabolite of amiodarone, has been suggested as a possible mechanism to explain the delayed QT-prolonging effects of amiodarone [25].

Drugs that affect autonomic tone may also lead to conflicting data: the complex relationship between QT and RR intervals may change depending on prevailing autonomic tone [26]. If species-specific, such effects could show no drug response preclinically but result in QT effects clinically (even using individual QT–RR plots to derive corrected QT values).

49.4 Preclinical Assays to Detect Delayed Repolarization

49.4.1 In Silico

Computational models have been developed to predict the hERG potency of NCEs (see [27]). While useful in early screening campaigns and guiding chemical synthesis, these models are not widely accepted for subsequent proarrhythmic risk assessments.

49.4.2 In Vitro

Owing to the emphasis on hERG current in regard to delayed proarrhythmia, numerous approaches have been used to evaluate drug effects on hERG current. In general, these approaches may be categorized as direct or indirect, based on the parameter(s) evaluated. Direct (functional) assessments provide determinations of IC_{50} values for block of hERG current expressed in heterologous expression systems measured using voltage clamp techniques. While formerly assessed using manual whole cell voltage clamp techniques, such studies have largely been supplanted by automated patch clamp platforms (see [18]). Examples of a less direct assessment include studies involving the measurement of Rb^+ or $Thallium^+$ flux with HEK or CHO cells transfected with I_{Kr} channels and binding assays which measure displacement of potent hERG ligands such as radiolabeled dofetilide, MK-49 , and astemizole. Indirect measures are more useful in detecting potential hazards associated with hERG, such as screening larger numbers of drug candidates prior to lead selection. Indirect measures are more difficult to translate into clinical risk assessments (typically as "safety margins"), which are typically based comparisons of IC_{50} values for hERG block vs. clinical exposures (based on C_{max} values) with considerations for plasma protein binding.

49.4.3 Proarrhythmic Models

There is a tacit assumption in ICH S7B that the integrated risk assessment for QT interval prolongation will reflect the risk of TdP. However, since QT interval prolongation is an imperfect surrogate marker of proarrhythmia, and the incidence of TdP is so low as to require inappropriately large numbers of patients in clinical studies to define the proarrhythmic risk, potentially useful in vitro and in vivo proarrhythmia models have been developed and described [28–30].

Since the identification of TdP, proarrhythmic risk has been investigated using mechanistic studies of inherited LQTS and proarrhythmic properties of several antiarrhythmic drugs (see Bialecki et al. [31], Chap. 48). A key element present in

many such models is the need for risk factors linked to TdP clinically, such as female gender, bradycardia, hypokalemia, or autonomic imbalance. They are therefore deemed "sensitized" models and are used principally as follow-up studies to confirm potential risk factors or in parallel to drug development when a family class effect is expected. The mechanisms of TdP have been well investigated, and evidence suggests that rhythm instability (such as rapid transitions from long to short cardiac cycle lengths) is often observed in adults just prior to TdP initiation [32–34]. The enhanced sensitivity likely increases spatial and temporal repolarization heterogeneity, enhancing the proarrhythmic substrate [35]. Despite such information, the QT interval duration remains as a popular (yet imperfect) surrogate. Alternative surrogates have included EADs, ectopic beats, dispersion of ventricular repolarization [36], heterogeneity and hysteresis of restitution [37], electrical alternans (action potential duration alternans) [38], beat-to-beat instability of QT interval duration [37], and electromechanical window [39]. In the absence of ventricular arrhythmias, it is not possible to define a risk threshold and, therefore, fully establish the predictive value of these surrogates. The comprehensive in vitro proarrhythmia assay initiative (CiPA, described below) represents an evolving preclinical paradigm that focuses on linking recognized proarrhythmic mechanisms of drugs with clinically adjudicated proarrhythmic risk.

49.4.4 In Vitro SCREENIT™ Rabbit Heart

This isolated heart preparation developed by Hondeghem (SCREENIT™ [40]) evaluates pro- or antiarrhythmic properties of NCEs using retrogradely perfused isolated female rabbit heart preparations according to the classical Langendorff technique. In this model, bradycardia is induced by AV node ablation and the heart is alternately paced at fast and slow stimulation rates; additional sensitization is accomplished using a hypokalemic buffer. Extracellular monophasic action potential recordings and ECG recordings may be used to evaluate proarrhythmic risk; triangulation of the monophasic action potential duration, reverse use dependence (greater prolongation of the repolarization at slow vs. rapid stimulation rates), and beat-to-beat variability of repolarization (temporal instability) are three major components of proarrhythmic risk in this model (leading to the acronym of TRIaD; for reviews, see Lawrence et al. [28] and Thomsen et al. [29]). This model, validated in a blinded assay on additional sets of positive and negative reference compounds, was shown to detect QT positive compounds and, more interestingly, selective in excluding false positives. Furthermore, the use of TRIaD parameters allows identification of those NCEs for which monophasic action potential duration prolongation is linked to antiarrhythmic activity.

49.4.5 The In Vitro Wedge Preparation

This preparation is also useful to demonstrate the effects of NCEs on repolarization variability (i.e., heterogeneity). Following the demonstration of transmural heterogeneity in guinea pig papillary muscles [41], it was specifically designed to measure

transmural dispersion across the ventricular wall [42, 43] with a special emphasis on M cells (localized in the midmyocardium of in vitro preparations) that were demonstrated to be very sensitive to AP prolongation by drugs and risk factors for TdP. In this technically difficult assay, drugs are perfused through native coronary arteries, and transmembrane action potentials are simultaneously recorded from epicardial, midmyocardial, and endocardial layers (obtained from edges of the sliced wedge), while an ECG-like trace is obtained across the preparation (typically rabbit hearts). The proarrhythmic surrogates used in this model include APD (specifically those from midmyocardial cells), and the interval between the peak and end of the pseudo T wave (QTpeak–QTend) is used as an index of transmural dispersion of repolarization (TDR, [44]). Indices of TDR may be useful to quantify proarrhythmic risk [40]. This model demonstrates the proarrhythmic potential of multiple proarrhythmic drugs [45–47] consistent with clinical outcomes. However, it should be noted that the existence of M cells in intact human hearts is still a matter of debate and has not been unequivocally demonstrated [48, 49].

49.4.6 In Vivo Chronic Atrioventricular (AV) Block

Based on bradycardia and electrolyte disorders identified as prominent risk factors for proarrhythmia, a chronic AV block dog model was developed and extensively used to analyze the mechanisms and risk factors associated with the use of Class I and Class III antiarrhythmic drugs, either alone or in combination (see [29, 31]). In this model, bradycardia is induced by formaldehyde injection into the AV node, resulting in chronic AV block; ventricular hypertrophy, electrical remodeling and rhythm instability that result all increase the susceptibility to TdP, while additional predisposing factors (hypokalemia) may further sensitize the model. The model may be modified to promote TdP with specific pacing algorithms to mimic the typical short–long–short sequences linked to the initiation of TdP and used to test pharmacological compound classes such as cisapride, almokalant, sertindole, or astemizole. In this model, QT or MAPD prolongation has been reported as a poor predictor of TdP, and other markers such as beat-to-beat variability seem to be more appropriate. Due to its very low throughput and technical challenges, this model has not been validated against a large panel of drugs, although it has been described as reproducible and highly sensitive for testing arrhythmogenic properties of drugs. A comparable model using Cynomolgus monkeys has also been developed (see [50]).

49.4.7 In Vivo Methoxamine-Sensitized Rabbit

In this in vivo model, chloralose-anesthetized rabbits treated with methoxamine (an α_1 adrenoceptor agonist) develop an increased sensitivity to delayed repolarization due to improper calcium handling leading to induction of ectopic beats [51, 52]. These effects are specifically marked for I_{Kr} blockers, leading to prominent QT prolongation, U waves, and finally polymorphic ventricular tachycardia. While

arrhythmias in this model are not associated with bradycardia, the electrophysiologic manifestation is similar to clinical TdP. Apart from the typical Class III antiarrhythmic compounds [53], this model has been used for several other NCEs including antibiotics such as sparfloxacin, levofloxacin, gatifloxacin, and Prulifloxacin [54, 55]. Interestingly, the proarrhythmic drug quinidine is ineffective in inducing arrhythmias in this model, probably because of its α_1-blocking properties; this model may also be insensitive to terfenadine [56], unless high doses are used [57]. The sensitivity to drugs other than Class III antiarrhythmic compounds remains to be demonstrated and limits the utility of this model in preclinical safety assessment.

49.5 Translation of Preclinical to Clinical Findings

In most cases, hard evidence regarding the predictive value of electrophysiologic preclinical testing is not readily available in the public domain. With a negative preclinical finding, subsequent development of a drug candidate may be halted and limited (if any) information provided in the public domain. Consequently, the scientific and medical community is left with high-profile examples of side effects in humans apparently not detected during preclinical assessments. Data have been generated to assess the value of preclinical tests to predict the potential of NCEs to prolong the QT interval of the ECG (and presumably the proarrhythmic potential of these drugs).

Published data suggesting that a 30-fold margin between the highest free C_{max} of a drug in clinical use and the hERG IC_{50} could be adequate to ensure an acceptable degree of safety from arrhythmogenesis with a low risk of obtaining false positives [58–60]. Published literature looking at the predictive value of preclinical QT-related models to humans is emerging [61–63]. Further work is required to extend the validation set in order to determine the confidence in the models in terms of their capacity to mimic the same physiological/pathophysiological mechanisms in humans and the confidence in their translation to humans (i.e., sensitivity, specificity, predictive value, as well as prevalence [1, 14, 16, 61]). However, there are areas that should be carefully considered to ensure optimization of the assays and ultimately increase the predictive value of preclinical testing. These include but are not limited to (1) species differences in the expression or functionality of the molecular target mediating the adverse effects, (2) differences in PK properties between test species and humans, (3) sensitivity of the test system, (4) optimization of the test conditions, (5) appropriate statistically powered study designs, (6) appropriate timing of functional measurements in relation to the time of maximal effect, (7) delayed/chronic effects of parent drug and/or metabolites, (8) difficulty of detection in animals using standard studies (e.g., arrhythmia), and (9) assessment of a suboptimal surrogate end point that predicts with some degree of confidence the clinical outcome (e.g., QT/QTc interval prolongation as a surrogate of TdP).

49.6 Clinical Considerations: QT Prolongation

This ICH E14 guidance issued in 2005 established the so-called clinical thorough QT (TQT) study whose focus was "to assess the potential of a drug to delay cardiac repolarization" [64]. TQT studies are designed to exclude a "threshold effect" below which QTc prolongation is considered to have no significant clinical consequence. This threshold effect is interpreted as a placebo-corrected change from baseline QTc (double-delta QTc) demonstrated by the two-sided 90 % confidence interval. A negative TQT study is concluded with an effect size of about 5 ms or less with the upper bound of the two-sided 90 % confidence interval below 10 ms. When this limit is exceeded (defining a "positive" TQT study), the QTc effect may significantly exceed 5 ms, and the upper bound of the two-sided 90 % confidence interval may exceed 10 ms. This definition was chosen to provide reasonable assurance that the mean drug effect on the QTc interval for therapeutic and reasonable supratherapeutic exposures is not greater than around 5 ms. In instances of a positive TQT study, further studies with intensive ECG monitoring in later stage clinical trials are encouraged to assess proarrhythmic risk. TQT studies typically include a negative (placebo) control for circadian variation, a positive control (typically moxifloxacin administered orally as a 400 mg single oral dose), and at least one dose of drug candidate expected to result in plasma concentrations that includes the maximum systemic exposure anticipated in the target population. While typically conducted in normal volunteers, less stringent evaluations may be conducted for oncologic drugs in patients with cancer (e.g., with cytotoxic agents [65]).

Human TQT studies are resource intensive requiring attention to specific details to ensure the necessary rigor to quantify small changes in the QTc interval (5 ms resolution vs. baseline values in the range of 400–450 ms, i.e., 1–2 %). The reliable and consistent assessment of the end of the QT interval was an earlier challenge that has been largely resolved by the use of qualified computer algorithms. Another challenge was posed by the fact that the QT interval varies with heart rate, with longer QT intervals at slower rhythms that may confound a drug's direct effect on repolarization. Presently, correction approaches employed include fixed formulae (Fridericia's formula, considered more appropriate compared to the previously popular Bazett's correction [66–68]), individualized correction factors (corrections based on RR–QT interval relations established for each subject), or beat-to beat measures [69, 70]; optimal fixed heart rate correction formulae also vary across species [71].

49.7 Clinical Practice Perspectives

The drugs frequently used in clinical practice that carry the greatest risk for QT prolongation and TdP are Class III (and some older Class I) antiarrhythmic drugs (such as sotalol, dofetilide, ibutilide, and azimilide) for which hERG inhibition and

QT prolongation are part of the therapeutic mechanism of action; the observed rate of TdP among these patients is about 1 % [72] (Chaps. 48 and 52). It is also likely that cardiac pathologies in this patient population predispose to proarrhythmic risk [73]. In addition, the presence of predisposing factors including hypomagnesemia, hypokalemia, bradyarrhythmias, coronary artery disease, and pre-existing cardiac rhythm disturbances may contribute to the incidence of TdP.

Noncardiac drugs can also cause TdP, such as antibiotics, antipsychotics, and antidepressants, for which TdP or QT prolongation is an undesirable side effect of the drug. The risk of TdP is lower than with Class III antiarrhythmic drugs (ranging from 0.01 to 0.1 % [74, 75]); however, these drugs are prescribed more frequently and with far less awareness for monitoring of the QT effects than the class III antiarrhythmic drugs [76]. Examples of drugs which have to be taken off the market due to the development of TdP include the gastrointestinal drug cisapride (Propulsid) and second-generation antihistamines astemizole (Hismanal) and terfenadine (Seldane; see [4]). For some drugs, warnings of the risk of QT prolongation and TdP were added to labeling, for example, droperidol (Inapsine).

TdP in clinical practice is often associated with polypharmacy and drug–drug interactions. A common pharmacodynamic interaction includes inadvertent prescription of multiple agents with hERG-blocking properties to a patient. For example, a patient taking a stable dose of a Class III antiarrhythmic agent for atrial fibrillation may present with an acute infection to a general practitioner in a primary care clinic or urgent care facility who is unaware of the situation and may prescribe a quinolone antibiotic that may predispose to TdP. In a review of medication records of >1 million patients, prescriptions of 1 QT-prolonging medication was identified in 23 % of patients, two agents in 9 % of patients, and three agents in 0.7 % of patients [77]. While these interactions rarely cause adverse outcomes, the concomitant use of multiple contraindicated drugs may cause drug-induced TdP in a substantial proportion of patients.

An additional clinical perspective in regard to polypharmacy is the QT prolongation and TdP risk in relation to drug–metabolism interactions. For example, when a widely used antihistamine terfenadine with potent hERG channel-blocking activity (withdrawn from the market in 1998) was prescribed together with inhibitors of the cytochrome P450 3A4 (such as antibiotics, antifungals, cimetidine, fluoxetine, amiodarone, or ketoconazole), the systemic levels of terfenadine could be increased up to 20-fold leading to marked QT prolongation and increased risk of TdP [78]. Such an effect has been termed “metabolic multiplication” [79].

Other drug–drug interactions commonly encountered in clinical practice that can predispose to TdP include (i) the use of a diuretic that may cause hypokalemia and hypomagnesemia which can further prolong QT interval and predispose to TdP in the setting of a hERG-blocking agent and (ii) aminoglycoside antibiotics that can impair renal function and lead to higher and potentially toxic levels of hRG-blocking drugs such as sotalol and dofetilide which are cleared through the kidney.

49.8 Future Preclinical Evaluations of TdP Proarrhythmic Risk: A Mechanistic Evaluation of Proarrhythmic Risk (CiPA)

While rigorous TQT studies provide a robust estimate of the extent of drug-induced QT prolongation at therapeutic and supratherapeutic concentrations in normal subjects, they do not ensure that detecting drug-induced QT prolongation is proarrhythmic in either normal subjects or patients with diseased hearts. Indeed the TQT study has been characterized as being highly sensitive but not very specific. The utility of the intense clinical focus on small changes in QT prolongation clinically (which may not represent any significant proarrhythmic risk) has recently been challenged [80, 81].

In the summer of 2013, a Think Tank was held at the US FDA facilities to discuss a new, integrated nonclinical paradigm to assess the proarrhythmic risk of novel drug candidates in the absence of a thorough QT study. This new paradigm, termed "Comprehensive In Vitro Proarrhythmia Assay" (CiPA) represents a departure from the prior ICH S7A and ICH S7B guidances, in that these guidances are designed to detect delayed repolarization (recognized as surrogate markers of proarrhythmia) from preclinical (primarily hERG current and QT prolongation) and clinical TQT studies. In contrast, the intent of CiPA is to evaluate proarrhythmic risk based upon a more comprehensive set of in vitro assays mechanistically linked to TdP along with more traditional in vivo QT studies. While recognizing that S7B and E14 guidances have been effective in preventing new products from withdrawals due to unacceptable TdP risk, evidence suggests that not all drugs that block hERG elicit TdP and that QT prolongation is highly sensitive but not very specific for predicting ventricular proarrhythmic risk [81]. In addition, it has been suggested that emphasis on hERG current assays as early (frontloaded) screening assays (and the associated stigma expected from adverse regulatory and commercial implications) likely contribute to the unwarranted attrition of drug candidates early during drug discovery, thereby negatively impacting evolving drug pipelines.

CiPA relies on data derived from human-derived ionic currents, human-derived myocytes, and in silico reconstructions of human ventricular cellular electrophysiology to assess a compounds' potential proarrhythmic liability. Specifically, the three components of CiPA are: (a) the in vitro evaluation of drug effects on individual human cardiac currents expressed in heterologous expression systems; (b) integrated, in silico reconstructions of ventricular activity as affected by measured effects on cardiac currents (see [82, 83]); and (c) confirmation of drug effects on human stem cell-derived cardiomyocytes (providing an integrated cellular response [84]). At present, standardized protocols have been defined to interrogate drug effects on seven prominent cardiac currents involved in repolarization (and of interest to the pharma community), including two depolarizing currents (fast and late sodium current [the later implicated in directly modulating repolarization] and L-type calcium current [I_{CaL}, involved in generate late calcium current during

cardiac repolarization]), and four repolarizing currents (the fast and slow delayed rectifier currents (I_{Kr} and I_{Ks} respectively), the inward rectifier I_{K1} [involved in defining terminal repolarization and setting the resting membrane potential], and the transient outward current I_{to} (responsible for defining the plateau height). The O'Hara–Rudy computer reconstruction [85] is one candidate in silico model expected to integrate drug responses on multiple cardiac channels and detect emergent proarrhythmic events (including early afterpolarizations). Finally, human stem cell-derived cardiomyocytes will provide cell-based integrated electrophysiological responses used to assess the veracity of in silico reconstructions. Such studies may involve microelectrode arrays [86, 87], voltage-sensitive dyes [88], or traditional (but lower throughput) transmembrane potential recordings (using microelectrode or perforated patch techniques [89, 90]). Collaborative efforts continue to evolve this novel paradigm (based on established proarrhythmic mechanisms) designed to enhance drug discovery, provide more specific proarrhythmic risk assessments, and eliminate the premature discontinuation of development of sorely needed promising new drugs.

49.9 Concluding Remarks

It is clear that the past 20 years has seen great progress in detecting and avoiding drugs that may predispose to TdP proarrhythmia. This progress is based largely on detecting delayed repolarization (a surrogate marker of proarrhythmia) preclinically (with various in vitro and in vivo models of varying complexity) and clinically (through TQT studies). Clearly, excessive delayed ventricular repolarization is considered proarrhythmic. However, various preclinical strategies now in place (coupled with an appreciation of drugs pharmacokinetics) ensure the absence of such excessive QT prolongation for newly evolving drugs. The assessment of proarrhythmic risk of subsequent drug candidates that cause minimal to modest repolarization delays (by mechanisms likely not related to typical hERG block) will pose a challenge for drug developers and regulators and will require novel strategies to define "safe" thresholds for reasonably avoiding proarrhythmic risk. The ability to define a more comprehensive assessment of proarrhythmic risk, beyond a simple IC_{50} value for hERG block or msec values characterizing QTc prolongation, is essential to promote the efficient advancement of novel therapeutics in drug discovery and ensure a safe stream of desperately needed therapeutic agents.

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Chapter 50
Treatment of Atrial Fibrillation and Atrial Flutter

Torsten Christ, Simon Pecha, and Norbert Jost

Abstract Atrial fibrillation (AF) is the most common arrhythmia in humans. Therapeutic goals are normalization of ventricular rate (rate control) or restoration of sinus rhythm (SR, rhythm control). Drugs can achieve both aims. Early therapeutic approaches included the use of plant glycosides, digitalis (from *Digitalis lanata*, *Digitalis purpurea*) for rate control and alkaloid, quinidine, for rhythm control. For the latter indication, sodium channel blockers became popular in the middle of the last century. However, awareness of disastrous ventricular proarrhythmia caused by sodium channel blockers in heart failure patients has reduced their use in AF. Amiodarone – a mixed channel blocker – is not associated with ventricular proarrhythmia, but its severe extracardiac toxicity limits its use in AF. Nevertheless, this compound has gained some popularity in treating atrial fibrillation and atrial flutter. Over the last two decades, intensive basic science research in the field of human atrial electrophysiology identified ion channels expressed selectively in the atrium but not in the ventricle (e.g., I_{Kur}, $I_{K,ACh}$, SK channels). Those channels have gained enormous attention since they could represent targets for atrial antiarrhythmic drug therapy without the risk for ventricular

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arrhythmia. However atrial-selective expression of a given ion channel is not sufficient to qualify it as a drug target. Blockade of atrial-selective ion channels should affect atrial electrophysiology to an extent sufficiently large to stop or to prevent AF. Blockers of I_{Kur} and $I_{K,Ach}$ have entered first trials in humans. Sarcoplasmic reticulum may represent another target. Enhanced spontaneous Ca^{2+}-release from the sarcoplasmic reticulum may drive enhanced cardiac automaticity, which is believed to initiate and/or to maintain AF. Usefulness of such interventions remains to be proven. Therefore, this chapter reviews classic antiarrhythmic drugs used in atrial fibrillation/flutter and some new compounds recently approved or under development.

Keywords Atrial fibrillation • Atrial flutter • Ion channel block • Proarrhythmic effects • Selectivity • Atrial selective

50.1 Introduction

Atrial fibrillation is characterized by extremely rapid, uncoordinated electrical activity of the atria. As a result, in the ECG regular P waves (Fig. 50.1) are lost. In AF, P waves are much more faster and irregular. Amplitude of P waves is clearly smaller in AF than in SR (Fig. 50.2). Uncoordinated electrical activity impairs mechanical function of the atria. Nevertheless, subsequent loss of atrial contractile performance leads, maybe somewhat unexpected, to only mild reduction in cardiac output. Critical reduction of cardiac output can occur when filling of the ventricles is compromised because of increased stiffness of the ventricles and/or ventricular inflow obstruction. The effect of AF on electrical activity of the ventricles depends on AV-conduction speed. The AV node cannot conduct faster than ~200 bpm to the ventricles, and slowing within the AV node is therefore essential to prevent atrial fibrillation which will lead to ventricular fibrillation, a serious rhythm disorder requiring immediate medical attention. The ventricular rate during AF may be within the physiological range but is often too fast. Since the speed of conduction within the AV node critically depends on the autonomic tone, in many patients with AF, the ventricular rate will increase quickly during exercise and/or anxiety, generating not only irregular but also a very fast heartbeat. Often patients will be aware of AF because of the rapid and irregular ventricular contractions. The highly irregular arterial pulse, termed “delirium cordis” or “arrhythmia absoluta,” is also one of the first clinical symptoms observed in patients with AF, a long time before it is recognized that atrial tachycardia is the cause of these symptoms. Consequently, slowing of the ventricular rate became the first goal in AF treatment and remained a mainstay up to now. Ultimately, the restoration of a normal sinus rhythm is the logical aim of any pharmacological intervention; however the risk-benefit ratio also has to be considered. This

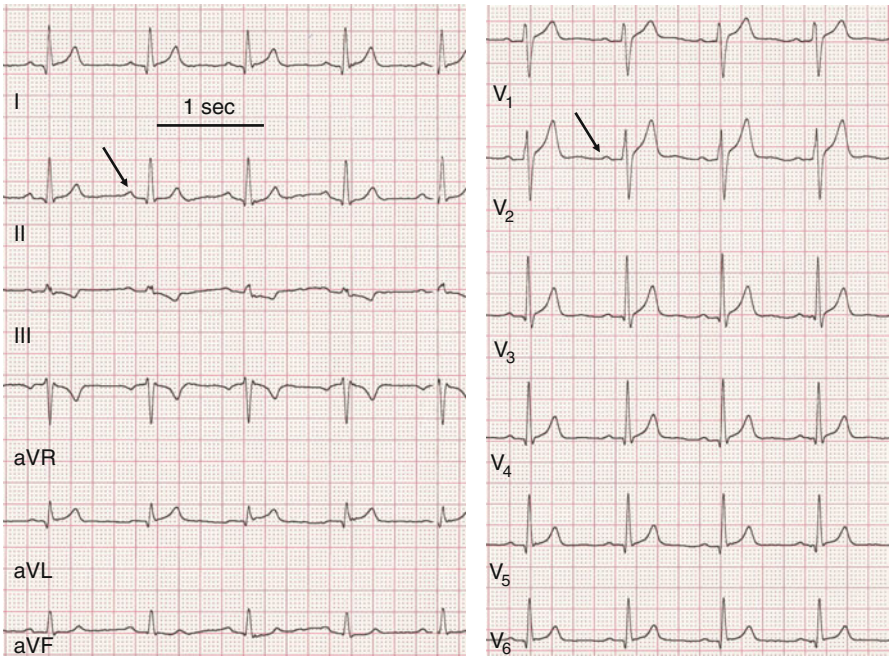

Fig. 50.1 Original ECG registrations from a patient in SR. *Arrows* indicate P waves. During normal sinus rhythm, P waves are upright in lead II and V2 and followed 1:1 by an QRS complex

chapter reviews the ion channels that affect atrial refractoriness and agents useful for terminating atrial fibrillation and atrial flutter and to prevent their reoccurrence.

50.2 Drugs Used for Rate Control

Many patients with a new-onset AF need slowing of the AV conduction (rate control), irrespective of whether restoration of the sinus rhythm will be a therapeutic goal. In patients, where sinus rhythm control is not a suitable treatment option, rate control may be a lifelong intervention. Digitalis glycosides were the first drug class used to treat patients with AF. Digitalis slows down AV-node conduction and thereby reduces the ventricular rate even during fast activation of the atria in AF. The enormous efficacy of this drug, with respect to slowing the heartbeat, is reflected in its name: "opium of the heart." However, proper dosing has always been a challenge since digitalis glycosides have a rather slow and complex pharmacokinetic in conjunction with a narrow therapeutic window that includes life-threatening side effects

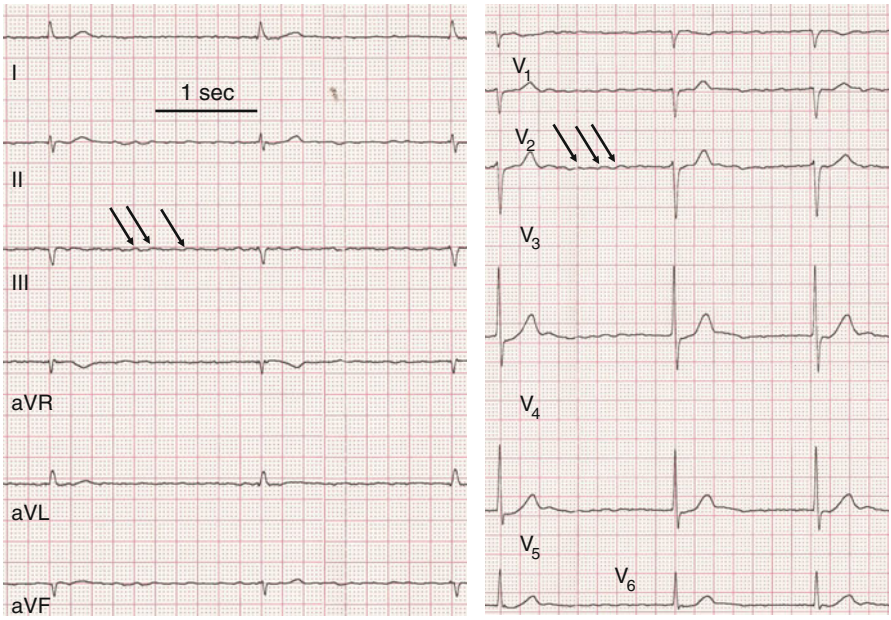

Fig. 50.2 Original ECG registrations from a patient with AF. *Arrows* indicate P waves are much faster, but smaller and QRS follows irregularly

[1]. Use of digitalis glycosides is safe when low doses are used and in some cases are controlled by monitoring serum levels of digoxin [2]. However, the vast majority of electrophysiological effects of digitalis glycosides in different regions of the heart give concerns about general safety of that drug class. Prospective data about digitalis efficacy in patients with AF are not available. Recently published large retrospective study with sophisticated statistical methods applied clearly indicates negative outcomes for digitalis treatment in patients with AF [3]. Actual guidelines of AHA/ACC and ESC still recommend digitalis use for rate control in AF. However, irrespective of whether we will have hard prospective data in the future, we have to expect restrictions on the use of digitalis in patients with AF, since two other drug classes with a more favorable safety profile can now be used for rate control.

L-type Ca^{2+}-channels critically regulate conduction in the AV node where Ca^{2+}-channels instead of sodium channels conduct upstroke of action potentials. Two L-type Ca^{2+}-channel blockers, diltiazem and verapamil, are able to provoke marked slowing of ventricular rate during AF [4, 5]. The β-adrenoceptor antagonists slow down AV conduction especially when sympathetic tone is increased as in case of exercise or excitement. Keeping in mind the beneficial effects of β-adrenoceptor antagonists in heart failure, this drug class is widely used in patients with AF and concomitant structural heart disease (~70 % in Europe). There are no obvious differences between different β-adrenoceptor antagonists with respect to slowing down AV conduction (Chaps. 5 and 8).

50.3 Antiarrhythmic Drugs

Atrial flutter is based on larger macro-reentry circuits compared to AF generating clearly distinguishable P waves in the ECG (see Fig. 50.3). Isolated atrial flutter is a rare condition [6]. AF and atrial flutter coexist in many patients. The larger reentry circuits in atrial flutter simplify treatment by catheter ablation and antiarrhythmic drugs. However, AF and atrial flutter probably respond to treatment aimed at prevention of recurrence or improvement of survival and cardiovascular complications in a similar way and can be treated as one entity [7]. Therefore, we do not differentiate between AF and atrial flutter. Classic antiarrhythmic agents can stop arrhythmias. They do so as they have marked effects on the excitability of cardiac tissue. This intervention may be highly effective in acute settings, and even serious side effects may be accepted as long as treatment duration is short and physicians give the drug under controlled conditions.

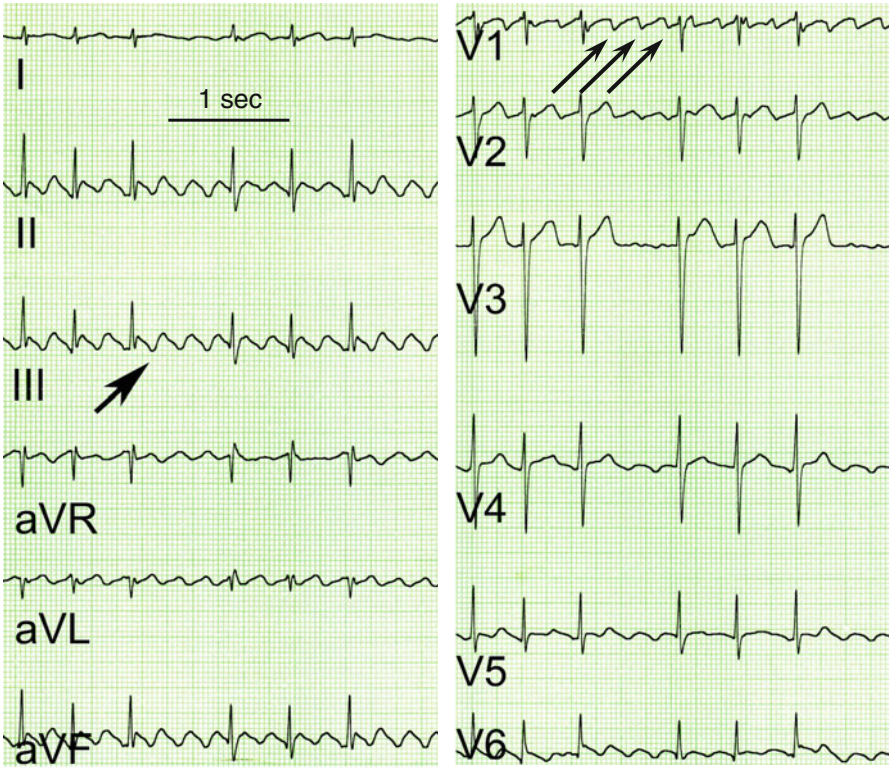

Fig. 50.3 Original ECG registrations from a patient with atrial flutter. *Arrows* indicate P waves there are much more P waves than QRS complexes. However, P waves are clearly distinguishable and are followed in a 3:1 or 2:1 mode by a QRS complex (best seen in V_2)

50.3.1 Class I Drugs

Efficacy of quinine to stop AF was first described in 1759 and introduced as a "pill in the pocket" approach for new-onset AF by a non-medic in 1922 [8]. Quinidine is the d-isomer of quinine, has a higher efficacy than quinine to stop AF, and was therefore used as an antiarrhythmic agent. From a general pharmacology perspective, quinidine shows a wide range of serious adverse effects. Quinidine affects gastrointestinal motility [9], and it should be noted that in the early days of quinidine treatment dosage was increased up to the point when patients started to vomit. Transient thrombocytopenia and hemolytic anemia can occur [10]. Quinidine also blocks α-adrenoceptors [11] and muscarinic receptors [12]. Reflex release of catecholamines upon vasodilation as well as release of inhibitory effects of acetylcholine will increase speed of AV conduction with a harmful increase in ventricular rate during AF. Increased AV conduction is especially harmful in the case of atrial flutter, since ventricular rate can reach critical high values. Therefore, quinidine is often used in conjunction with other drugs that slow AV conduction. Pharmacokinetic properties gave rise to concern on its therapy. Quinidine has high plasma protein binding and can thereby increase serum levels of other drugs bound to plasma proteins [13]. Cytochrome P450 enzymes extensively metabolize quinidine, and many of its metabolites show activity. Most importantly, quinidine can provoke life-threatening ventricular arrhythmias: torsades de pointes. The first ventricular proarrhythmic effects of quinidine were reported as early as in 1922. Systematic studies reveal an incidence of about 5 % [14]. Despite its unfavorable adverse effects, quinidine is still recommended when other drugs have failed to convert AF since there is no doubt about its remarkable efficacy (see Chap. 48).

Quinidine and its congeners were later classified as so-called class I drugs since they slow maximum upstroke velocity of cardiac action potentials, indicating sodium channel block. The obvious efficacy of quinidine has gained enormous interest to search for class I drugs. The result of this effort resulted in a dozen of different class I drugs. From the point of cardiac cellular electrophysiology, they differ with respect to their effect on action potential duration (APD). So class I drugs were later subclassified (e.g., IA, IB, and IC; prolongation, shortening or no effect on APD). See Table 50.1 and also Chaps. 48 and 52.

However, it should be noted that the initial intention to search for congeners of quinidine was driven by the unfavorable selectivity profile regarding extracardiac targets and the slow pharmacokinetics of quinidine. Ajmaline, another plant alkaloid, was a next, less toxic follower of quinidine [15]. It gained wide acceptance in Germany after successful self-experiments by the German cardiologist Kleinsorge, and details were published in 1954 [16].

Lidocaine was initially introduced as a local anesthetic in 1946 and first used as an antiarrhythmic agent in 1950 [17]. Its short half-life makes the drug attractive in emergencies, and the drug was used for many years in the clinical setting of acute myocardial infarction (even as intramuscular injection at that time). Lidocaine use in this indication was stopped because of excess mortality [18]. Lidocaine actions

Table 50.1 Summary of drugs used for AF

Drug	Introduced/approved	Class	I_{Na}	I_{Kr}	I_{Kur}	$I_{K,ACh}$	AR	MR	Noncardiovascular toxicity	Cardiovascular toxicity
Quinidine	1918	IA	+	+	+	+	α_1	+	Thrombocytopenia, cinchonism, pruritus, rash	QRS prolongation, torsades de pointes
Disopyramide	1962	IA	+	+				+	Anticholinergic effects, blurry vision	Congestive heart failure exacerbation, torsades de pointes
Propafenone	1976	IC	+	+			$\beta_{1/2}$		Metallic taste, dizziness blurry vision, bronchospasm	QRS prolongation, congestive heart failure exacerbation
Flecainide	1975	IC	+	+					Dizziness, headache, blurry vision	QRS prolongation, excess mortality
Sotalol	1992 VT/VF 2000 AF	II/III	+			$\beta_{1/2}$			Bronchospasm	Bradycardia, torsades de pointes
Ibutilide	1995	III		+					None	Torsades de pointes
Dofetilide	2000 US only	III		+					None	Torsades de pointes
Amiodarone	1967 VT/VF only	III	+	+			α_1		Pulmonary (hypersensitivity pneumonitis, chronic interstitial infiltrates), hepatitis, thyroid (hypothyroidism or hyperthyroidism), photosensitivity, blue-gray skin discoloration with chronic high dose, nausea, ataxia, tremor, alopecia	Sinus bradycardia
Dronedarone	2009	III	(+)	+		+	α_1 $\beta_{1/2}$		Hepatotoxicity, anorexia, nausea;	Sinus bradycardia

(continued)

Table 50.1 (continued)

Drug	Introduced/approved	Class	I_{Na}	I_{Kr}	I_{Kur}	$I_{K,ACh}$	AR	MR	Noncardiovascular toxicity	Cardiovascular toxicity
Vernakalant	2010 Europe only	New	+	+	(+)			(+)	Dysgeusia, sneezing, paresthesia	QT prolongation, hypotension
Ranolazine	2008	New	+/+	+			$\beta_{1/2}$		Dizziness, nausea, headache	QT prolongation

Drugs are listed based on their approval. Class means classification according the Vaughan Williams scheme. "New" means drugs classified as new drugs not represented by the Vaughan Williams classification

INa sodium current (peak), *IKr* delayed rectifier current, *IKur* ultrarapidly activating rectifier current, *IK,ACh* acetylcholine activated potassium current, *AR* adrenoceptor, *MR* muscarinic receptor. For further details, see text

+ indicates blockade of the respective target

+/+ for ranolazine indicates blockade of both peak and late sodium current

seem to be restricted to ventricles (see Chap. 48). Whereas lidocaine can prolong ERP in ventricular tissue [19], it was found almost ineffective in atrial tissue from the same species [20]. The reason for this finding remains unclear. One concern is that higher concentrations are needed to affect atrial relative to ventricular tissue. However, even almost neurotoxic concentrations of lidocaine are not able to convert AF in humans [21].

Disopyramide is another rather curious example. The drug can effectively stop AF, but its profound negative inotropic effects are troublesome [22]. Ironically, because of this "side effect," disopyramide gained popularity in treating patients with hypertrophic cardiomyopathy. Disopyramide seems to be safe in patients with hypertrophic cardiomyopathy [23]. From the beginning, disopyramide's marked antimuscarinic effects had limited patient acceptance [24]. However, this initially unwanted effect regained interest in some forms of vagally induced AF [25]. Disopyramide blocks many different potassium channels including $I_{K,ATP}$ [26]. Relevance of potassium channel blockade to its overall activity is unclear. Disopyramide was popular for conversion of AF in the 1980s but is no longer recommended in the North-American and European guidelines. It remains open to question if disopyramide may offer advantages in vagally induced AF.

Propafenone was tested in 1970s in Germany. It is structurally related to propranolol and blocks β_1- and β_2-adrenoceptors but not muscarinic receptors [27]. Propafenone is therefore classified as a mixture of a class I drug and a nonselective β-adrenoceptor antagonist. It has gained wider acceptance and is still recommended as a second-line drug to convert AF in people without structural heart disease. Taste complaints represent a strange side effect [28].

Flecainide was the last compound labeled as class I drug and represents a remarkable advance in drug development. Flecainide shows high selectivity for sodium channels, and therefore unwanted effects are mainly restricted to sodium channel block in nerve cells. Such adverse effects occur in about 30 % of patients chronically treated with the drug and illustrate general limitations of sodium channel block [29]. Obviously unwanted effects can be reduced by administration on demand instead of continuous drug administration. The drug was initially approved to treat ventricular tachycardia and later for supraventricular arrhythmias. However, severe proarrhythmia in patients treated with flecainide after myocardial infarction stopped its use in this indication [30]. Putative causes for flecainide's proarrhythmic action are discussed in hundreds of review articles (including in Chap. 48 of this book); however, the exact mechanism remains unclear. It should be noted that flecainide proarrhythmia could not be reproduced in a sophisticated rat model of myocardial infarction [31]. The latter rather surprising finding led to the idea that the proarrhythmic effect of flecainide may be mediated rather via blockade of other channels than sodium channels such as the hERG (not functional in rat heart). Nevertheless, use of flecainide is no longer accepted in patients with compromised ventricular function. Since many younger patients suffering from AF are free of structural heart disease, flecainide is becoming a popular drug in such patients. There is a consensus that flecainide seems to be safe in this population [32].

50.3.2 Class II Drugs

The β-adrenoceptor antagonists were initially reported as class II antiarrhythmic drugs. Obviously, they do not affect excitability of cardiomyocytes directly, but can prevent harmful arrhythmogenic actions of endogenously released catecholamines. Therefore, they are not able to stop arrhythmias in general. Efficacy of prophylactic β-adrenoceptor antagonist treatment is restricted to situations where AF is the result of acute stress such as postoperative atrial fibrillation [33]. Besides this indication, the efficacy of β-adrenoceptor antagonists in AF is not convincingly proven. Even in the setting of heart failure, where catecholamine levels are clearly elevated, β-adrenoceptor antagonists do not have any impact on the occurrence of AF [34, 35].

50.3.3 Class III Drugs

Sotalol (MJ 1999) is the oldest class III drug [36]. It was initially developed as a competitive β-adrenoceptor antagonist and was intensively tested for its ability to prevent ventricular arrhythmias in the setting of experimental myocardial infarction (so-called class II action) [37]. Somewhat unexpected for a β-adrenoceptor antagonist, sotalol was not only effective against arrhythmias but caused a remarkable positive inotropy. The surprising finding could be later explained by APD prolongation. Sotalol blocks potassium currents that are active during the plateau phase (later identified as I_{Kr}, conducted via hERG channels) (see Chap. 48). The use of sotalol was not widely propagated until the early 1990s, when class I drugs had lost acceptance in ventricular arrhythmias and the compound was believed to fill the gap. To avoid the harmful negative inotropy of β-adrenoceptor antagonists that are given acutely in patients with heart failure, the (d)-enantiomer of sotalol, devoid of adrenoceptor antagonist activity but still blocked potassium channels, was introduced to clinical use. However, it became quickly clear that (d-)-sotalol provoked severe ventricular proarrhythmia not only in patients with heart failure [38] but also in an animal model with left ventricular hypertrophy [39]. This quickly resulted in the loss of status for racemic sotalol in the treatment of ventricular tachycardia. Subsequently, sotalol was tested for its anti-AF activity [40]. Racemic sotalol is still frequently used for the prevention of reoccurrence of AF [41]. Its role in converting recent-onset AF is less popular. There are theoretical considerations in the use of sotalol for that application. Any (even electrical) conversion of AF can be followed by severe sinus bradycardia or even sinus arrest [42]. β-Adrenoceptor antagonists are expected to aggravate such a scenario. Since most of the class III agents show the phenomena of reverse-use dependence with excessive APD prolongation at low heart rate, occurrence of *torsades de pointes* arrhythmia is facilitated [43]. This phenomenon was realized as a dangerous scenario since the 1960s when quinidine (a potent hERG blocker) was frequently used for conversion of AF [44]. From this background, a fixed combination of hERG block with a β-adrenoceptor antagonist may be at least questionable. Nevertheless, application in patients with AF is still

popular, for example, in the United States [45, 46]. There is a consensus that sotalol should not be used in case of left ventricular hypertrophy or left ventricular failure.

Amiodarone is another agent classified as a class III antiarrhythmic drug. It was initially developed as a vasorelaxant. The very first study about amiodarone effects on AP showed marked APD prolongation without obvious effects on upstroke velocity [47]. Therefore, amiodarone was classified as a so-called class III drug (APD prolongation only). More than 15 years later, patch-clamp studies revealed sodium as well as calcium channels blocked by amiodarone [48]. Sodium channel block was later found to be use dependent and stronger at depolarized membrane potential [49, 50]. Thus, amiodarone shares typical class I drug features. In addition to the block of ion channels, amiodarone acts as an antagonist at β-adrenoceptors [51]. The relative contribution of different targets affected for the overall activities is less clear, but the blockade of sodium channels may play an important role (compare dronedarone section). Severe hypotension that results because of vasorelaxation, might complicate its use, when given as rapid intravenous injection. The biggest advantage of amiodarone compared to class I drugs is its low incidence for ventricular proarrhythmia [52]. The reason for the difference compared to other class III drugs is unclear [43]. The almost unique feature among antiarrhythmic drugs made amiodarone very attractive when it becomes clear that class I drugs have failed in patients with ventricular arrhythmias and structural heart disease. Consequently, amiodarone was approved for the treatment of life-threatening ventricular arrhythmias. After successful introduction of implantable cardioverter/defibrillators, amiodarone (like any other antiarrhythmic drugs) has lost popularity in this field (Chap. 8). Amiodarone not only suppresses ventricular arrhythmias but also prevents the recurrence of AF. In addition, amiodarone can convert AF; however, the onset of effect is delayed compared to class I drugs (hours vs. minutes). Low propensity for ventricular proarrhythmia makes amiodarone very attractive for treating AF, but the drug was never approved for this indication. Nevertheless, off-label use to prevent reoccurrence of AF is enormously popular (~60 % of all prescriptions in one US population) [45], but needs careful consideration given its extracardiac toxicity. Some of the unwanted effects are rather irreversible and even life threatening. Many of the amiodarone toxic effects are described as cumulative toxicity, and that could be reduced by lower dosages and shorter duration of treatment. Obviously, amiodarone use in younger patients is problematic. Large retrospective trials suggest that a remarkable number of younger patients are treated with amiodarone. Many of them are expected to be free of structural heart disease and could therefore be treated with less toxic class I drugs [46]. There are other issues that need to be addressed. In case of AF, relapse under continued treatment with amiodarone, the indication to continue drug application has to be carefully checked. There is no doubt that amiodarone can slow AV conduction and thereby control rate during AF. However, drugs much less toxic can achieve this goal; amiodarone is not recommended for this indication. Besides, in any controversy about the appropriate indication for amiodarone in AF, there is a general consensus that chronic amiodarone treatment needs intense follow-up. Patients have to undergo several clinical and biochemical tests at a fixed time schedule [53]. One of the most disastrous side

effects of amiodarone is its thyrotoxicity. Therefore, it is logical to search for a compound that is structurally related to amiodarone but free of iodine.

Dronedarone is the result of such effort, and like its congener amiodarone, dronedarone blocks a number of different ion channels and adrenoceptors. From the viewpoint of cellular electrophysiology, dronedarone shares many acute effects of amiodarone (e.g., APD prolongation), but it lacks pronounced sodium channel block as seen after chronic treatment with amiodarone [54]. Based on clinical results with amiodarone, it is logical to use dronedarone in patients with heart failure in order to reduce sudden cardiac death. However, the drug failed in this indication because of causing excess mortality due to worsening of heart failure [55], and it is noteworthy that the dronedarone, in contrast to its closely related parent compound amiodarone, was never approved for ventricular arrhythmias. The next step was testing dronedarone for its activity in AF. Like amiodarone, dronedarone is able to convert recent AF [56], but dronedarone, too, was never approved for that indication. Dronedarone prolongs the time to AF recurrence after conversion of AF [57], and the drug was approved by fast track in 2010 for that indication. Dronedarone is clearly less effective compared with amiodarone [58]. In rare cases, dronedarone can induce liver injury, including even several cases of acute liver failure leading to liver transplants [59]. Recently FDA addressed these life-threatening events in a warning letter (http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm). Dronedarone can increase mortality in some patients with permanent AF, and serious safety concerns lead to restrictions in its use (http://www.fda.gov/Drugs/DrugSafety/ucm264059.htm). Dronedarone is recommended as first-line therapy to prevent reoccurrence of AF. However, even if excess mortality is restricted to some patient populations (severe heart failure, persistent AF), it remains questionable whether a drug that can cause such harm should be prescribed for an arrhythmia that is not directly life threatening. Dronedarone has many pleiotropic effects, which are recently summarized in an excellent review [60]. What role of dronedarone should be in the treatment of AF remains to be determined. However, one can conclude that the initial hope to get a substitute for amiodarone that combines the advantages of amiodarone (efficacy against VF and AF without ventricular proarrhythmic potency) with the advantages of advanced drug design (freedom of extracardiac toxicity) could not yet be achieved.

Dofetilide and ibutilide are structurally related to the experimental hERG blocker E-4031, and all of these compounds show high selectivity. In contrast to class I drugs, pure hERG blockers do not lead to CNS side effects. Both dofetilide and ibutilide can effectively stop AF and prevent reoccurrence of AF [61, 62]. However, since blockade of hERG channels is now recognized as the leading cause for drug-induced proarrhythmias in general [63], the acceptance for that drug class is very limited (see Chaps. 48 and 49). In some countries, both drugs were never approved for AF. On the other hand, several studies report dofetilide as a safe drug as long as dosage is adjusted carefully based on QT measurements even in patients with left ventricular dysfunction [64].

50.4 Novel Targets Sites: Atrial-Selective Ion Channel Block

50.4.1 Potassium Currents

50.4.1.1 Ultrarapidly Activating Potassium Current (I_{Kur})

In the human heart, the shape of the action potentials differs remarkably between atrium and ventricle (Chap. 46). While ventricular action potentials show a long-lasting plateau phase at positive membrane potentials, atrial repolarization is characterized by a pronounced phase I repolarization leading to a deep notch with a plateau voltage clearly in the negative range. One reason for this difference is the existence of I_{Kur}, encoded by Kv1.5, in atria only [65]. Therefore, blockade of I_{Kur} represents a promising example of an atrial-selective ion channel block target [66]. I_{Kur} blockade increased the force of contraction in atrial tissue from patients in SR as well as in AF [67], and this helped to reverse contractile dysfunction in AF. However, there are several limitations. Whereas the first report in a goat model of AF showed a clear increase in refractoriness upon mixed I_{to}/I_{Kur} block by AVE0118 [68], the same compound rather shortened APD_{90} in atrial tissue obtained from patients with SR [69]. Reduced expression of Kv1.5 in AF and inactivation of I_{Kur} at higher rates in AF [70] have questioned the value of Kv1.5 as a drug target for AF. Besides this theoretical consideration, Kv1.5 blocker prolongs APD_{90} in AF. Recent in vitro study implicate effectiveness in human atrial tissue even at higher rates underlying the importance of rather complex interactions complicating prediction of drug effects based on patch-clamp data. One of the most advanced I_{Kur} blockers such as D0103 (Xention Ltd, UK) has now progressed to first studies in man [71].

50.4.1.2 Acetylcholine-Activated Potassium Current ($I_{K,ACh}$)

Even in the first reports of electrical remodeling in human AF, an increased inward rectifier current was described [72]. Later it was suggested that not only the increased expression of Kir 2.1–2.4 encoding I_{K1} was responsible, but also the existence of constitutively active $I_{K,ACh}$ could be an underlying cause [73]. This concept has raised enormous interest, since blockade of constitutively active $I_{K,ACh}$ could represent not only atrial selective ($I_{K,ACh}$ believed to be expressed in the atrium only) but also AF selective ($I_{K,ACh}$ becoming constitutively active in AF). The former assumption has been questioned recently by the finding that highly selective blockers of $I_{K,ACh}$ can affect ventricular action potentials [74]. However, it should be noted that experiments were performed in rat ventricles. Regarding the latter findings, it should be noted that in dogs, blockade of $I_{K,ACh}$ prolongs atrial APD even in tissues obtained from control animals, which reveals important species differences [75]. Reports of in vitro effects of $I_{K,ACh}$ blockers on human atrial tissue are still lacking. First report on in vivo effects of $I_{K,ACh}$ blockers in humans gave disappointing results [76], questioning whether the effect size is sufficient to evoke robust effects on refractoriness.

50.4.1.3 Calcium-Activated Potassium Channels

Small-conductance calcium-activated potassium channels (SK), also named calcium-activated potassium channels, were first described in the CNS where they contribute to transient hyperpolarization following an action potential [77]. Availability of selective blockers of SK has gained interest. SK channels are expressed in cardiomyocytes, and their activity showed the expected calcium dependency [78]. Interestingly, SK blockers prolong APD in atrial but not in ventricular tissue obtained from humans [79]. This finding makes SK channels highly attractive as an atrial-selective antiarrhythmic intervention. SK channel block has clear antiarrhythmic affects in different animal models. In human atrial tissue, SK expression was found to be reduced in AF [79]. Overall, the relevance of SK block for excitability in human atrium at higher rates and at increased intracellular calcium concentrations needs to be determined.

50.4.2 Atrial-Selective Sodium Block

50.4.2.1 Late Sodium Current

Sodium currents are known to activate and inactivate very quickly within a few milliseconds. However, a small amount of sodium currents may not inactivate completely during a test pulse and is therefore called late sodium current ($I_{Na,late}$). Definition and quantification of $I_{Na,late}$ varies, but most importantly $I_{Na,late}$ was found to be increased in atrial myocytes obtained from patients with AF compared to those from SR [80]. Ranolazine was used in a vast majority of in vitro studies as a selective blocker of $I_{Na,late}$. This assumption is based mainly on data from patch-clamp studies where ranolazine shows selectivity for $I_{Na,late}$ over $I_{Na,peak}$ [81]. However, in intact cardiac muscle preparations, ranolazine depresses maximum upstroke velocity in a use-dependent manner [82]. This prototypical class I activity occurs in the same concentration range where it blocks $I_{Na,late}$ [80]. Thus, discrimination between effects on $I_{Na,peak}$ and $I_{Na,late}$ is complicated. Furthermore, ranolazine blocks hERG channels [83] and β-adrenoceptors [84, 85]. These findings suggest that ranolazine pharmacodynamics is similar to that of propafenone. Although ranolazine has antiarrhythmic activities [86], it is hard to say to what extent it relates to the blockade of $I_{Na,late}$. From the general pharmacodynamics perspective, it would be of interest to have more selective blockers of $I_{Na,late}$ available, at least as a tool to study physiological importance of $I_{Na,late}$ in human heart under physiological and pathophysiological conditions.

50.4.2.2 Peak Sodium Current

Blockade of sodium channels is highly effective in converting AF. Therefore, sodium channels may remain an interesting drug target. Atrial-selective actions could be achieved when the sodium channel blocker has a higher affinity for sodium

channels in atrium than in ventricle, but this has never been shown. Differences in biophysics per se or different channel properties because of differences in membrane voltages from where they operate can modulate channel function, and drug binding is another possibility. Early studies in human cardiomyocytes showed not only identical current densities in atrial compared to ventricular cells but also similar voltage dependency of activation and inactivation [87, 88]. However, on the level of action potentials, it was consistently demonstrated that the resting membrane potential in atrial tissue was about 5 mv less negative than in ventricular [79, 89] tissue. Thus, more sodium channels should be inactivated in the atrium resulting in a higher affinity for sodium channel blockers. For ranolazine, it was proposed to block preferentially atrial sodium channels because of different resting membrane potential [90]. However, modifying resting membrane potential alone has hardly any effect on the absolute reduction in maximum upstroke velocity evoked by ranolazine [82]. Sodium channel blockers can shift steady-state inactivation curves to more negative potentials and thereby bring more channels to an inactivated state at any given membrane potential. Such shifts by ranolazine was reported to be larger in atrial than in ventricular dog myocytes [90]. In contrast, even in the same species (dog), effects of ranolazine on maximum upstroke velocity were almost identical in size when measured in atrial and ventricular tissue [82]. At present, atrial preferential blockade of $I_{Na,peak}$ by ranolazine seems rather unlikely.

50.5 Newly Approved Drugs: Classification Under Discussion

50.5.1 Vernakalant

Vernakalant consists to the bulk of agents initially developed as blockers of I_{Kur} [91] and thereby promising atrial-selective increase in refractoriness. It was approved in Europe as intravenous injection for the acute conversion of AF. Vernakalant's efficacy is not inferior to class I drugs such as propafenone and flecainide [92, 93]. Proper classification of the drug remains problematic since the blockade of I_{Kur} in human atrial cardiomyocytes is small and the effect on the shape of AP is very little compared to other I_{Kur} blockers [94]. Clinically proven antiarrhythmic efficacy is most probably the result of use-dependent depression of maximum upstroke velocity indicating relevant sodium channel block [94]. Sodium channel blockade-related effects such as conduction delay and negative inotropy were reported in atria and in ventricles [95, 96] and that resembled the effect of flecainide arguing against atrial-selective sodium channel block. APD in human atrial tissue is slightly prolonged because of hERG channel block [94] so vernakalant would be classified as class IC (like flecainide) in earlier days. Blockade of $I_{K,ACh}$ by vernakalant is sometimes used as another argument to classify the drug as an atrial-selective antiarrhythmic agent. However it should be noted that even flecainide blocks both $I_{K,ACh}$ and I_{Kur} [97, 98]. Intravenous vernakalant converts AF faster than oral propafenone and flecainide

[92, 93]. This finding just illustrates basic principles in pharmacokinetics (faster onset of drug effect when applied intravenously compared to oral) than it indicates general superiority of vernakalant over older, nicely established drugs. Taken all of these into consideration, we may say that it is least questionable whether vernakalant represents a major advantage in pharmacological conversion of AF.

50.6 Novel Targets: Kinases

One reason for the disappointing high relapse rate under "conventional" antiarrhythmic drug therapy could be the fact that the ion channel blocking effect just limits excitability but lets the assumed trigger event – generation of spontaneous impulse – untouched. Impulse formation within (atrial) working myocardium can occur when – after a regular action potential – a critical amount of Ca^{2+} is released from the sarcoplasmic reticulum, sufficiently large to generate a critical depolarizing net inward current that leads to depolarization with a subsequent additional action potential [99]. Catecholamines are known to promote that mechanism, and it is assumed that many of the targets involved are activated because they are phosphorylated by protein kinase A (PKA) and/or Ca^{2+}/calmodulin-dependent kinase II (CaMKII). Both PKA and CaMKII-dependent targets have been reported to be hyperphosphorylated in atrial tissues obtained from patients with AF. Consequently, it was proposed to block kinase as a causative therapeutic intervention in AF [100]. However, others could not confirm this increased target phosphorylation in AF [101]. More importantly in an animal model on AF, Ca^{2+}-signaling was found to be "silenced," [102] and arrhythmias were absent in atrial tissue from patients with AF [101] suggesting that abnormal impulse generation within the atrial tissue may not be the leading cause for the maintenance of AF in humans.

50.7 Concluding Remarks

From a historical point of view, pharmacological treatment of AF starts with the slowing of AV conduction and blockade of sodium channels to convert AF. Both objectives can now be achieved by employing drugs, which are less toxic than those were previously used. In spite of remarkable advantages in drug development, available options still show drugs with limited efficacy and serious adverse effects. Decision making in individual patients should be based on regularly updated guidelines published by AHA/ACC and ESC [103, 104]. It should be noted that such guidelines not only reflect scientific points but also discuss differences in regulatory aspects and availability of drugs in different countries [105]. Intensive basic science work in human atrial tissue as well as the use of sophisticated animal models for AF have identified new putative targets to gain atrial-selective antiarrhythmic drugs [106]. As a result of these intensive investigational and developmental works, the

first agents have reached the level of clinical application. Future research will show if the new drug targets can help to increase the efficacy and safety of pharmacological treatment of AF.

Conflict of Interest The authors declare no conflict of interest.

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Chapter 51
Use of Mechanical Devices to Reduce Stroke in Atrial Fibrillation

Peter Pollak and David Holmes

Abstract Atrial fibrillation is common, and its incidence is increasing. The preponderance of strokes occurring in non-valvular atrial fibrillation is attributable to thromboembolism from clot formed within the left atrial appendage (LAA). Current standard of care involves long-term oral anticoagulation to decrease the risk of clot formation; however, this strategy is complicated by a narrow therapeutic window with a significant incidence of bleeding complications. Early evidence suggests that surgical obliteration of the left atrial appendage reduces stroke risk, and more recently several percutaneous approaches to left atrial appendage treatment have been developed aimed at eliminating the appendage cavity to reduce stroke risk through plugging or ligation. The most studied device, the Watchman device (Boston Scientific, Marlborough, MA), has been shown to be non-inferior to adjusted-dose warfarin in non-valvular atrial fibrillation at reducing the risk of stroke. Unanswered questions surround optimal patient selection criteria for device occlusion of the left atrial appendage and comparison with novel oral anticoagulants. Moreover, multiple devices are in development and early stages of evaluation. Device-based occlusion of the left atrial appendage is a promising alternative to long-term oral anticoagulation to reduce stroke risk in patients with non-valvular atrial fibrillation.

This chapter describes the role of the left atrial appendage in cardioembolic stroke in patients with atrial fibrillation and the basis of appendage closure to reduce stroke risk. We review the procedurally relevant anatomy of the left atrial appendage and discuss the surgical and percutaneous approaches and devices used to close the left atrial appendage.

Keywords Atrial fibrillation • Left atrial appendage • Closure • Stroke • Device • Watchman • AtriClip • PLAATO • WaveCrest • Amplatz cardiac plug

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51.1 Introduction

Atrial fibrillation is the most common arrhythmia encountered in clinical practice with a lifetime risk of one in four for patients over age 40 [1]. It affects approximately between 2.7 and 6.1 million people in the United States, yet remains underdiagnosed [2]. The incidence of atrial fibrillation is increasing with the aging population, affecting 12 % of those between 75 and 84 years of age and one third of those over age 80 [3, 4]. While men seem to have slightly more atrial fibrillation compared to women, its associated mortality is higher in women The overall incidence of atrial fibrillation is lower among African Americans than Whites with the same risk factors [5]. The prevalence of atrial fibrillation is expected to double by 2050 [6] (see also Chap. 50).

Beyond symptoms attributable to irregular heart rhythm, the diagnosis of atrial fibrillation (AF) confers a fivefold increased risk of stroke [7]. Moreover, the risk of stroke associated with atrial fibrillation increases with increasing age [8]. The severity of a stroke is also greater when associated with atrial fibrillation [9]. A post hoc analysis of 3,950 patients in the Stroke Prevention in Atrial Fibrillation (SPAF) trials found 68 % of strokes in AF patients attributable to a cardioemoblic source [10].

Asymptomatic paroxysmal atrial fibrillation is also associated with a significant risk of stroke [11]. In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) of 2,580 patients over age 65 with hypertension but no known history of atrial fibrillation and a permanently implanted pacemaker or defibrillator, 10 % were found to have asymptomatic episodes of atrial fibrillation with an atrial rate >190 for 6 min. This finding significantly increased the risk of stroke from 0.69 %/year to 1.6 %/year. In heart failure patients, the implications are even more dramatic. Detection of atrial fibrillation >3.8 h/day is associated with a ninefold increase in the risk of thromboembolic event [12].

The left atrial appendage (LAA) has been established as the predominant source of thromboembolism in non-valvular atrial fibrillation. In a review of 23 studies examining the LAA, thrombus was noted in 17 % and present in the LAA in 91 % of those cases [13]. It is believed the stagnation of blood flow within the appendage during atrial fibrillation is the predominant mechanism for thrombus formation. This reasoning is supported by the association of low LAA velocities with increased risk of stroke [14].

The mainstay of treatment to reduce stroke risk in patients with atrial fibrillation is oral anticoagulation. Antiarrhythmic therapies, whether ablation or pharmaceutical, have not established a role in reducing the risk of stroke in atrial fibrillation. Vitamin K antagonists (VKA) remain the mainstay of oral anticoagulation in patients with atrial fibrillation reducing risk of stroke by 64 % compared with placebo and by 39 % when compared to oral antiplatelet agents [15]. However, VKA have a narrow therapeutic index and multiple limitations. Patients must constantly monitor and adjust their dosing. The drug's hepatic metabolism is impacted by

changes in diet and subject to multiple drug interactions. The risk of bleeding is significant varying between 1 and 12 major bleeds per 100 patient-years [16]. Moreover, patients taking VKA may be exposed to risk without benefit. In the *A*trial Fibrillation *C*lopidogrel *T*rial with *I*rbesartan for prevention of *V*ascular *E*vents (ACTIVE W), patients who did not maintain at least 65 % of the time in therapeutic range saw risk without benefit from use of warfarin [17]. New oral anticoagulants including anti-Xa inhibitors (e.g., apixaban and rivaroxaban) and direct thrombin inhibitors (e.g., dabigatran) may have improved safety profiles and efficacy; however, over the course of care longitudinally, they will still be associated with increased risks of hemorrhage.

These challenges and dangers posed by long-term oral anticoagulation combined with the established role of the LAA in the etiology of stroke for patients with atrial fibrillation have driven the development of strategies to reduce stroke risk by directly treating the LAA.

The balance of this chapter will focus on the anatomy and physiology of LAA and review the devices and approaches to decreasing stroke risk in atrial fibrillation by mechanically altering the LAA.

51.2 Left Atrial Appendage Anatomy and Morphology

The LAA is a vestigial remnant of the embryologic left atrium and lies on the posterior lateral aspect of left atrium. It is a highly variable and complex structure approximately 2–4 cm in length with its opening adjacent to the left superior pulmonary vein ostium. The body of the appendage lies freely in the pericardial space. The left circumflex coronary artery and great coronary vein run adjacent and inferior to the appendage (often within 2 mm), while the left phrenic nerve is adjacent and lateral [18].

The morphology of the appendage body is highly variable and unique to each individual. Histologically, the wall of the LAA is rugated forming the pectinate ridges, and between those ridges the wall may be only 400 μm (Fig. 51.1) explaining its fragility and the relatively high risk of perforation with instrumentation [19]. The LAA gross morphology has been categorized into four cardinal shapes (Fig. 51.2) by CT and MRI analysis with implications for stroke risk: the cactus, chicken wing, wind sock, and cauliflower [20]. The relative distribution and associated stroke or TIA were, respectively: cactus (30 and 12 %), chicken wing (48 and 4 %), wind sock (19 and 10 %), and cauliflower (3 and 18 %).

Though traditionally thought to serve no cardiac function, the LAA generates atrial natriuretic peptide and contributes to compliance of the left atrium [21]. The LAA is also electrically active, and the source of non-pulmonary vein atrial fibrillation triggers in 32 % of patients >80 years old [22]. Amputation or ablation of the LAA may thus decrease the overall burden of atrial fibrillation in some patients.

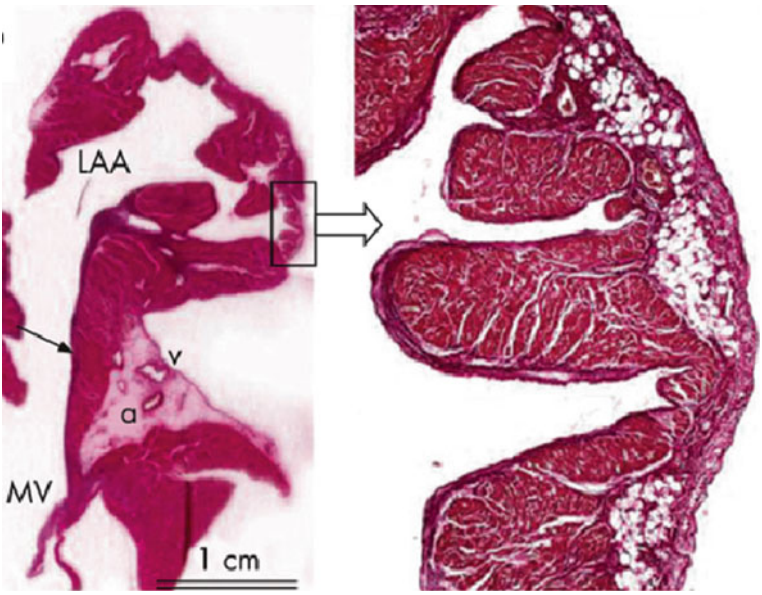

Fig. 51.1 Left atrial appendage histology slide depicting thin wall between pectinate ridges. The LAA is a very thin-walled structure as depicted here; the tissue between the pectinate ridges is less than 400 μm in thickness accounting for the ease of inadvertent perforation and pericardial effusion during instrumentation (Adapted with permission from Ref. [19])

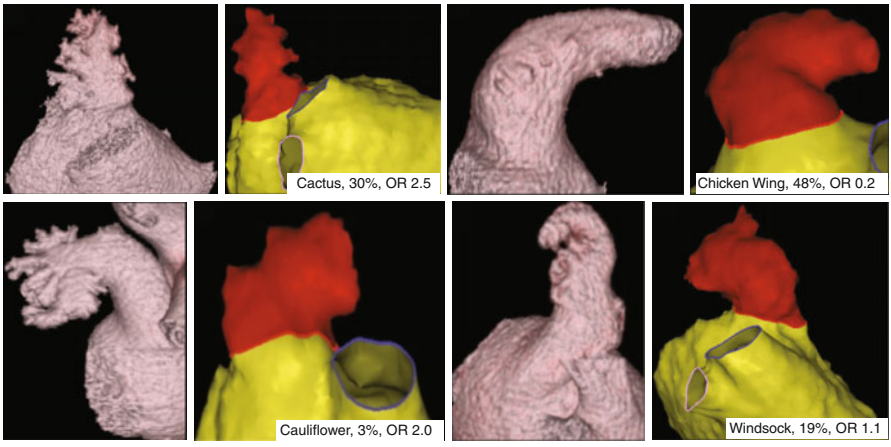

Fig. 51.2 Composite figure of LAA morphologies. LAA morphology categories include cactus, windsock, cauliflower, and chicken wing. Their prevalence (relative percent) and the odds ratio (OR) for stroke are listed [20] (Adapted with permission from Ref. [20])

51.3 Left Atrial Appendage Closure

Closure of the LAA was first explored in the 1940s, but interest waned with the development of vitamin K antagonists. More recently interest resurfaced and has been explored initially with surgical approaches performed in conjunction with concomitant heart surgeries. As is often the case with surgical technique developments, the data are limited to case series and retrospective analyses with the notable exception of the Left Atrial Appendage Occlusion Study II (LAAOS II). Three surgical devices, the AtriClip (AtriCure, West Chester, OH), TigerPaw (Maquet, Rastatt, Germany), and Endoloop suture (Johnson and Johnson, Cincinnati, OH), have been developed and tested. Percutaneous LAA closure has been an attractive idea and prompted the development of multiple devices which can broadly be categorized as "plugs" which are placed internally occluding the appendage at the ostium and "ligatures" which close the appendage from the epicardium by cinching around the ostium. Data with percutaneous devices has been slow to accumulate given slow regulatory approval and is dominated by the relatively large randomized trials of the Watchman device (Boston Scientific, Plymouth, MN) (see Table 51.1 and Fig. 51.3).

51.4 Surgical LAA Closure

Surgical closure of the LAA is widely performed with a concomitant cardiac surgical procedure, whether bypass grafting and valve repair or replacement and often in conjunction with a surgical Cox maze procedure. Surgical techniques have been detailed elsewhere and include suture exclusion, stapled exclusion, and amputation with oversewing [23].

Initial retrospective analyses of patient having undergone surgical LAA closure were positive. In one study of 205 high-risk patients undergoing mitral valve replacement (predominantly for rheumatic disease), 58 had surgical LAA closure which was associated with a significantly reduced risk of thromboembolic event (17 % vs. 34 %) [24]. Notably, incomplete LAA closure was noted in six patients (10 %), which was associated with an increased risk of thromboembolism. The Left Atrial Appendage Occlusion Study (LAAOS) intended to study the safety of surgical LAA closure and prospectively randomized 77 patients with atrial fibrillation and risk factors undergoing CABG (+/− valve surgery) to LAA ligation versus control (52 and 25, respectively) [25]. The study was not powered for efficacy, and a learning curve was demonstrated with improvements in successful closure after performing four procedures. A high rate of incomplete closure was noted (55 % of suture-mediated closures and 28 % of staple-mediated closures). The high rate of incomplete surgical closure was substantiated in a retrospective study of 137 patients over 10 years who had undergone surgical LAA closure with subsequent TEE at the Cleveland Clinic [26]. Surgical closure was successful in 40 % of the time, and unsuccessful closure was associated with thrombus in 41 % of cases but

Table 51.1 Left atrial appendage devices

Device	Manufacturer	Comment
Surgical		
AtriClip	AtriCure	Clip device closes base of LAA. 95 % success in the initial trial
TigerPaw	LAAx Inc.	Creates mattress suture closure of LAA. 93 % success in the initial trial
Endoloop snare	Johnson & Johnson	0 Prolene ligature. 75 % had residual leak by CT
Percutaneous – plug		
PLAATO	ev3 Inc.	First percutaneous device tested in trials. No longer in production
Watchman	Boston Scientific	Only device subjected to prospective randomized trials in comparison to warfarin
Amplatz cardiac plug	St. Jude Medical	Shallow profile to allow deployment in multiple lobed LAA
WaveCrest	Coherex Medical	Shallow with most retention barbs
Occlutech	Occlutech	No retention barbs to minimize risk of LAA perforation. Relies on loops to hold LAA trabeculae
LifeTech LAmbre	LifeTech	Hinged ball to facilitate placement orthogonal to LAA ostium
Cardia Ultrasept LAA	Cardia Inc.	Ball hinge between anchor and sealing membrane to increase conformity
Epicardial		
Lariat	SentreHeart Inc.	Magnetic rail created between endocardial and epicardial surfaces. Clinically approved in US without randomized data
Aegis	Aegis Medical	Loop snare with no endocardial component. Monitors for cessation of LAA electrical activity

These are LAA closure devices with published data or currently under development. Devices can be broadly categorized by delivery method as surgical or percutaneous. Percutaneous devices are divided by function into "plug" style and "ligature" style. Their manufacturer and distinguishing features are listed

none with excision. Similarly, among 94 patients at the Mayo Clinic (Minnesota) with surgical LAA closure who underwent TEE for postoperative AFib, new thrombus was seen in 28 %, and seen significantly more often when the LAA was incompletely closed (47 % vs. 12 %, $P=0.002$), and LAA amputation was associated with significantly less residual patency than ligation (51 % vs. 17 %, $P<0.0001$) [27]. LAA amputation was employed as a strategy in the LAAOS II trial in 92 % of cases when complete occlusion was required by the study protocol [28]. Amputation of the LAA appears to be a superior strategy of surgical LAA closure when compared to ligation which is associated with a significant rate of incomplete closure. Moreover, incomplete LAA closure is consistently associated with increased risk of thrombus formation [29].

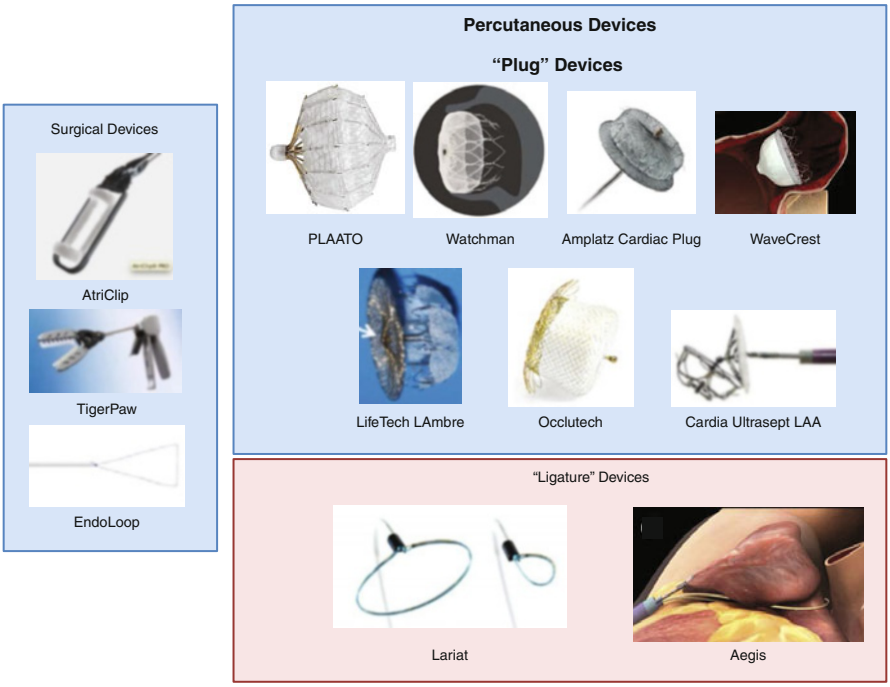

Fig. 51.3 LAA closure devices. Devices are categorized as surgical or percutaneous, and percutaneous devices are of two general styles – "plugs" which fill and occlude the LAA from within and "ligatures" which cinch and occlude the LAA from the outside

51.5 Surgical Devices

Three surgical devices have been developed for LAA closure; however, data remains limited. The AtriClip device (AtriCure, West Chester, OH) is a mechanical clip surgically placed under direct visualization at the base of the LAA. In the US experience, it successfully occluded the LAA in 67 of 70 (95 %) patients, and the LAA remained occluded in 98 % of patients at 3 months [30]. There were no device-related adverse events.

The TigerPaw device (LAAx Inc., Livermore, CA acquired by Maquet, Rastatt, Germany) is likewise surgically placed under direct visualization. It consists of a series of male and female U-shaped barbs buttressed by a soft silicone ring intended to form mattress suture-style closure at the base of the LAA. In the initial study of 60 implants, there was a single device-related adverse event (minor tissue tear requiring suture), and complete closure (by TEE) was noted acutely in 56 (93 %) and in all 54 who had 90-day follow-up imaging [31].

Finally, the Endoloop suture (Johnson & Johnson, Cincinnati, OH) is an 0 Prolene ligature secured at the base of the LAA to close it off. It was initially tested in 12 patients without any immediate procedural complications, yet in 9 (75 %) there was residual patency by postoperative CT assessment [32].

51.6 Percutaneous LAA Closure

Percutaneous closure of the LAA is an attractive idea for multiple reasons. Many patients have atrial fibrillation with accompanying stroke risk, and the LAA has been established as the predominant location of thrombus formation in the left atrium. While surgical LAA amputation is generally effective, most patients with atrial fibrillation do not have concomitant need for cardiac surgery, so a low-risk percutaneous procedure to accomplish the same effect is desirable particularly in an older, frail population. Moreover, while anticoagulation effectively reduces stroke risk in AF, the bleeding risk of oral anticoagulation is cumulative, may be prohibitive for some patients, and augmented by concomitant use of antiplatelet agents, so a device or procedure is sought which could reduce stroke risk while obviating the need for anticoagulation.

Percutaneous devices for LAA closure include "plugs" and "ligatures." All percutaneous devices are placed in a cardiac catheterization laboratory using a combination of fluoroscopic and transesophageal (TEE) guidance. The use of TEE guidance during the procedure offers the benefit of ensuring adequate LAA closure and appropriate device positioning before concluding the case. All approaches require adequate anticoagulation (usually with unfractionated heparin), while any device is in the left atrium; however, management of peri-procedural anticoagulation and antiplatelet medicines have varied across devices and trials and may be a source of disparity in outcomes (e.g., access site bleeding and peri-procedural stroke).

The "plug" devices are all endocardial and placed via transvenous transseptal approach using combined fluoroscopic and transesophageal imaging guidance. No LAA closure device has been approved for clinical use in the United States. The devices which have been studied in humans or approved for clinical use in Europe (CE Mark approval) include the PLAATO device (Appriva Medical, Sunnyvale, CA – removed from market), the Watchman device (Boston Scientific, Maple Grove, MN), the WaveCrest device (Coherex Medical, Salt Lake City, UT), and the Amplatz Cardiac Plug (St. Jude Medical, St. Paul, MN).

The first widely studied percutaneous LAA closure device was the PLAATO device (Appriva Medical, Sunnyvale, CA). It is composed of a self-expanding nitinol frame with retention barbs wrapped in an impermeable membrane. Placement involved unsheathing the device within the ostium of the LAA using a 12F delivery sheath. Preclinical studies revealed subsequent endothelial ingrowth sealing off the opening to the appendage. Patients were treated with aspirin and clopidogrel but not anticoagulation before and following the procedure.

The early clinical experience was collated from feasibility trials in multiple centers in Europe and North America. In 111 patients with non-valvular atrial fibrillation, an average CHADS2 score of 2.5, and a contraindication to anticoagulation, device placement was successful in 108 (97.3 %). A single patient died, and two patients suffered stroke during an average of 9.8 months of follow-up. The two strokes (2.2 % per patient-year) compared favorably with the 6.3 % per year

predicted stroke rate based on the study population risk profile. Five patients (4.5 %) developed pericardial effusion which was without sequelae in four of the five. The patient who died developed hemopericardium following transseptal puncture (before device deployment) and required emergent cardiac surgery. This patient's recovery was complicated by DVT, intracranial hemorrhage on anticoagulation, and subsequent death [33]. The authors concluded percutaneous LAA closure could be performed reliably with acceptable risk.

Five-year follow-up was possible in 64 patients from the North American experience (the European feasibility trial required only 1-year follow-up). The study group experienced a stroke/TIA rate of 3.8 % per year, a 42 % reduction compared to the 6.6 % per year rate predicted [34]. Similarly in the European experience of 180 patients who underwent PLAATO device placement, the annualized observed stroke rate of 2.3 %/year over 129 patient-years was less than the 6.6 %/year predicted rate [35]. Device placement was successful 90 % of the time, and there were eight procedure-related major adverse events (MAEs). Despite these initially promising results, the PLAATO device was withdrawn from the market and further study.

The Watchman device (Boston Scientific) has been the most extensively studied percutaneous device for LAA closure. Similar to the PLAATO device, it is made of a self-expanding nitinol wire frame with retention barbs and covered with a PET membrane. Delivery is via a 14F sheath with the device unsheathed in the LAA ostium. It is available in five sizes from 21 to 33 mm diameter with recommended 20 % oversizing. The procedure is performed with TEE and fluoroscopic guidance, and patients are treated with aspirin and clopidogrel peri-procedurally with oral anticoagulation for 45 days following implantation until TEE verification of complete closure. Patients without leak around the device (<5 mm of flow by TEE) are then switched to aspirin and clopidogrel for the balance of 6 months at which point aspirin alone is continued indefinitely.

The Percutaneous Closure of the Left Atrial Appendage versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) trial and the Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation versus Long-Term Warfarin Therapy (PREVAIL) trial of the Watchman device are the only prospective randomized trials of percutaneous LAA closure. The PROTECT-AF was a non-inferiority trial of 707 patients with atrial fibrillation and stroke risk and who were eligible for anticoagulation. Patients were randomized 2:1 (463 device, 244 control/warfarin) and followed initially for 1,065 patient-years [36]. Non-inferiority was met and maintained out to 1,500 patient-years of follow-up [37]. The composite primary efficacy endpoint (stroke, death, or systemic embolism) was less (3.0 per 100 patient-years) in the device arm compared to the control arm (4.9 per 100 patient-years, >99.9 % for non-inferiority). In the successfully treated population, the results were even better (1.9 vs. 4.6 per 100 patient-years). Surprisingly, cardiovascular death was 74 % lower in the device group (0.7 vs. 2.7 per 100 patient-years) than the control group (see Fig. 51.4). Moreover, the device group experienced a 94 % reduction in hemorrhagic stroke (0.1 vs. 1.6 per 100 patient-years). As expected, the control group experienced more major bleeding (4.1 %) and

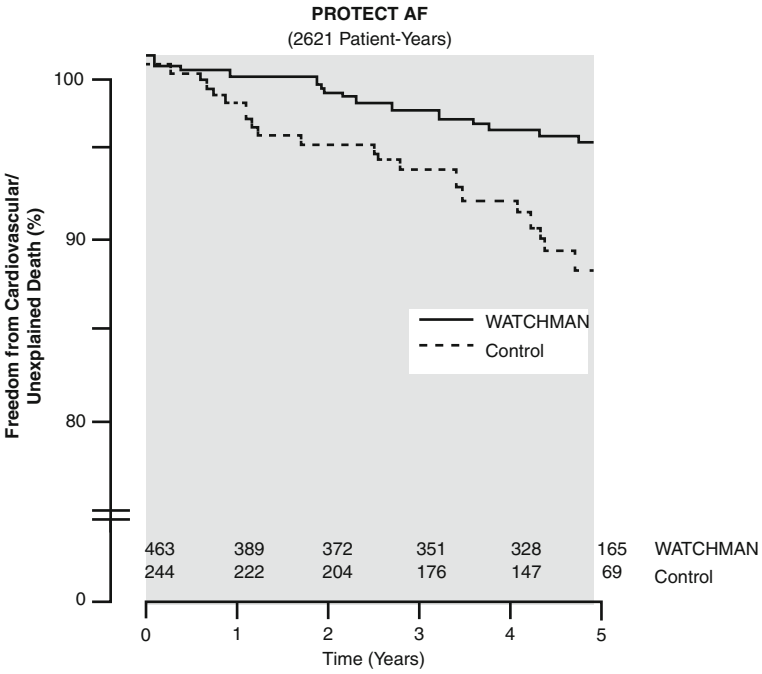

Fig. 51.4 Mortality benefit of the Watchman device. In randomized trial data patients who received the Watchman device had a lower mortality than those continued on standard therapy (Data prepared by Boston Scientific for FDA Panel meeting December 11, 2013. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM377935.pdf. Accessed Nov 4, 2014)

hemorrhagic stroke (2.5 %), while the device group experienced more procedure-related complications (pericardial effusion 4.8 %, major bleeding 3.5 %, device embolization 0.6 %, procedure-related ischemic stroke 1.1 %). The overall increased risk of procedural complication was offset over time by the reduction in hemorrhagic stroke relative to the anticoagulated control arm. Notably, the observed rate of ischemic stroke in the control arm (1.6 per 100 patient-years) was lower than that predicted by their risk profile. In this study, 86 % of patients were able to stop anticoagulation at 45-day follow-up, which rose to 92 % at 6 months. In the continued access protocol (CAP) registry data of 460 patients with device implants following PROTECT-AF, the rate of procedural complication by experienced operators improved substantially (2.2 % pericardial effusion, 0 % peri-procedural stroke) [38]. Sub-analyses from the PROTECT-AF data revealed a significant improvement in quality of life following device placement and no increased risk related to unclosed iatrogenic atrial septal defects [39, 40]. The overall results of the PROTECT-AF and CAP data were positive suggesting a role for device therapy in stroke reduction for patients with non-valvular atrial fibrillation.

Nevertheless, concern remained over the safety and efficacy profiles of the device prompting the PREVAIL trial which randomized 407 patients at 41 US centers in the same 2:1 fashion and with the same medication plan as PROTECT-AF [41]. Importantly, inclusion criteria for PREVAIL were revised to a higher CHADS2 score of 2 or more (vs. 1 or more) targeting a higher-risk population than in PROTECT-AF (avg. CHADS2 score 2.6 vs. 2.2). The trial was required to include new sites and new operators to test the durability of the safety profile; thus 39 % of implants were performed by new operators. Nevertheless, implant success was 95 % (improved from 90 % in PROTECT-AF), while procedural complication rate was significantly lower than previously documented (4.2 % vs. 8.7 % overall). There were no peri-procedural strokes. Pericardial effusions requiring surgery decreased significantly (1.6–0.4 %, $P=0.027$), and 98 % of patients could discontinue warfarin at 6 months (up from 92 % in PROTECT-AF). The trial was marked by a low event rate in the control arm, which experienced a single ischemic stroke and no hemorrhagic strokes. Overall, the pre-specified statistical endpoint for non-inferiority was not met; however, the co-primary endpoints and safety endpoints were met supporting the safety and efficacy of the Watchman device even with novice implanters.

All trials involving the Watchman device required patient eligibility to take oral anticoagulation; however, a major interest in device-based stroke reduction in atrial fibrillation is for patients who cannot be safely anticoagulated. Thus the ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP) sought to address the use of the Watchman device in patients who were ineligible for warfarin [42]. A total of 150 patients with an average CHADS2 score of 2.8 were prospectively enrolled and treated with aspirin plus 6 months of clopidogrel. There were six cases of device-related thrombus, but only one associated with stroke giving an annualized device thrombus-related stroke rate of 0.3 % per year. The observed overall stroke rate of 1.7 % per year represents a 77 % reduction compared with the expected rate of 7.3 % per year based on the CHADS2 score.

Importantly, the vast majority of patient who receive a Watchman device were able to stop warfarin, and this percentage increased with increased experience in device placement and patient selection. In the most recent study, PREVAIL, 99 % of patients who received a Watchman device were able to stop taking warfarin (see Table 51.2).

The Amplatz Cardiac Plug (St. Jude Medical) is another percutaneous transcatheter device for LAA closure. It is composed of two woven nickel-titanium self-expanding discs with retention barbs on the distal disc and a polyester patch embedded within the discs. The distal disc is placed within the LAA and holds the proximal disc flush against the ostium. Aspirin plus clopidogrel is used peri-procedurally but not oral anticoagulation. The early European experience with the device was summarized retrospectively by Park et al. [43]. The experience involved 137 patients who underwent procedure with a 96 % (132 of 137) success rate and 7 % (10 of 137) serious complication rate [43]. In a prospective Asia-Pacific study, 20 patients ineligible for warfarin underwent device implant with 95 % success. No stroke or death occurred during the 12-month follow-up [44].

Table 51.2 Warfarin cessation in Watchman trials

Visit	PROTECT-AF ($N=408$)	PREVAIL ($N=252$)	CAP ($N=566$)
45 day	87 %	92 %	96 %
6 month	92 %	98 %	99 %
12 month	93 %	99 %	96 %

Across all trial data of Watchman usage, all but a small percentage of patients were able to stop warfarin. With increased experience with device placement and patient selection, 99 % of patients were able to stop warfarin usage following device placement. Data prepared by Boston Scientific for FDA Panel meeting December 11, 2013. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM377935.pdf. Accessed Nov 4, 2014

The WaveCrest device (Coherex Medical) is a percutaneous device for left atrial appendage occlusion with a similar profile to the PLAATO and Watchman devices. It is made of a self-expanding nickel-titanium frame with multiple retention barbs and covered with a polyester membrane. It is designed to have a shorter shallower profile than the Watchman device to allow placement in appendages with multiple lobes, and its delivery system allows contrast injection during deployment to determine placement and adequacy of seal. Preclinical work in 12 dog models with percutaneous implants revealed full coverage by neointima in 30 days and complete endothelialization by 180 days [45]. In the WAVECREST I trial of 73 patients in Europe, Australia, and New Zealand, device implant was successful in 70 (96 %), and closure as determined by core lab TEE was successful in 67/69 (97 %) [46]. The protocol for dual antiplatelet therapy was 90 days followed by aspirin alone unless patients had prior stroke and were taking oral anticoagulation. In that case, oral anticoagulation was continued until LAA closure was documented by TEE. Based on these results, the device received CE Mark approval for commercial use in Europe. A US pivotal trial, WAVECREST II, is planned to begin in 2014.

Other plug-style devices are in various stages of development. The Occlutech LAA occluder (Occlutech International AB, Helsingborg, Sweden) is a self-expanding nitinol mesh plug with a polymer covering. Distinguishing features include the absence of barbs for anchoring, instead relying on closed loops to engage the LAA trabeculations and a pivoting ball connection with the delivery system to facilitate orthogonal deployment in the LAA. The LifeTech LAmbre device (LifeTech Scientific, Shenzhen, China) also seals the LAA ostium with a cover but is anchored using an umbrella anchor. It has completed first-in-man implants in Asia and is planning a CE Mark trial [47]. Finally, the Cardia Ultrasept (Cardia Inc., Eagan, MN) is a two-component plug device with a distal self-expanding nitinol cage with retention barbs attached to a sealing membrane by an articulating joint. It is designed to be fully retrievable and allow for stable anchoring in tortuous anatomies. The first-in-man experience in Brazil was noted to be positive.

51.7 Epicardial Devices

The disadvantages of any endocardial device include risk of device-related thrombus or infection, complication from transseptal puncture, and the need for antithrombotics. Placement of an epicardial ligature to cinch the LAA closed holds the promise of avoiding these risks and has driven interest in two devices, the Lariat system (SentreHeart, Palo Alto, CA) and the Aegis device (Aegis Medical, Vancouver, Canada).

The Lariat system (SentreHeart) is commercially approved for tissue apposition and has been marketed and used for LAA occlusion in warfarin-ineligible patients. It involves a two-part magnetically coupled system combining intracardiac and epicardial components to place a loop around the base of the left atrial appendage that is tightened to close it off. The intracardiac component of the system contains a wire with a magnetic tip that is introduced via transseptal puncture into the tip of the LAA. The epicardial component also contains a magnet and is introduced epicardially so the two magnets connect through the thin LAA tissue to form a rail. The loop is delivered over this rail and around the LAA. Because it requires epicardial access and maneuvering, adhesions interfere with device delivery. The Lariat system is not recommended for use with multilobed or superiorly directed appendage morphologies.

The Lariat device has not undergone a prospective randomized trial and was approved for clinical use in the United States for tissue apposition under the 510 K pathway. [A 510(k) is a premarket submission made to FDA to demonstrate that a class I, II, or III device intended to be marketed for human use is at least as safe and effective, that is, substantially equivalent to a legally marketed device that is not subject to premarket approval. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims.] In a retrospective analysis of 154 patients with a median CHADS2 score of 3 at eight US centers, the device was successfully deployed in 94 %, while procedural success was 86 % (i.e., device deployment with residual shunt <5 mm). Major bleeding occurred in 14 (9.1 %) patients and significant pericardial effusion in 16 (10.4 %) [48]. In terms of efficacy, death, MI, or stroke occurred in 4 patients (2.9 %), and 63 patients had documented TEE follow-up revealing 3 (4.8 %) with thrombi and 13 (20 %) with residual leak. Notably this population was biased towards higher-risk patients with 62 % having a history of prior major bleeding and 14 % with prior hemorrhagic stroke. Peri-procedural medication was left to individual practitioners. Twenty-four percent had dual antiplatelet therapy, and 23 % had oral anticoagulation at discharge following procedure. Pericarditis is a known complication, but data were not routinely collected for this study.

The Aegis device (Aegis Medical) is a percutaneous epicardial loop suture device placed around the base of the LAA and tightened to close the LAA from the outside [49]. The LAA is grasped and held while the loop suture is placed around it. The Aegis device is different from the Lariat system in two important ways. It does not require endocardial access, thus eliminating the risk of catheter- or wire-related

thrombus, procedural anticoagulation, and catheter-induced air embolism. It is designed to detect electrical activity within the LAA, and adequate closure is determined by cessation of LAA electrical activity. Because the LAA contributes to the generation of atrial fibrillation, terminating its electrical activity may reduce the overall burden of atrial fibrillation.

51.8 Guideline Recommendations for LAA Closure

Guidelines for the management of patients with atrial fibrillation were updated by the European Society of Cardiology in 2012 and in 2014 from the American College of Cardiology and American Heart Association in conjunction with the Heart Rhythm Society [50, 51]. Both guidelines address surgical LAA closure citing the high rate of incomplete closure and give a IIb recommendation only for surgical *excision* of the appendage during concomitant heart surgery. In the United States, the Lariat system is the only commercially available LAA closure device and has not been subject to randomized trials or long-term data analysis, so no recommendation is made regarding device closure of the LAA. In the European guidelines, where multiple devices have received CE Mark approval for clinical use, percutaneous device closure of the LAA is given a IIb recommendation for patients with atrial fibrillation at *high stroke risk* and with *contraindications to long-term anticoagulation*.

51.9 Novel Oral Anticoagulants

Until recently warfarin was the only pharmaceutical agent used for long-term oral anticoagulation in atrial fibrillation. In the time since the initial PLAATO and WATCHMAN trials began, three new drugs have seen approval and widespread adoption as alternatives to warfarin. None of the medications require the monitoring and dose adjustment of warfarin, and all have demonstrated favorable safety and efficacy profiles in comparison to warfarin. Dabigatran is an oral direct thrombin inhibitor which was studied in the Randomized Evaluation of Long-Term Anticoagulation Therapy Study Group (RE-LY) trial at two doses, 110 mg and 150 mg twice daily [52]. The 150 mg dose was approved for use. Rivaroxaban and apixaban are both oral factor Xa inhibitors which were studied in the Rivaroxaban Once Daily Oral Factor Xa Inhibition compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial respectively [53, 54]. These trials have included more than 34,000 patients randomized to warfarin or a novel oral anticoagulant (NOAC) accumulating a great volume of data about the safety and efficacy of both warfarin and the NOACs. For example, across the 17,000 patients who received

Table 51.3 Comparison of stroke reduction strategies

		Stroke and systemic embolism		Major bleeding	
Trial (N)	CHADS2	Warfarin	Watchman		
PROTECT-AF	2.2				
1065 pt y		3.2	2.6		
1588 pt y		2.7	2.3		
2621 pt y*		2.2	1.7		
CAP	2.5				
1350 pt y		1.2			
RE-LY (12,098)	2.2		Dabigatran 150 mg BID		Warfarin
		1.7	1.1	3.11	3.36
ROCKET-AF (14,264)	3.5		Rivaroxaban		
		2.2	1.7	5.6	5.4
ARISTOTLE (18,201)	2.1		Apixaban		
		1.6	1.3	2.13	3.09

Data available from the randomized LAA device trials (all using the Watchman device) is presented alongside data from the three randomized trials of novel oral anticoagulants. Stroke and systemic embolism data and major bleeding data are number per 100 patient-years.
*Data prepared by Boston Scientific for FDA Panel meeting December 11, 2013. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM377935.pdf. Accessed Nov 4, 2014

warfarin in these trials, the annualized rates of stroke or systemic embolization were 1.70 (RE-LY), 2.20 (ROCKET-AF), and 1.60 (ARISTOTLE), so the 0.71 seen in PREVAIL appears notably lower than expected (see Table 51.3). The rates of major bleeding were consistent across treatment groups and trials: 2.13 % versus 3.09 % (apixaban vs. warfarin), 5.6 % versus 5.4 % (rivaroxaban vs. warfarin), and 3.11 % versus 3.36 % (dabigatran 150 vs. warfarin). These rates illustrate the cumulative risk of long-term anticoagulation and underscore the need for an alternative strategy to reduce stroke risk in patients at increased risk of bleeding.

Nevertheless, no LAA closure devices have been directly compared to NOAC therapy. Future trials of LAA closure devices will likely focus on patients with contraindications to long-term anticoagulation (in keeping with the ESC guidelines).

51.10 Concluding Remarks

Patients with atrial fibrillation are at increased risk of cardioembolic stroke, and 90 % of intracardiac thrombi form in the left atrial appendage. Closure of the left atrial appendage reduces the risk of stroke in atrial fibrillation and can be accomplished surgically or percutaneously. Surgical ligation has a high rate of residual patency, which may paradoxically increase the risk of thrombus formation and stroke, while TEE-guided surgical amputation is more successful. Multiple devices

have been developed to occlude or ligate the left atrial appendage. Surgical placement of the AtriClip (AtriCure) and TigerPaw (Maquet) devices to ligate the appendage has a high procedural success rate but limited efficacy data. Percutaneous devices can be broadly divided into devices that plug the LAA and those that ligate the appendage. The most studied device is the Watchman (Boston Scientific), which is placed via transseptal puncture to occlude the LAA. Its safety and efficacy compared to warfarin therapy have been established in the PROTECT-AF and PREVAIL trials. Conceptually a percutaneous LAA closure device must trade procedural risk for the benefit of avoiding bleeding risk from long-term anticoagulation. The novel oral anticoagulants add another dimension to this area by altering the associated bleeding risk compared to warfarin and have not yet been tested in comparison to LAA closure devices. Percutaneous LAA closure devices offer an important therapeutic option to patients who are intolerant or ineligible for long-term anticoagulation and may be a desirable alternative for patients who wish to avoid anticoagulation.

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Chapter 52
Antiarrhythmic Drugs and Management of Ventricular Arrhythmias

J. William Schleifer and Komandoor Srivathsan

Abstract While many advances have occurred in the nonpharmacologic treatment of ventricular arrhythmias, antiarrhythmic medications remain indispensable in the acute treatment and prevention of recurrent ventricular arrhythmias. Additionally, it is important to understand the effects of medications on neurohormonal modulation and defibrillation thresholds. Some antiarrhythmics have specialized uses for specific arrhythmias, and some can be used in the electrophysiology lab for diagnostic testing and aid during ablations. In contrast, amiodarone is effective for various arrhythmias, but it has many extracardiac toxicities. This chapter discusses the pharmacology and clinical use of antiarrhythmics for diagnostic and therapeutic management of ventricular arrhythmias.

Keywords Amiodarone • Antiarrhythmic medications • Cardioversion • Potassium channel blocker • Sodium channel blocker • Ventricular arrhythmia • ICD • QT interval • Ventricular tachycardia • Ventricular fibrillation

Abbreviations

ECG	Electrocardiogram
ICD	Implantable cardioverter-defibrillator
QTc	Corrected QT interval
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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52.1 Introduction

52.1.1 Spectrum of Ventricular Arrhythmias

Ventricular arrhythmias range from the benign isolated premature ventricular contractions (PVCs) to ventricular tachycardia (VT) and ventricular fibrillation (VF) which are common causes of sudden cardiac death. Other ventricular arrhythmias are bradyarrhythmias such as the ventricular escape that occurs in patients with complete heart block or the accelerated idioventricular rhythm that occurs in patients suffering a myocardial infarction who are reperfused. Idioventricular rhythm and ventricular escape rhythms are never pharmacologically suppressed and, depending on the clinical context, may be an indication for pacing if there are no reversible causes. The pharmacologic treatment of ventricular arrhythmias therefore is limited to the tachyarrhythmias, including PVCs, VT, and VF.

While increasing burden of PVCs correlates with worsened prognosis in patients with ischemic cardiomyopathy, pharmacologic suppression of PVCs arising from this substrate has been associated with increased mortality [1, 2]. On the other hand, frequent PVCs can lead to the development of a cardiomyopathy similar to tachycardia-induced cardiomyopathy that is reversible with antiarrhythmic medications or catheter ablation [3].

Nonsustained VT is defined by three or more ventricular beats that continue for less than 30 s. These arrhythmias are self-limited. In patients with ischemic cardiomyopathy and a mildly reduced ejection fraction (35–40 %), nonsustained VT is an indication for an electrophysiology study to determine whether patients would benefit from an implantable cardioverter-defibrillator (ICD), based on the results of the Multicenter Unsustained Tachycardia Trial (MUSTT) [4]. Nonsustained VT also may be considered as a risk marker in the consideration of ICD implantation for primary prevention of sudden death in patients with hypertrophic cardiomyopathy. Otherwise, nonsustained VT is approached similarly to frequent PVCs: treated with suppressive antiarrhythmics only if it causes tachycardia-induced cardiomyopathy or produces significant symptoms.

On the other hand, sustained VT is treated with much more urgency and frequently requires pharmacologic suppression. Unless it occurs in patients with structurally normal hearts, it is an indication for ICD implantation for secondary prevention. Monomorphic VT may not necessarily cause immediate hemodynamic instability. In the hemodynamically stable patients, that stability may be short in duration. Any patient with hemodynamically stable monomorphic VT should have an electrocardiogram (ECG) performed to aid in distinguishing the rhythm from a supraventricular tachycardia with aberrant conduction and to aid in localizing the exit site of the VT. Because of the risk of hemodynamic collapse or tachycardia-induced cardiomyopathy is high during VT, every attempt must be made to return the patient to a normal rhythm either by acute administration of an antiarrhythmic medication or by synchronized direct-current cardioversion with sedation.

Polymorphic ventricular tachycardia and ventricular fibrillation are rarely hemodynamically stable arrhythmias except in patients who have mechanical cardiovascular support devices. All patients require defibrillation acutely. Whereas the ECG of monomorphic VT gives much information about the exit site and type of tachycardia, the main information about the substrate and cause of polymorphic VT and VF will be obtained from the sinus rhythm ECG and any cardiac monitor that shows the initiation of the arrhythmia. Sinus rhythm ECGs may show a Brugada pattern, a prolonged QT, ST-segment elevation, epsilon waves, left ventricular hypertrophy, or frequent PVCs. PVCs may also be seen to initiate the episode if the patient happened to be connected to a cardiac monitor. If the arrhythmia is PVC induced, suppression of those PVCs is accomplished either pharmacologically or by catheter ablation. If the patient has a structurally normal heart and a Brugada pattern or long QT syndrome, other medications can be used to prevent VF in these conditions. The QT interval often prolongs during acute ischemia; furthermore, VF can occur in acute ischemia despite an otherwise normal corrected QT interval (QTc). Therefore, any patient with VT or VF and suspected ischemia should undergo coronary angiography with intent to revascularize critical atherosclerotic lesions.

After a patient has an episode of cardiac arrest regardless of cardiac substrate, or sustained VT with structural heart disease, ICD implantation is indicated for secondary prevention (Chaps. 7 and 8). Multiple trials demonstrate that ICDs reduce mortality compared to antiarrhythmics. In particular, ICDs reduced 2-year mortality by 27 % compared to amiodarone or sotalol in the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial [5], 3-year mortality by 20 % compared to amiodarone in CIDS (Canadian Implantable Defibrillator Study) [6], and 23 % compared to amiodarone or metoprolol in CASH (Cardiac Arrest Study Hamburg) [7]. A meta-analysis of these studies estimates a 28 % reduction in the relative risk of death, with a 50 % reduction in risk of arrhythmic death [8]. In patients with a reduced ejection fraction because of ischemic or irreversible nonischemic cardiomyopathy, an ICD is indicated for primary prevention based on several investigations. A pooled analysis of these trials found a 25 % relative reduction in all-cause mortality in patients receiving an ICD for primary prevention and with an absolute mortality reduction of 7.9 % in patients already receiving optimal medical therapy [9]. Because no mortality benefit was seen in patients receiving an ICD immediately after myocardial infarction or surgical revascularization, a waiting period is required before an ICD should be implanted [10, 11]. Table 52.1 summarizes the key ICD trials evaluating mortality benefit in primary and secondary prevention.

Certain types of VT in patients with structurally normal hearts respond well to medical therapy and catheter ablation; therefore, ICD implantation is not indicated in right ventricular outflow tract tachycardia, fascicular tachycardia, or idiopathic ventricular tachycardia originating from the aortic cusps. These tachycardias in a structurally normal heart have a low risk of causing sudden cardiac death.

Table 52.1 Summary of trials comparing ICD implantation with antiarrhythmic medications

Trial	Inclusion criteria	Treatment groups (n)	Results
Secondary prevention			
Antiarrhythmics versus implantable defibrillators (AVID) (1997) [5]	Patients with VF arrest, sustained VT Mean follow-up: 8.2 ± 12.2 months	Empiric amiodarone (356), randomized to amiodarone (79), amiodarone after sotalol failure (58), EPS-guided sotalol (13) vs. ICD implantation (507)	27 % mortality reduction after 2 years in ICD group 12.4 % of ICD group were later started on sotalol or amiodarone 9.8 % of antiarrhythmics group later received an ICD
Canadian Implantable Defibrillator Study (CIDS) (2000) [6]	Patients with VF arrest or sustained VT without recent MI or electrolyte abnormality Mean follow-up: 2.9–3.0 years	Empiric amiodarone (331) vs. ICD implantation (328)	Cumulative 20 % risk reduction in mortality and 33 % reduction in arrhythmic mortality; 21.4 % of patients randomized to amiodarone received an ICD; 28.1 % of patients randomized to ICD were later placed on amiodarone
Cardiac Arrest Study Hamburg (CASH) (2000) [7]	Patients with VT/VF arrest not related to MI, cardiac surgery, electrolyte abnormalities, or proarrhythmia Mean follow-up: 57 ± 34 months	Empiric amiodarone (92) vs. metoprolol (97) vs. ICD implantation (99) The 58 patients randomized to propafenone were excluded later due to an interim analysis showing 61 % higher relative risk of all-cause mortality compared to ICD	Death rates were 36.4 % in ICD arm and 46.6 % in the combined metoprolol and amiodarone groups, but did not reach significance ($p = 0.08$) (no significant difference between amiodarone and metoprolol groups)
Primary prevention			
Multicenter Unsustained Tachycardia Trial (MUSTT) (1993) [4]	Patients with ischemic cardiomyopathy and an LVEF ≤40 % with ≥3 beats asymptomatic unsustained VT ≥4 days after MI, without current exercise-induced ischemia; inducible sustained VT on EPS Mean follow-up: 39 months	2,202 enrolled and underwent EPS; 767 had inducible sustained VT; 704 randomized; 351 received EPS-guided therapy, with 158 receiving antiarrhythmics and 161 receiving ICDs	2-year death rate in patients with no therapy 28 % vs 22 % in the patients treated with EPS-guided therapy; there was a 9 % risk of cardiac death in patients with an ICD compared to 37 % in patients without an ICD

Multicenter Automatic Defibrillator Implantation Trial (MADIT) (1996) [1]	LVEF ≤35 %; history of MI ≥3 weeks prior; revascularization ≥3 months prior; NYHA I–III; ≥3 beats asymptomatic unsustained VT; inducible sustained VT on EPS Mean follow-up: 27 months	101 received conventional therapy; 95 received ICDs (45 transthoracic; 50 transvenous)	Stopped early because of significant reduction of mortality in ICD group (HR 0.46, CI 0.26–0.82); 74 % in conventional group on amiodarone; 11 in the conventional therapy group received an ICD
Prophylactic ICD after Coronary Artery Bypass Graft (CABG-Patch) (1997) [11]	LVEF ≤35 %, abnormal signal-averaged ECG Mean follow-up: 32 months	Of 1422 eligible patients, 900 randomized to ICD (446) or control (454)	No significant difference in all-cause mortality or cardiac death between groups (HR 1.03; CI 0.75–1.41)
Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) (2002) [2]	LVEF ≤30 %, history of MI; revascularization ≥3 months prior; NYHA I–III Mean follow-up: 20 months	1232 patients randomized to defibrillator (742) or conventional therapy (490)	Stopped early because of significant reduction of mortality in ICD group (HR 0.69, CI 0.51–0.93); 22 patients in conventional therapy group received an ICD
Cardiomyopathy Trial (CAT) (2002) [3]	Dilated cardiomyopathy within 9 months of diagnosis; LVEF ≤30 %, NYHA II–III Mean follow-up: 5.5 years	104 patients randomized to ICD (50) or control (54)	Underpowered, because mortality for all patients (5.6 %) was significantly below predicted; no significant difference between groups
Amiodarone versus implantable cardioverter-defibrillator: randomized trial (AMIOVIRT) (2003) [4]	Nonischemic dilated cardiomyopathy with LVEF ≤35 %, asymptomatic nonsustained VT, NYHA classes I–III Mean follow-up: 2 years	103 patients randomized to ICD (51) or amiodarone (52) (mean dose 300 mg)	3-year survival (88 % in ICD group vs. 87 % with amiodarone) and arrhythmia-free survival (63 % in ICD group and 73 % with amiodarone) were not significantly different
Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) (2004) [10]	LVEF ≤35 % with an MI 6–40 days prior and reduced heart rate variability or elevated resting heart rate >80 beats/min; excluded patients with NYHA IV HF, recent CABG or 3-vessel PCI Mean follow-up: 30 months	674 patients randomized to ICD (332) or control (342); 36 % had PCI and 24 % had thrombolysis only; 95 % received ACE inhibitors and 87 % received beta-blockers	No difference in mortality was observed (HR 1.08; $p = 0.66$); the decrease in arrhythmic death in the ICD group was offset by an increased rate of death from nonarrhythmic causes

(continued)

Table 52.1 (continued)

Trial	Inclusion criteria	Treatment groups (n)	Results
Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) (2004) [5]	Nonischemic cardiomyopathy with LVEF ≤35 % with PVCs or nonsustained VT; NYHA classes I–III Mean follow-up: 29 months	458 patients randomized to standard medical therapy (229) or standard medical therapy with an ICD (229)	ICD significantly reduced mortality from arrhythmia (HR 0.20, CI 0.06–0.71), but there was no significant difference in all-cause mortality
Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) [6]	Ischemic or nonischemic cardiomyopathy, EF ≤35 %, QRS ≥120 ms, NYHA classes III–IV; hospitalization for HF in the preceding year Mean follow-up: 14.8 months in control group; 16 months in CRT-P and CRT-D groups	Randomized to optimal medical therapy alone (308), optimal medical therapy with CRT-D (595), or optimal medical therapy with CRT-P (617)	26 % of patients within the control group withdrew to receive CRT devices; mortality was significantly higher in the control group (25 %), but not significantly different between the CRT-P (21.2 %) and the CRT-D (17.6 %) groups, with the greatest effect in the CRT-D group
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (2005) [7]	LVEF ≤35 % from ischemic or nonischemic cause; NYHA classes II–III Mean follow-up: 45.5 months	2,521 patients randomized to placebo (847), amiodarone (median dose 300 mg) (845), and ICD (829)	ICD significantly reduced mortality (HR 0.77; CI 0.62–0.96); amiodarone did not significantly reduce mortality compared to placebo (HR 1.06); 11 % of medically treated patients received an ICD

CABG coronary artery bypass grafting, *CI* confidence interval, *CRT-D* cardiac resynchronization therapy with defibrillator, *CRT-P* cardiac resynchronization therapy with pacing only, *EPS* electrophysiology study, *HF* heart failure, *HR* hazard ratio, *ICD* implantable cardioverter-defibrillator, *MI* myocardial infarction, *NYHA* New York Heart Association functional class, *PCI* percutaneous coronary intervention, *VF* ventricular fibrillation, *VT* ventricular tachycardia

52.1.2 Acute Approach to the Patient with a Ventricular Arrhythmia

The acute assessment of the patient requires a rapid assessment of hemodynamic stability as well as an evaluation for contributing conditions. The prerequisite to appropriate treatment is an understanding of the substrate responsible for the ventricular arrhythmias. This includes careful analysis of the ECG in sinus rhythm, the ECG in tachycardia if available, other laboratory investigations, echocardiogram, chest X-ray, and other indicated tests. Cardiac magnetic resonance imaging has become very useful for evaluating particular arrhythmogenic substrates, including myocarditis, cardiac sarcoidosis, arrhythmogenic right ventricular dysplasia/cardiomyopathy, hypertrophic cardiomyopathy, and ischemic cardiomyopathy.

52.1.3 Role of Antiarrhythmic Medications in the Acute and Chronic Treatment of Ventricular Arrhythmias

The acute treatment of ventricular arrhythmias often cannot be delayed for multiple investigations. In numerous studies, empiric therapy is non-inferior to electrophysiologic study-guided therapy and centers around two pharmacologic targets. First, a reduction in catecholamine stimulation to the heart is essential to suppress automaticity as well as triggered activity producing VT. Catecholamines are blocked with beta-adrenergic receptor antagonists (beta-blockers), and their production is suppressed by anxiolytics, sedation, general anesthesia, and sympathetic denervation in the form of a left stellate ganglion blockade or excision. Ion channel modulation by antiarrhythmic medication is chosen primarily on the basis of medications that are least likely to cause hemodynamic deterioration. As will be discussed below, since amiodarone is the most effective medication for ventricular arrhythmias over a wide variety of substrates, has less proarrhythmic potential than other antiarrhythmics, and has a relatively straightforward dosing regimen with no requirement for serum level monitoring in the acute setting, it is usually the antiarrhythmic of choice. The potential difficulties with amiodarone come after the acute arrhythmia is treated: the activity on ion channels may interfere with the inducibility of the arrhythmia in the electrophysiology laboratory; the prolonged half-life of this medication makes its effects long lasting; and the long-term toxicities to other organ systems all should be considered.

Despite a great number of innovations in the nonpharmacologic therapy of ventricular arrhythmias including catheter ablations and ICD therapies, antiarrhythmic drugs remain a cornerstone of therapy. Antiarrhythmic medications are often used in conjunction with ICD and catheter ablation to reduce the risk of tachycardia reoccurring. While acute pharmacologic cardioversion and maintenance of sinus rhythm in patients with an ICD are their primary uses, antiarrhythmic medications can be used in the electrophysiology lab to observe its effects during electrophysiology

study and ablation. Therefore, in the management of patients with ventricular arrhythmias, antiarrhythmic medications are indispensable. This chapter will thoroughly review the potential uses of antiarrhythmic medications, particularly in the context of ventricular arrhythmias. Then, the pharmacology and clinical uses of each individual medication will be discussed.

52.2 Clinical Use of Antiarrhythmic Medications

52.2.1 Acute Pharmacologic Cardioversion

Pharmacologic cardioversion is an attractive alternative to direct-current cardioversion in conscious patients since it does not require sedation or cause discomfort. For successful pharmacologic cardioversion, antiarrhythmics must be administered in an intravenous formulation and must act rapidly. One of four medications can be used.

Procainamide is a sodium and potassium channel blocker but also functions as a negative inotrope. It can cause significant hypotension, particularly in patients with reduced systolic function. Therefore, it is useful only in hemodynamically stable patients with preserved ejection fraction. It is safely used in patients with preexcitation. Because supraventricular arrhythmias with preexcitation may be indistinguishable from VT originating from the base of the heart, procainamide can be used in this setting.

Lidocaine is a sodium channel blocker that exercises its antiarrhythmic effect on fast sodium channels; it most significantly affects ventricular tissues. Lidocaine preferentially binds to inactive sodium channels and thus has a more pronounced effect during acute ischemia. For this reason, lidocaine has historically been preferred for use in VT during acute ischemia, although amiodarone is also effective for this indication.

In patients presenting with VT, whether monomorphic stable VT or VT/VF arrest, amiodarone has been shown repeatedly to be superior to lidocaine [12–14]. While oral amiodarone takes time to load to reach effective levels, intravenous amiodarone is effective acutely and can be loaded safely [15, 16, 20]. Some formulations have diluents (polysorbate 80 and benzyl alcohol) that can cause hypotension; other formulations do not.

The potassium channel blocker nifekalant (available in Japan) has also been studied in the acute setting to treat malignant ventricular arrhythmias, including arrhythmias during acute ischemia [17, 18]. As a potassium channel blocker, it does have the potential to cause torsade de pointes by prolonging the QT interval.

The treatment of pulseless VT or ventricular fibrillation (VF) cardiac arrest also involves using antiarrhythmic medications in addition to pressors if the patient cannot be successfully defibrillated. Amiodarone, lidocaine, bretylium, and nifekalant have been compared in randomized trials. Amiodarone is more effective than lido-

caine, with 12 % of patients treated with lidocaine surviving to hospital admission compared to 23 % with amiodarone [19]. Nifekalant is also more effective than lidocaine in VT/VF arrest [19, 20]. Bretylium prevents the release of norepinephrine and also blocks potassium channels. Although it is as effective as amiodarone in converting ventricular arrhythmias to sinus rhythm, bretylium causes severe hypotension because of the effects on norepinephrine release, and it is no longer available in the USA [21]. Neither nifekalant nor amiodarone reduces the systolic function; and while both block potassium channels, torsade de pointes is rare [22, 24]. In the one randomized study of nifekalant and amiodarone in VT/VF arrest, amiodarone appeared to be more effective in converting patients to sinus rhythm [23].

52.2.2 Preventing Recurrence of Ventricular Arrhythmias

In patients with structural heart disease and sustained ventricular arrhythmias or sudden cardiac death, implantable cardioverter-defibrillators (ICDs) reduce mortality, with a 28 % relative risk reduction in mortality and a 50 % reduction in arrhythmic death [8]. Although the ICD treats ventricular arrhythmias, it does not prevent their recurrence. ICD shocks are associated with significant discomfort and distress and can cause anxiety disorders, including posttraumatic stress disorder. Antiarrhythmics can prevent ventricular arrhythmia recurrence.

In choosing which antiarrhythmic to use to prevent VT or VF or to suppress PVCs, many factors must be taken into account. The patient's substrate, comorbid conditions, age, and frequency of ventricular arrhythmias must be taken into account. Initial comparison studies demonstrated that electrophysiologic study was not an effective method of guiding medical therapy [24]. Later, the combination of beta-blockers with amiodarone was demonstrated to suppress ventricular arrhythmias more effectively than sotalol or beta-blockers alone, with a hazard ratio of 0.27. However, the side effects and toxicities associated with amiodarone led to a discontinuation rate of 18 % at 1 year [25]. Because of these toxicities, it is reasonable to delay initiating amiodarone until after other therapies have failed. On the other hand, patients with frequent VT and multiple shocks should likely be treated with the most effective regimen, beta-blocker with amiodarone.

The multitude of antiarrhythmic choices can be confusing. However, the vast majority of patients with ventricular tachycardia presenting to a hospital will have a history of myocardial infarction, heart failure, or renal dysfunction, all of which significantly limit the available options. Essentially, the only antiarrhythmics found to be safe in patients with heart failure are amiodarone, dofetilide, and lidocaine or mexiletine. If the patient is having acute coronary syndrome, then lidocaine or amiodarone can be used. Sotalol could be considered for chronic treatment in patients with ischemic cardiomyopathy, but not with an ejection fraction (EF) <40 %. Significant renal insufficiency limits the choice of antiarrhythmics to amiodarone, mexiletine, or propafenone. Table 52.2 lists the medications (with standard doses) that can be useful for the treatment of VT.

Table 52.2 Drugs and doses for treating ventricular arrhythmias

Drug	Indication	Initiation	Maintenance	Dose reduction
Quinidine	Chronic treatment (≤600 mg/day for prevention of VF in Brugada syndrome)	Quinidine sulfate immediate release 200–400 mg q6h	Quinidine sulfate: 300 mg q8h–q12h Quinidine gluconate: 324 mg q8h–q12h	Reduce by 25 % if CrCl <10 mL/min
Procainamide	Acute treatment Procainamide challenge to uncover Brugada ECG	17 mg/kg at 20–50 mg/min 10 mg/kg at 50 mg/min	1–4 mg/min Not applicable	Reduce infusion by 33 % for CrCl 10–50 mL/min; reduce by 67 % for CrCl <10 mL/min
Lidocaine	VT/VF arrest or monomorphic VT	1 mg/kg first bolus; 0.5–0.75 mg/kg subsequent boluses	1–3 mg/min Plasma levels: 1.5–5.0 mcg/mL	Hepatic failure or heart failure
Mexiletine	Chronic treatment	150 mg q8h	150–300 mg q8h	Hepatic failure or heart failure
Flecainide	Chronic treatment	100 mg q12h	100 mg q12h; max 200 mg q12h	Reduce by 50 % if CrCl <50 mL/min
Esmolol	Acute beta blockade	0.5 mg/kg bolus	0.05 mg/kg/min infusion	Titrate to effect
Amiodarone	VT/VF arrest Stable VT	300 mg bolus 150 mg bolus, then 1 mg/min × 6 h, then 0.5 mg/min × 12 h; repeat 150 mg bolus if VT recurs	400–800 mg q12h for 1–2 weeks, then 400–800 mg daily; reduce dose to 400 mg daily if possible	Hepatic enzymes >3× upper limit of normal
Nifekalant	VT/VF arrest	0.2–0.3 mg/kg bolus	0.2 mg/kg/h drip	Reduce 50 % for CrCl <50 mL/min
Sotalol	Chronic treatment	80 mg q12h; increase dose every 3 days	240 mg/day divided into 2–3 doses	Dose q24h for CrCl 30–60 mL/min; dose q36h–q48h for CrCl 10–30 mL/min

CrCl creatinine clearance, *ECG* electrocardiogram, *max* maximum dose, *VF* ventricular fibrillation, *VT* ventricular tachycardia

Acutely, patients with electrical storm who have been urgently cardioverted, whether externally or internally by their ICDs, require medication to prevent further ventricular arrhythmias and shocks. For most patients, this requires normalizing electrolytes, suppressing catecholamines with beta-adrenergic antagonists, modulating cardiac ion channels with antiarrhythmics such as amiodarone and lidocaine, and suppressing the sympathetic drive with sedation, analgesia, or even general anesthesia. In patients with heart failure, hemodynamic support can reduce the occurrence of ventricular arrhythmias. Ultimately, catheter ablation may provide definitive nonpharmacologic therapy to prevent recurrence of ventricular arrhythmias. Figure 52.1 illustrates an algorithmic approach to suppressing ventricular arrhythmias in electrical storm.

52.2.3 Neurohormonal Modulation to Reduce Mortality

Beta-adrenergic antagonists, angiotensin-converting enzyme inhibitors, angiotensin-II AT_1 receptor blockers, and aldosterone receptor antagonists have been proven to reduce all-cause and cardiovascular mortality in patients with reduced ejection fraction or patients with myocardial infarction in multiple trials. Meta-analyses indicate

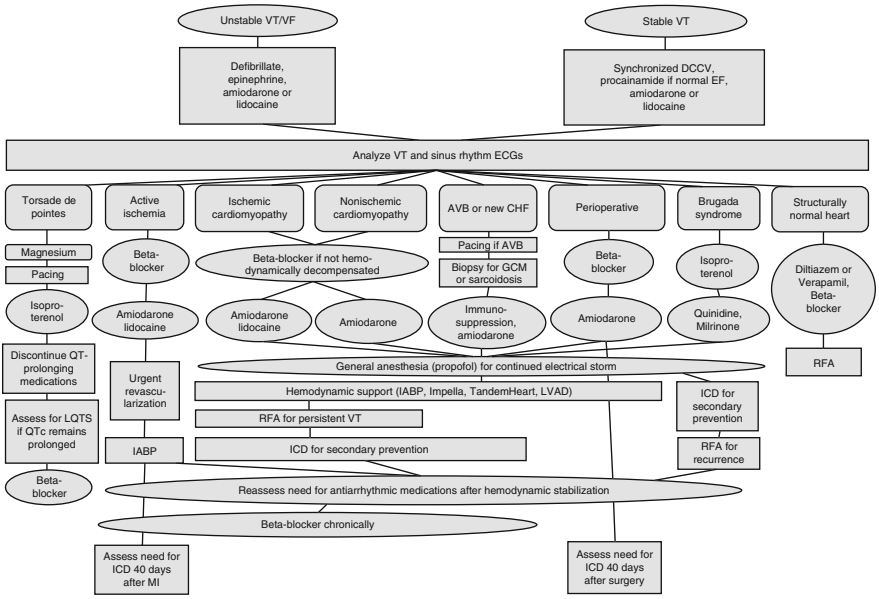


Fig. 52.1 An algorithmic approach to suppressing ventricular arrhythmias and stabilizing patients in electrical storm. Abbreviations: *AVB* atrioventricular block, *CHF* congestive heart failure, *DCCV* direct-current cardioversion, *ECG* electrocardiogram, *EF* ejection fraction, *GCM* giant cell myocarditis, *IABP* intra-aortic balloon pump, *ICD* implantable cardioverter-defibrillator, *LQTS* long QT syndrome, *LVAD* left ventricular assist device, *MI* myocardial infarction, *QTc* corrected QT interval, *RFA* radiofrequency ablation, *VF* ventricular fibrillation, *VT* ventricular tachycardia

substantial reduction in arrhythmic mortality as well. Beta-blockers reduce the relative risk of sudden cardiac death in patients with heart failure by 31 %, with the vast majority of the data in patients on metoprolol or carvedilol [26]. After myocardial infarction, angiotensin-converting enzyme inhibitors reduce the relative risk of sudden cardiac death by 20 % [27]. The aldosterone antagonists (spironolactone and eplerenone) reduce the odds of sudden cardiac death by 23 % in patients with an ejection fraction ≤45 % [28]. These medications are more extensively discussed in prior chapters on medical management of heart failure, ischemic coronary artery disease, and hypertension, but they deserve mention here as essential components in managing patients with ventricular arrhythmias with these substrates (Chaps. 5, 8, 20, 36 and 38).

52.2.4 Effect on Defibrillation Threshold

By affecting the membrane potential, amiodarone raises the defibrillation threshold, and sotalol decreases the defibrillation threshold [29]. This is rarely clinically significant, with changes averaging less than 2 J. Reassessment of defibrillation threshold after changing medication is not recommended.

52.2.5 Use of Antiarrhythmics in the Electrophysiology Lab

By using procainamide as a continuous infusion in the electrophysiology lab to slow a monomorphic VT, the VT cycle length slows as fast sodium channels are blocked. A slower VT cycle length is more likely to be hemodynamically stable, so patients can tolerate being in VT during mapping and ablation. Additionally, procainamide, ajmaline (not available in the USA), or flecainide can be used in patients in whom Brugada syndrome is suspected to uncover a type 1 Brugada ECG pattern in order to determine the patient's risk of future ventricular arrhythmias [30].

52.3 Specific Uses for Antiarrhythmic Drugs

52.3.1 Classification

The most widely known classification of antiarrhythmic drugs is the Vaughan-Williams classification, proposed in the 1970s. The classification is based on the preeminent property of the particular antiarrhythmic, despite the fact that many antiarrhythmics have effects on more than one ion channel or receptor.

Four classes were proposed: class I, which contains drugs that block the inward sodium current (I_{Na}), is subdivided into three subgroups. Group 1a slows conduction by blocking sodium channels but also prolongs repolarization by blocking potassium

channels. Group 1b antiarrhythmics have minimal effect on the rate of conduction, because they bind to the sodium channel in the inactive state, and shorten repolarization. Group 1c slows conduction by inactivating active sodium channels and has no effect on repolarization. Class II contains most of the beta-adrenergic receptor blockers; however, sotalol, a nonselective beta blocker, is classified with class III because it also blocks potassium channels. All antiarrhythmics in class III prolong repolarization because they block potassium channels. Finally, class IV includes only the L-type calcium channel blockers that inhibit the inward calcium current ($I_{Ca\text{-}L}$), the non-dihydropyridine calcium channel blockers diltiazem and verapamil (Chap. 37). Drugs such as digoxin, ivabradine, and adenosine that are also used to treat arrhythmias are not included in this classification. Since ibutilide, digoxin, and ivabradine have no role in treating ventricular arrhythmias, they will not be discussed further in this chapter. The primary ion currents affecting the cardiac action potential and the drugs modulating those currents are depicted in Fig. 52.2 (also see Chap. 46).

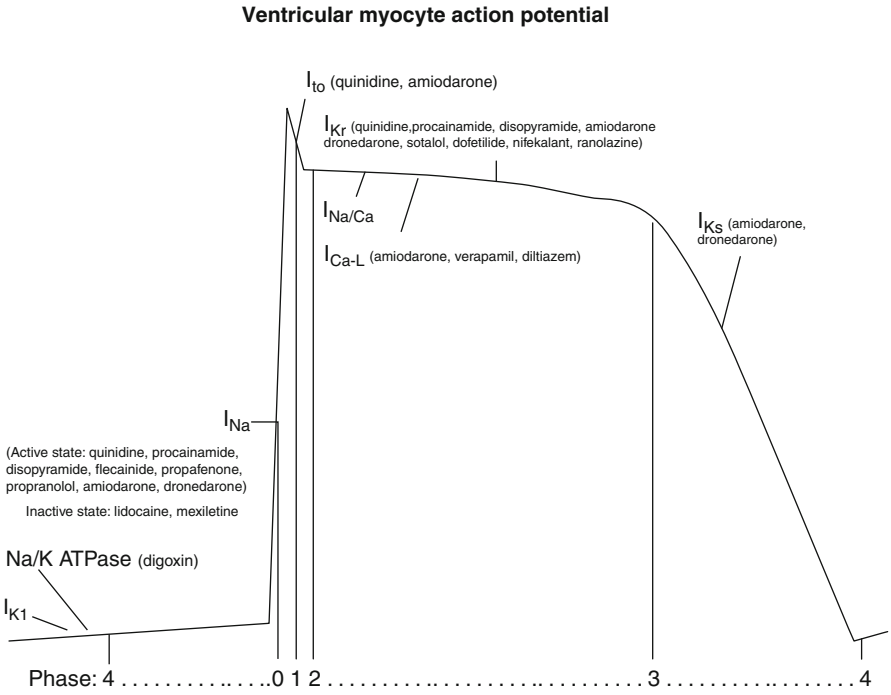
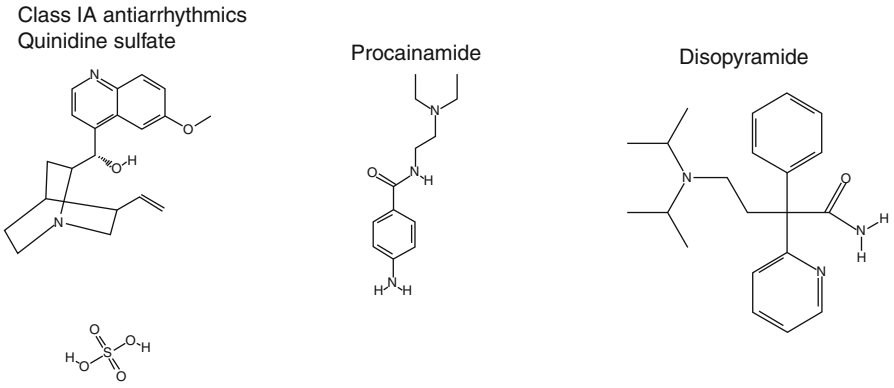


Fig. 52.2 The ventricular myocyte action potential, contributing ionic currents, and the primary pharmacologic agents that affect those currents. *Abbreviations*: $I_{Ca\text{-}L}$ L-type calcium channel current, I_{K1} inward rectifier potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Na} fast inward sodium current, I_{to} transient outward potassium current, I_{K1} inward rectifier potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Kur} ultra-rapid delayed rectifier potassium current, I_{Na} fast inward sodium current, $I_{Na/Ca}$ sodium/calcium exchanger, I_{to} transient outward potassium current, *Na/K ATPase* sodium/potassium adenosine triphosphatase

Following further investigations, the limitations of the Vaughan-Williams classification became increasingly apparent. The European Society of Cardiology Working Group on Arrhythmias attempted in 1991 to reclassify the antiarrhythmics based on electrophysiologic effects in a scheme called the Sicilian Gambit [31]. The goal was to classify antiarrhythmics based on the predominant clinically important effect, rather than the in vitro targets. It focuses on the impact each antiarrhythmic has on specific vulnerable parameters related to the arrhythmia mechanism. While this classification is advantageous in that it is flexible to incorporate many additional medications with various mechanisms of action, it has not obtained widespread utilization due to its complexity; therefore, the Vaughan-Williams classification will provide the organizational structure for further discussion of antiarrhythmics. The pharmacologic and pharmacokinetic properties of each antiarrhythmic drug are compared in Table 52.3. A table based on the Sicilian Gambit reflects the action of each antiarrhythmic as shown in Table 52.4.

52.3.2 Sodium Channel Blockers (Vaughan-Williams Class I)



52.3.2.1 Quinidine and Hydroquinidine

Quinidine and its analogue hydroquinidine not only inhibit the I_{Na} and I_{Kr} currents but also inhibit the I_{to} current responsible for phase 1 and 2 early repolarization. This inhibition helps to normalize the dispersion between epicardial and endocardial potentials, which is abnormal in Brugada syndrome. Over the long term, quinidine is effective in reducing the incidence of recurrent ventricular arrhythmias in Brugada syndrome [32–34]. Acutely, the sodium current, calcium cycling, and electrocardiogram (ECG) abnormalities associated with Brugada syndrome can be normalized by intravenous isoproterenol or milrinone, which via beta-adrenergic stimulation or phosphodiesterase inhibition lead to enhanced sodium and calcium channel function.

Table 52.3 Major electrophysiologic actions, pharmacokinetics, adverse effects, and indications of antiarrhythmics commonly used to treat ventricular tachyarrhythmias

Class	Antiarrhythmic	Mechanism of action (channels inhibited)	Electrophysiologic effects	Pharmacokinetics	Noncardiac adverse effects	Cardiac adverse effects	Indications
IA	Quinidine (quinidine sulfate has 75 % the quinidine base as does quinidine gluconate)	I_{Na} (intermediate recovery, moderate blockade), I_{to}, I_{Kr}, muscarinic, α	QRS prolonged JT prolonged APD prolonged; HV, AERP, and VERP prolonged	Vd 2–3 L/kg, less in CHF b: 70 % $t_{1/2}$:6–8 h longer in CHF Metab: H Excr: U Preg: C	Lightheaded, diarrhea, nausea, emesis, tinnitus, blurred vision, rash, weakness, tremor, blood dyscrasias	QRS and QTc prolonged; AVN block; TdP; syncope; toxicity worse with digoxin	AF, VT, BrS, SQTS, VF with early repolarization
IA	Procainamide	I_{Na} (intermediate recovery, moderate blockade), I_{Kr}	QRS prolonged JT prolonged APD prolonged; HV, AERP, and VERP prolonged	Vd 2 L/kg, less in CHF; Metab: H $t_{1/2}$: 2–5 h; NAPA 6–8 h Excr: U (50 % procainamide, 80 % NAPA) Preg: C	Lupus symptoms, diarrhea, nausea, blood dyscrasias	QTc and QRS prolonged; AVN block	AF, VT, WPW, unmasking BrS

(continued)

Table 52.3 (continued)

Class	Antiarrhythmic	Mechanism of action (channels inhibited)	Electrophysiologic effects	Pharmacokinetics	Noncardiac adverse effects	Cardiac adverse effects	Indications
IA	Disopyramide	I_{Na} (intermediate recovery, moderate blockade), I_{to}, I_{Kr}, $I_{K(ATP)}$, muscarinic	QRS prolonged JT prolonged APD prolonged; HV, AERP, and VERP prolonged	Vd: 0.8–2 L/kg b : 60–83 % $t_{1/2}$: 4–10 h Metab : H Excr : U 80 % Preg: C	Xerostomia, constipation, urinary hesitancy, rash	Hypotension, CHF, syncope, QTc prolonged	AF, VT, HCM
IB	Lidocaine	I_{Na} (rapid recovery, mild blockade)	No marked effect on most intervals; APD and JT can slightly shorten	Vd: 1.1–2.1 L/kg, less in CHF Biphasic $t_{1/2}$: 7–30 m, 90–120 m Metab: H Excr: U Preg: B	Delirium, psychosis, seizure, nausea, tinnitus, dyspnea, bronchospasm	Bradycardia, hemodynamic collapse, AVN block	VT, VF
IB	Mexiletine	I_{Na} (rapid recovery, mild blockade)	No marked effect on most intervals; APD and JT can slightly shorten	Vd: 5–7 L/kg b: 50–60 % $t_{1/2}$: 10–14 h Metab: H Excr: U Preg: C	Lightheaded, tremor, ataxia, paresthesias, blood dyscrasias	CHF, AVN block	VT, LQTS 3

IC	Flecainide	I_{Na} (slow recovery, marked blockade), I_{Kr}, I_{Kur}	PR prolonged QRS prolonged APD prolonged AH, HV prolonged	Vd: 5–13 L/kg b: 85–90 % $t_{1/2}$: 7–22 h Metab: H Excr: U Preg: C	Dizziness, tremor, vision disturbance, dyspnea, nausea	Sinus node dysfunction, AVN block, prolonged QRS	AF, AVNRT, VT, CPVT
IC	Propafenone	I_{Na} (slow recovery, marked blockade), I_{Kr}, I_{Kur}, β, α	PR prolonged QRS prolonged APD prolonged AH, HV, and VERP prolonged	Vd: 252 L b: 3–10 % $t_{1/2}$: 2–10 h or 10–32 h Metab: H Excr: U Preg: C	Dizziness, fatigue, nausea, diarrhea, zerostomia, tremor, blurred vision	AVN block, VT, CHF, QRS prolonged	AF, VT
II	Atenolol	β_1	Sinus rate slowed ERP–AVN prolonged	b: 50 % $t_{1/2}$: 6–7 h Excr: F 50 %, U 40 % Preg: D	Dizziness, fatigue, depression, impotence	Bradycardia, hypotension, CHF, AV block	AF, AFL, AT, AVNRT, VT, CPVT, LQTS, OTVT
II	Carvedilol	β_1, β_2, α	Sinus rate slowed ERP–AVN prolonged	Vd: 115 L b: 25–35 % $t_{1/2}$: 7–10 h Metab: H Excr: F Preg: C	Hyperglycemia, dizziness, fatigue, diarrhea	Bradycardia, hypotension, AV block, syncope, edema	AF, AFL, AT, VT, HCM, ICM, NICM

(continued)

Table 52.3 (continued)

Class	Antiarrhythmic	Mechanism of action (channels inhibited)	Electrophysiologic effects	Pharmacokinetics	Noncardiac adverse effects	Cardiac adverse effects	Indications
II	Esmolol	β_1	Sinus rate slowed ERP–AVN prolonged	Vd: 3.4 L/kg $t_{1/2}$: 9 m Metab: RBC esterases Excr: U Preg: C	Dizziness, nausea	Bradycardia, hypotension, AV block	AF, AFL, AT, AVNRT, VT, CPVT, HCM, LQTS, OTVT
II	Metoprolol	β_1	Sinus rate slowed ERP–AVN prolonged	Vd: 3.2–5.6 L/kg b: 40–50 % $t_{1/2}$: 3–4 h Metab: H Excr: U Preg: C	Dizziness, fatigue, diarrhea, depression, dyspnea	Bradycardia, hypotension, AV block, syncope, edema	AF, AFL, AT, AVNRT, VT, CPVT, HCM, LQTS, OTVT, ICM, NICM
II	Propranolol	β_1, β_2, I_{Na}	Sinus rate slowed ERP–AVN prolonged	Vd: 4 L/kg b: 25 % $t_{1/2}$: 3–6 h Metab: H Excr: U Preg: C	Sleep disorder, dizziness, nightmares, hyperglycemia, diarrhea, bronchospasm	Bradycardia, edema, CHF, hypotension, AV block	AF, AFL, AT, AVNRT, VT, CPVT, HCM, LQTS, OTVT
II	Nadolol	β_1, β_2	Sinus rate slowed ERP–AVN prolonged	Vd: 2 L/kg b: 30 % $t_{1/2}$: 20–24 h Metab: none Excr: U Preg: C	Depression, dizziness, fatigue	Bradycardia, hypotension, AV block, edema	AF, AFL, AT, AVNRT, VT, CPVT, HCM, LQTS, OTVT

III	Amiodarone	I_{Na}, I_{Ca}, I_{Kr}, I_{K1}, I_{Ks}, I_{to}, β, α, nuclear T3 receptor	Sinus rate slowed QRS prolonged JT prolonged APD prolonged AH, HV, AERP, VERP, and ERP–AVN prolonged	Vd: 18–148 L/kg b: 35–65 % $t_{1/2}$: 26–107d Metab: H Excr: F Preg: D (congenital hypo- or hyperthyroidism)	Corneal microdeposits, thyroid abnormalities, ataxia, nausea, emesis, constipation, photosensitivity, skin discoloration, ataxia, dizziness, peripheral neuropathy, tremor, hepatitis, cirrhosis, pulmonary fibrosis or pneumonitis	Hypotension, bradycardia, AV block	AF, AFL, AT, AVNRT, VT, VF
III	Dronedarone	I_{Na}, I_{KACh}, I_{Ca}, I_{Kr}, I_{K1}, I_{Ks}, β	Sinus rate slowed QRS prolonged JT prolonged APD prolonged AH, HV, AERP, VERP, and ERP–AVN prolonged	Vd: 1400 L b: 4–15 % $t_{1/2}$: 13–19 h Metab: H Excr: F 84 %, U 6 % Preg: X	Increased creatinine, diarrhea, nausea, dermatitis, weakness	Prolonged QT, bradycardia	AF
III	Sotalol	I_{Kr}, β_1, β_2	Sinus rate slowed JT prolonged APD prolonged AH, AERP, VERP, and ERP–AVN prolonged	Vd: 1.2–2.4 L/kg b: 90–100 % $t_{1/2}$: 12 h Metab: none Excr: U Preg: B	Fatigue, dizziness, weakness, dyspnea, bronchitis, depression, nausea, diarrhea	Bradycardia, palpitations, edema, QT prolonged, syncope, TdP	AF, VT

(continued)

Table 52.3 (continued)

Class	Antiarrhythmic	Mechanism of action (channels inhibited)	Electrophysiologic effects	Pharmacokinetics	Noncardiac adverse effects	Cardiac adverse effects	Indications
III	Dofetilide	I_{Kr}	JT prolonged APD prolonged AERP and VERP prolonged	Vd: 3 L/kg b: 90 % $t_{1/2}$: 10 h Metab: H Excr: U Preg: C	Dizziness, insomnia, dyspnea, nausea, diarrhea	QT prolonged, TdP, VT, chest pain, AV block	AF
IV	Verapamil	$I_{Ca\text{-}L}$	Sinus rate slowed PR prolonged AERP shortened AH and ERP–AVN prolonged	Vd: 3.9 L/kg b: 20–35 % $t_{1/2}$: 3–7 h Metab: H Excr: U Preg: C	Headache, gingival hyperplasia, constipation, rash, dyspepsia	Edema, CHF, hypotension, bradycardia, AV block	AF, AFL, AVNRT, fascicular VT
IV	Diltiazem	$I_{Ca\text{-}L}$	Sinus rate slowed PR prolonged AERP shortened AH and ERP–AVN prolonged	Vd: 3–13 L/kg b: 40 % $t_{1/2}$: 3–4.5 h Metab: H Excr: U, F Preg: C	Headache, dizziness, rash, weakness, rhinitis	Edema, AV block, hypotension, bradycardia	AF, AFL, AVNRT, fascicular VT

N/C	Ranolazine	I_{Na}, I_{Kr}	Sinus rate slowed JT prolonged APD prolonged AERP and VERP prolonged	b: 76 % $t_{1/2}$: 7 h Metab: H Excr: U 75 %, F 25 % Preg: C	Headache, dizziness, syncope, nausea, dyspnea	Bradycardia, QT prolonged, hypotension	Angina
N/C	Adenosine	Activation of A_1, A_2, and I_{KATP}	PR prolonged AH and ERP–AVN prolonged	$t_{1/2}$: <10s Metab: blood and tissue enzymes Preg: C	Headache, dizziness, flushing, dyspnea, nausea	Chest pressure, AV block, hypotension	SVT, OTVT

α alpha adrenergic receptor, *A* adenosine receptor, *AERP* atrial effective refractory period, *AF* atrial fibrillation, *AFL* atrial flutter, *AH* atrial–His interval, *APD* action potential duration, *AT* atrial tachycardia, *AVN* atrioventricular node, *AVNRT* atrioventricular nodal reentry tachycardia, *β* beta-adrenergic receptor, *b* bioavailability, *BrS* Brugada syndrome, *CHF* congestive heart failure, *CPVT* catecholaminergic polymorphic ventricular tachycardia, *ERP–AVN* effective refractory period of the atrioventricular node, *Excr* excreted, *F* feces, *H* hepatic, *HCM* hypertrophic cardiomyopathy, *HV* His–ventricular interval, I_{Ca} L-type calcium channel current, *ICM* ischemic cardiomyopathy, I_{K1} inward rectifier potassium channel, I_{KACh} muscarinic receptor-gated potassium channel, I_{KATP} adenosine-activated potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Kur} ultra-rapid delayed rectifier potassium current, I_{Na} fast inward sodium current, I_{to} transient outward potassium current, *JT* interval from J point to termination of the T wave, *LQTS* long QT syndrome, *Metab* metabolism, *N/C* not classified, *NICM* nonischemic cardiomyopathy, *OTVT* outflow tract ventricular tachycardia, *Preg* pregnancy category, *QTc* corrected QT interval, *SQTS* short QT syndrome, *SVT* supraventricular tachycardia, $t_{1/2}$ half-life, *T3* triiodothyronine, *TdP* torsade de pointes, *U* urine, *Vd* volume of distribution, *VERP* ventricular effective refractory period, *VF* ventricular fibrillation, *VT* ventricular tachycardia, *WPW* Wolff-Parkinson-White syndrome

Table 52.4 Effects of currently available antiarrhythmic drugs adapted from the Sicilian Gambit classification [35]

	Channels									Receptors					Pumps
	Na			Ca	K				I_f	α	β_1	β_2	M_2	A_1	Na/K ATPase
Drug	Fast	Med	Slow		I_{K1}	I_{to}	I_{Kr}	I_{Ks}							
Lidocaine	○														
Mexiletine	○														
Flecainide			●				○								
Ajmaline		●													
Propafenone		●					○				⊙	⊙			
Quinidine		●				⊙	⊙			○			○		
Procainamide		●					⊙								
Disopyramide		●					⊙						○		
Propranolol	○										●	●			
Atenolol											●				
Carvedilol										●	●	●			
Metoprolol											●				
Nadolol											●	●			
Amiodarone		○		○	○	○	●	○		⊙	⊙	⊙			
Dronedarone		○		○	○		●	○			⊙	⊙			
Sotalol							●				●	●			
Ibutilide							●								
Dofetilide							●								
Nifekalant							●								
Ranolazine			○				●								
Ivabradine									●						
Verapamil	○			●						⊙					
Diltiazem				⊙											
Atropine													●		
Digoxin															●
Adenosine														●	

α alpha adrenergic receptor, A_1 adenosine receptor type 1, β_1 beta-1 adrenergic receptor, β_2 beta-2 adrenergic receptor, *Ca* L-type calcium channel, I_{K1} inward rectifier potassium channel, I_{Kr} rapid delayed rectifier potassium current, I_{Ks} slow delayed rectifier potassium current, I_{Na} fast inward sodium current, I_{to} transient outward potassium current, M_2 muscarinic receptor type 2, *Na/K ATPase* sodium/potassium adenosine triphosphatase. Relative potency: ● = high; ⊙ = moderate; ○ = low

Malignant early repolarization syndromes, with J-point elevation in the inferolateral leads or notching of the ST segment, are associated with recurrent ventricular arrhythmias and sudden death. Quinidine reduces recurrence of ventricular arrhythmias, likely again by blocking I_{to} and normalizing the repolarization between the epicardium and endocardium [35]. Quinidine also shows promise in short QT syndrome, significantly reducing arrhythmia recurrence more than any other antiar-

rhythmic [36]. This action is likely also related to the I_{Kr} inhibition in combination with the I_{to} inhibition. Because of the I_{Kr} inhibition, quinidine has a significant risk of torsade de pointes, estimated at 2–8 % per patient per year. Additionally, it has many adverse side effects, including nausea, diarrhea, tinnitus, delirium, and hemolytic anemia. These adverse effects prevent it from being commonly used unless a particular syndrome benefits substantially from its use.

52.3.2.2 Procainamide

Procainamide blocks both I_{Na} and I_{Kr} and is available predominantly in intravenous formulation. Because of an approximately 50 % risk of drug-induced lupus erythematosus if used chronically as well as a marked risk of bone marrow suppression, it is rarely used in oral formulation and is unavailable in most countries.

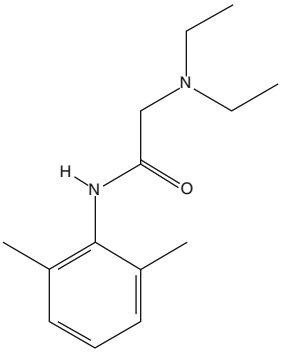
52.3.2.3 Disopyramide

Because of its negative inotropy, disopyramide is commonly used as a second-line agent in patients with hypertrophic cardiomyopathy. Otherwise, it is rarely used for its antiarrhythmic properties because of substantial antimuscarinic symptoms including urinary retention, xerostomia, and constipation. It is contraindicated in patients with systolic heart failure.

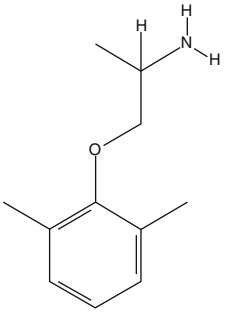
52.3.2.4 Lidocaine and Mexiletine

Class IB antiarrhythmics

Lidocaine



Mexiletine

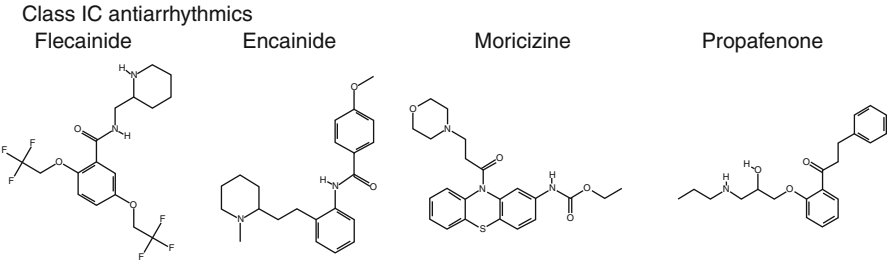


These sodium channel blockers have minimal effect on atrial tissue but are effective for ventricular arrhythmias. Patients who respond well to lidocaine would theoretically respond well to mexiletine, an oral formulation modified so it does not undergo

extensive first-pass metabolism. Lidocaine and mexiletine bind to sodium channels in their inactive state. Lidocaine and other local anesthetics undergo rapid redistribution within the body, so that if the medication is discontinued, its cardiovascular effect rapidly diminishes even though its half-life is 2 h. Therefore, it must be given as a continuous infusion and monitored regularly because of its narrow therapeutic window. Neurologic side effects must be identified quickly since they can progress rapidly to seizures.

Mexiletine is relatively well tolerated but can still produce neurologic toxicity symptoms like lidocaine. It is useful to further reduce ventricular arrhythmias in patients already on amiodarone [37]. Mexiletine also prevents ventricular arrhythmias in long QT syndrome type III, which involves a gain of function mutation in the SCN5A sodium channel.

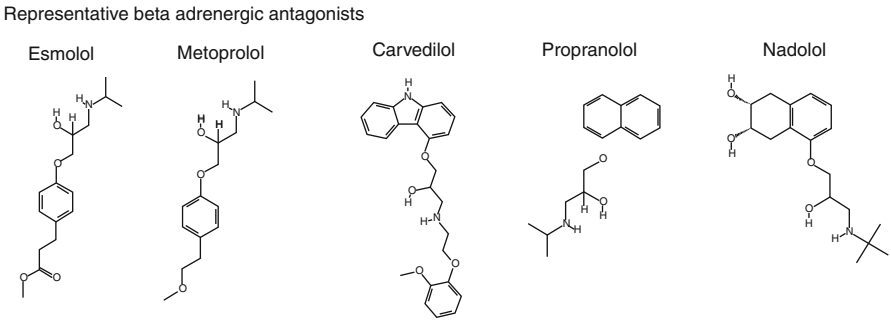
52.3.2.5 Flecainide, Encainide, Moricizine, and Propafenone



These sodium channel blockers predominantly slow conduction by inhibiting the I_{Na} current while the channels are in the active state. Flecainide does have weak potassium channel inhibition, but not enough to cause a clinically observable QT prolongation. Propafenone has a mild beta-adrenergic receptor blockade. With the exception of propafenone, the class 1C antiarrhythmics were studied for suppression of ventricular arrhythmias and premature ventricular contractions in the CAST and CAST-II trials, and they increased mortality in patients with a prior myocardial infarction [1, 2, 38]. Although propafenone was not specifically studied, it is still avoided in patients with coronary artery disease for this reason and in patients with heart failure because it is a negative inotrope. It was also shown to increase mortality relative to metoprolol or amiodarone in patients with prior VT or VF arrest in the Cardiac Arrest Study Hamburg [7]. While these antiarrhythmics can be used in patients with structurally normal hearts, they are second line after beta-adrenergic antagonists, verapamil, or diltiazem, which have significantly less proarrhythmic potential. In patients with catecholaminergic polymorphic ventricular tachycardia

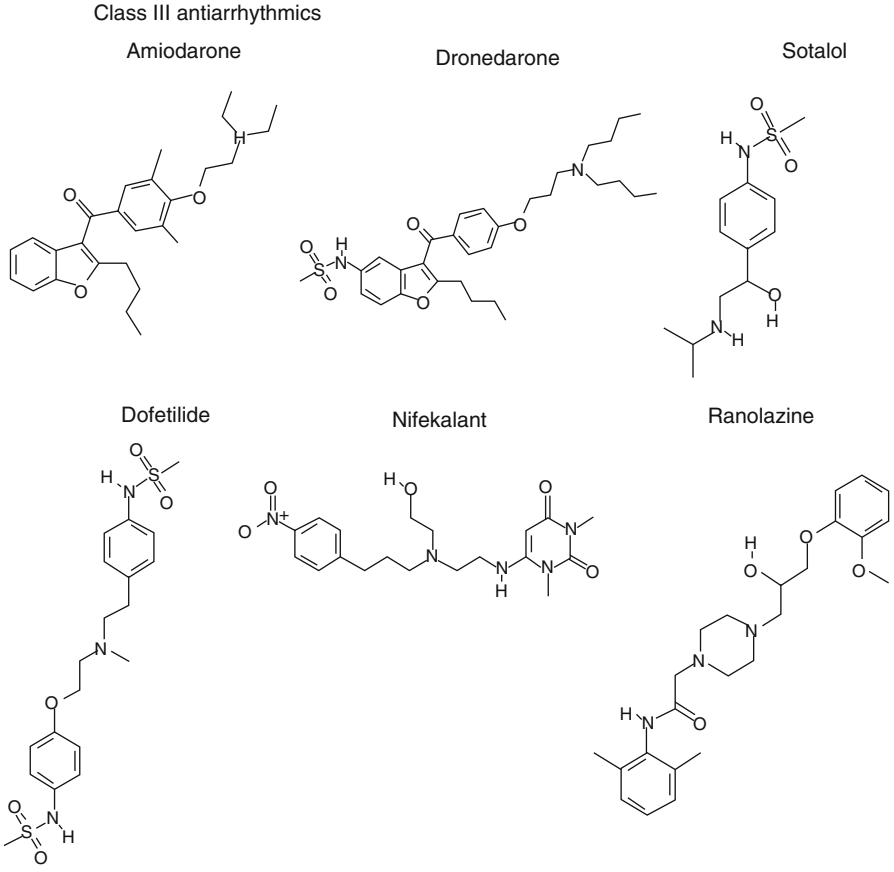
with persistent arrhythmias despite beta blockade, flecainide is a useful adjunct therapy and is effective in reducing ventricular arrhythmias [39].

52.3.3 Beta-Adrenergic Antagonists (Vaughan-Williams Class II)



Beta-adrenergic antagonists significantly reduce morbidity and mortality after myocardial infarction and improve systolic function in patients with heart failure (Chap. 8). They not only cause reverse remodeling but also prevent sudden cardiac death and ventricular arrhythmias [31]. In patients with sustained VT regardless of substrate, empiric treatment with metoprolol was non-inferior to electrophysiologically guided antiarrhythmic therapy [40]. The combination of amiodarone with beta-adrenergic antagonists provided the most effective suppression of ventricular arrhythmias in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial [30]. Beta-adrenergic antagonists also prevent ventricular arrhythmias in patients with structurally normal hearts. VF in long QT syndrome types I and II may be mediated by catecholamines, and beta-blockers are first line in these conditions. Catecholaminergic polymorphic VT is a bidirectional VT resulting from a mutation in the ryanodine receptor. Beta-adrenergic antagonists prevent the development of calcium overload in the sarcoplasmic reticulum caused by this mutation. Idiopathic VT, particularly that arising from the right ventricular outflow tract, is stimulated by catecholamines and is often adequately suppressed by beta-adrenergic antagonists. In the absence of cardiogenic shock, beta-adrenergic antagonists are an excellent adjunctive therapy for electrical storm. Of the available intravenous beta-blockers, esmolol is the shortest acting and most easily available as a drip.

52.3.4 Potassium Channel Blockers (Vaughan-Williams Class III)



52.3.4.1 Amiodarone

Amiodarone is lipophilic with hepatic metabolism and has a complex pharmacodynamic action and a very long half-life. Not only does it block potassium channels, sodium channels, L-type calcium channels, beta-adrenergic receptors, and alpha-adrenergic receptors, but it also may interfere with the effects of thyroxine, tissue-level conversion of thyroxine to triiodothyronine, and binding of thyroid hormones to their nuclear receptors. Amiodarone is effective in many different substrates. While it can prolong the QTc, amiodarone rarely causes drug-induced torsade de pointes. Furthermore, amiodarone is safe to use in patients with ischemic coronary artery disease, decompensated heart failure [41], and cardiac arrest [42]. Therefore, it is the antiarrhythmic of choice when treating ventricular arrhythmias in a patient where the substrate is unknown.

In the CAMIAT and EMIAT trials, amiodarone significantly reduced arrhythmic and cardiac death after myocardial infarction [43, 44]. Amiodarone compared to placebo reduced the relative risk of all-cause mortality by 13 % [45]. ICDs, however, significantly reduce mortality more than amiodarone; the AVID trial demonstrated a mortality reduction in patients with ICDs compared to amiodarone with a hazard ratio of 0.6 [5]. This mortality benefit of ICDs increases with time [46]. In patients with nonischemic cardiomyopathy and an ejection fraction ≤35 %, amiodarone was found to have no significant mortality difference compared to ICD implantation in the AMIOVIRT trial [15]. In the larger SCD-HeFT trial, ICD implantation significantly reduced mortality compared to amiodarone in both ischemic and nonischemic cardiomyopathy [18]. In patients who have an ICD, the optimal suppression of ventricular arrhythmias, and therefore, the best prevention of ICD shocks, is amiodarone combined with a beta-adrenergic antagonist as demonstrated in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial [30]. The data from this trial demonstrated that while amiodarone does raise the defibrillation threshold, it was to a small degree, from 8.53 ± 4.29 J to 9.82 ± 5.84 J [33]. This would require retesting only in patients with a narrow safety margin between their defibrillation threshold and their device's maximum output (also see Chap. 7).

Amiodarone is available in both intravenous and oral formulations. The aqueous form has a much lower risk of hypotension than prior intravenous formulations because of changes in the diluent [47]. Oral amiodarone is loaded to 10–14 g over 2 weeks; faster loads have not demonstrated a clinical benefit [48]. Most toxicities from amiodarone are extracardiac and dose related. The most potentially life-threatening toxicity is pulmonary fibrosis, with an estimated incidence of 5–15 % in patients taking more than 400 mg a day and <2 % in patients taking 400 mg or less per day [49]. Amiodarone-induced thyroid toxicity is complex and related in part to the large iodine load and the Wolff-Chaikoff effect but also related to thyroiditis caused by amiodarone itself. While some studies report that lower amiodarone doses are approximately as efficacious as higher doses [50], the life-threatening nature of recurrent VT leads to patients with frequent ventricular arrhythmias being maintained on high doses of amiodarone. Pulmonary function tests at baseline as well as regular chest X-rays, thyroid function tests, liver transaminase levels, and ECGs are recommended for monitoring for toxicities.

52.3.4.2 Dronedarone

While the similar medication dronedarone was designed to have fewer toxicities than amiodarone, there are only case reports of its use in VT, and its use for ventricular arrhythmias is off label at this time [51]. Dronedarone is contraindicated in New York Heart Association class III or IV heart failure, because of increased mortality [52].

52.3.4.3 Sotalol

Sotalol is a renally excreted beta-adrenergic antagonist (Class II activity) that also inhibits potassium channels (prolonging cardiac action potential), making it

similar to other Class III antiarrhythmics. While significant beta-blocking effect occurs at oral doses as low as 25 mg, significant Class III effects are seen only at daily doses of 160 mg and above. In oral form, it is given twice daily, with initial monitoring of the QTc recommended as sotalol causes dose-related QTc prolongation (mean increase in QT interval by 25 msec, 40 msec, and 54 msec with 80 mg, 120 mg, and 160 mg doses). Besides bradycardia, it has few side effects. A trial evaluating D-sotalol demonstrated increased mortality in patients with ejection fractions <40 % [53]. Further studies in patients receiving the racemic mixture of both enantiomers, D- and L-sotalol, demonstrate that racemic sotalol does reduce ventricular arrhythmias. In the D-, L-Sotalol Implantable Cardioverter-Defibrillator Study, racemic sotalol significantly increased the likelihood of survival without a first shock (61 % vs. 38 % in the placebo group) [54]. Sotalol did not affect the risk of death, but heart failure exacerbation was more common in the sotalol group (14 %) more frequently than in the placebo group (9 %) [54]. L-sotalol is a much more potent beta-adrenergic receptor antagonist (Class II effect) than the D enantiomer. However, both D- and L-sotalol are equipotent with regard to potassium channel blockade (Class III effect).

52.3.4.4 Dofetilide

The I_{Kr} blocker dofetilide is approved for atrial arrhythmias only, but it has been shown to reduce the frequency of ventricular arrhythmias in retrospective analysis [55]. While the DIAMOND trial evaluated its use to treat atrial fibrillation in patients with reduced ejection fraction and found it to be safe [56], dofetilide has not been prospectively evaluated for treatment of ventricular arrhythmias. Thus, the use of dofetilide for ventricular arrhythmias is off label.

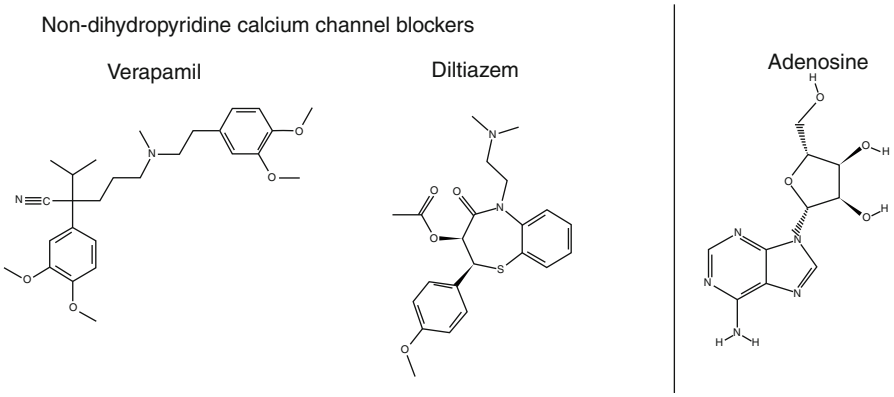
52.3.4.5 Nifekalant

Nifekalant is an intravenous I_{Kr} blocker available in Japan that effectively terminates VT. It results in torsade de pointes in <4 % of uses [24]. Nifekalant may be safely used in patients with reduced systolic function, because it is not a negative inotrope.

52.3.4.6 Ranolazine

The antianginal medication ranolazine has sodium and potassium channel blocking effects. Although not officially classified as an antiarrhythmic medication, it fits best with the class III antiarrhythmics because of its potassium channel blockade. Retrospective studies show that ranolazine suppresses ventricular arrhythmias, currently an off-label use [57]. Placebo-controlled trials are ongoing.

52.3.5 Calcium Channel Blockers (Vaughan-Williams Class IV)



The L-type calcium channel blockers verapamil and diltiazem are also vasodilators (Chap. 37), and they can cause marked hypotension without terminating most VT. The potential for hemodynamic deterioration makes calcium channel blockers contraindicated for treating wide complex tachycardias of unknown etiology. They are effective for known right outflow tract VT, idiopathic left VT, or fascicular VT (right bundle branch block with left axis deviation with a QRS duration of 105–140 ms) [58, 59]. While these are classically called "verapamil-sensitive tachycardias," diltiazem is just as effective as verapamil [60].

52.3.6 Adenosine

While some outflow tract VTs are adenosine sensitive, adenosine may also be used diagnostically to distinguish VT from a supraventricular arrhythmia. Adenosine causes transient AV block through adenosine receptors and can also affect atrial repolarization through the ligand-gated potassium channels I_{Kado}. It has no effect on reentrant VT due to structural heart disease [61]. Since adenosine is rapidly metabolized, it can temporarily block the AV node without causing hemodynamic collapse. Figure 52.3 illustrates the use of adenosine to diagnose VT.

52.4 Concluding Remarks

Many antiarrhythmics are effective for ventricular arrhythmias. Each has a slightly different pharmacologic profile and toxicities. While many antiarrhythmic drugs exist, only beta-blockers (including sotalol), amiodarone, lidocaine, and mexiletine are acceptable for use in patients with structural heart disease who have VT. While antiarrhythmic

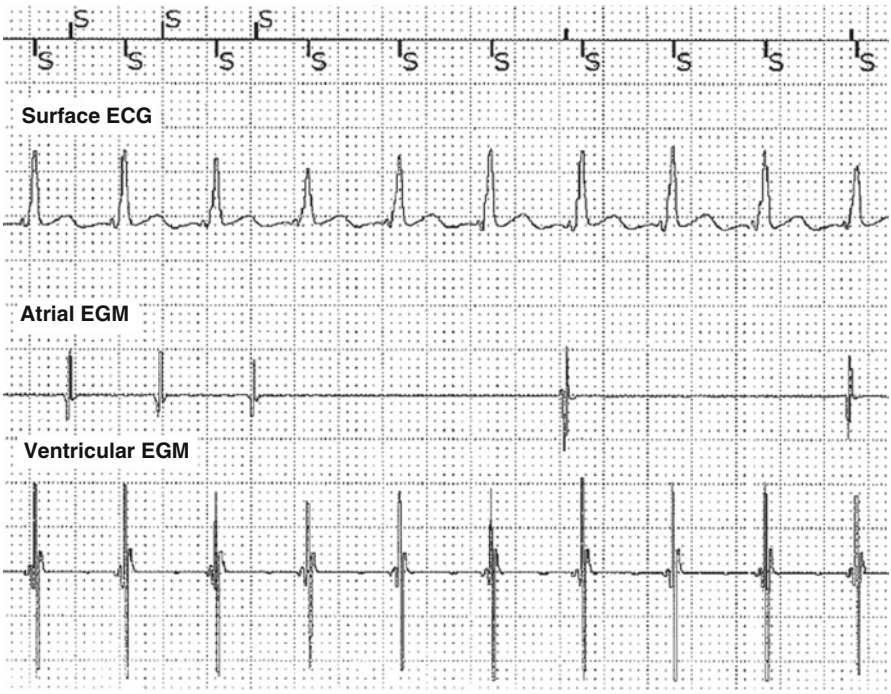


Fig. 52.3 A 52-year-old man presented with an incessant narrow-complex tachycardia that persisted despite overdrive pacing. Intravenous adenosine caused transient AV block, proving that the arrhythmia was ventricular tachycardia. Abbreviations: *ECG* electrocardiogram, *EGM* electrogram, *S* sensed

drugs prevent recurrence of VT, an ICD is also required in patients with structural heart disease to reduce mortality. Amiodarone is useful for many types of ventricular arrhythmias in many different substrates but causes many noncardiac adverse effects over time. Sotalol is an alternative to amiodarone and other beta-blockers for long-term prevention of VT: less effective, but less toxic. Lidocaine is easily given by infusion, but patients must be closely monitored for toxicity. Lidocaine's oral derivative mexiletine can be used in combination with amiodarone for additional reduction in VT recurrence. Intravenous amiodarone, lidocaine, and nifekalant are useful for VF arrest; of these, amiodarone appears to be the most effective. Other antiarrhythmics have particular niches in treating particular conditions. Quinidine is useful for long-term treatment in Brugada syndrome and short QT syndrome. Flecainide is useful in addition to beta-blockers for catecholaminergic polymorphic VT. Verapamil and diltiazem should be used only in patients known to have fascicular VT with no structural heart disease. Adenosine is useful for demonstrating ventriculoatrial dissociation during VT but will terminate only right ventricular outflow tract tachycardia. Other drugs including dronedarone, dofetilide, and ranolazine may reduce recurrence of VT, but these medications are currently not approved for that indication. Each medication's side effect profile and the patient's cardiovascular history must be considered when initiating a particular antiarrhythmic medication.

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Chapter 53
Cardiac Arrest and Cardiopulmonary Resuscitation: Recent Advances in Management Approach for Cardiopulmonary Resuscitation

Allan R. Mottram and Karen Serrano

Abstract Outcomes from cardiac arrest are overwhelmingly poor regardless of location or type of arrest. However, we know that all cardiac arrest is not the same: Cardiac arrest with an initial shockable rhythm has better survival than that with an initial non-shockable rhythm; in-hospital cardiac arrest has better survival than out-of-hospital cardiac arrest; traumatic cardiac arrest has poorest survival overall. While the overall survival statistics are concerning, it should be noted that incremental improvements have been realized through the application of research-driven interventions. For the clinician, this means the availability of research-based algorithms and treatment guidelines that can easily be applied at the bedside. These interventions can be simple or complex and include such recommendations as early high-quality cardiopulmonary resuscitation (CPR), early activation of the emergency medical services (EMS) system, therapeutic hypothermia, early cardiac catheterization, seizure control, and coordinated regional efforts to improve care. In fact, the coordinated development and implementation of resuscitation guidelines have been associated with marked improvements in survival to hospital discharge following cardiac arrest [1].

Keywords Cardiac arrest • Sudden cardiac death • Cardiopulmonary resuscitation • CPR • Therapeutic hypothermia • Defibrillation

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53.1 Introduction

Outcomes following cardiac arrest are overwhelmingly poor regardless of the etiology of the arrest. It is estimated that there are over 420,000 EMS-assisted out-of-hospital cardiac arrests and almost 210,000 in-hospital cardiac arrests each year in the United States [2]. Survival to hospital discharge for EMS-treated nontraumatic cardiac arrest is approximately 10 %. While patients who arrest in hospital seem to have better survival to discharge, these patients are similarly challenging to manage and have overall poor survival statistics [2–4]. Table 53.1 outlines estimated survival rates based on location of arrest; it should be noted that these estimates are quite variable across the literature from which they are based. Of importance when considering these survival estimates is that those with shockable initial rhythms (ventricular fibrillation, pulseless ventricular tachycardia) have much better survival than those with non-shockable rhythms (asystole, pulseless electrical activity).

Cardiac arrest is a time-dependent, dynamic process as conceptualized by Weisfeldt and Becker in their 3-phase model of ventricular fibrillation cardiac arrest, which describes a progressive disruption of cardiac electrophysiology, circulation, and metabolism [5]. From cardiac arrest through the first 4 min is considered the electrical phase during which defibrillation is most likely to be successful [3, 6]. This phenomenon is most likely due to a time-dependent decay of a shockable ventricular fibrillation rhythm to a lower amplitude rhythm that is poorly responsive to defibrillation [7, 8]. Chest compressions gain importance after 4 min, which is likely due to the ischemic heart being less responsive to defibrillation [9]. Lastly, significant metabolic dysfunction (the metabolic phase) occurs at approximately 10 min as a result of global ischemia. Lack of return of spontaneous circulation by this time is associated with significantly worse survival.

Of course, there is considerable heterogeneity within the cardiac arrest population. The Weisfeldt-Becker model described above refers to ventricular fibrillation cardiac arrest, which is but one type of cardiac arrest. This heterogeneity extends beyond the type of cardiac arrest to such factors as age, gender, duration of arrest, and comorbidities among other factors, all of which make cardiac arrest treatment and cardiac arrest research extremely challenging.

Challenges aside, it is clear that aggregate outcomes can be improved by timely provision of specific interventions from lay people to paramedics, emergency department staff, and intensive care unit staff. Early identification and activation of the emergency response system, high-quality basic life support including good chest compressions, early defibrillation, expert application of advanced cardiac life support principles, and advanced post-resuscitation care can all improve patient outcome. Advances in care of the cardiac arrest patient have been seen with the advent of chest compressions, defibrillation, skilled airway management, therapeutic hypothermia, early percutaneous coronary intervention, and seizure control. Further incremental

Table 53.1 Estimated survival from out-of-hospital and in-hospital cardiac arrest

	Incidence	Survival (%)
Out-of-hospital [1, 59]	0.5/1000	9
In-hospital [60]	0.17 ± 0.09 per bed/year	17

advances will be seen through careful resuscitation research, application of promising research findings, and meticulous attention to detail in the provision of postarrest care.

53.2 Overview: Current Advanced Cardiac Life Support (ACLS)

Management of cardiac arrest and the current approach to ACLS can be thought of in terms of the arrest phase and the postarrest phase. While there are interventions that may be applicable in either phase such as airway management, current research on management of the cardiac arrest patient tends to focus on early intervention from lay persons and EMS in the arrest phase and advanced care in centers of excellence in the postarrest phase. Figure 53.1 outlines the current ACLS algorithm for adult cardiac arrest.

During the arrest phase, the focus must be on early defibrillation and high-quality chest compressions. Early defibrillation is best accomplished via the use of automated external defibrillator (AED) and activation of the emergency medical system.

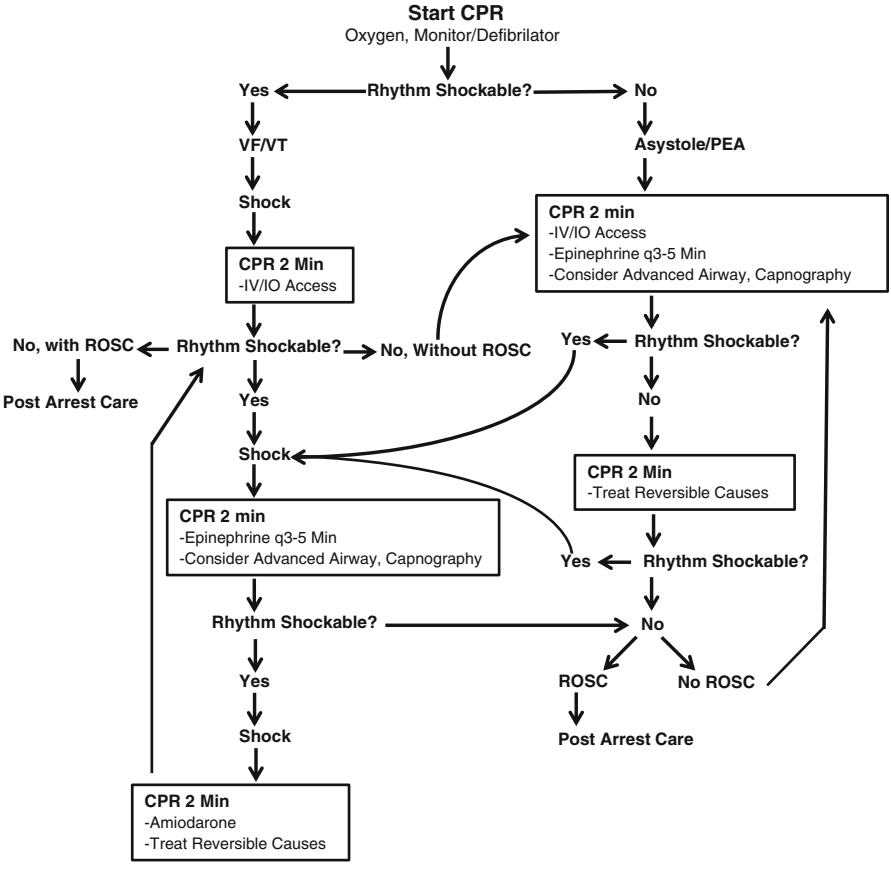

Fig. 53.1 ACLS algorithm for adult cardiac arrest

With regard to CPR, compression-only CPR is favored as it is thought to be as good or better than conventional CPR with ventilations [10–15]. However, there is evidence that conventional CPR may be superior in young patients, those with cardiac arrests of noncardiac origin, those with delay to CPR initiation, and those with prolonged arrests of cardiac etiology [10, 16].

Improving outcomes in the postarrest phase is dependent on multiple factors and is best managed in a hospital setting that enables multidisciplinary teams to work collaboratively, optimizing all aspects of the patient's care. Such teams should be skilled in managing the brain injury, myocardial dysfunction, systemic ischemia/reperfusion injury, and persistent effects from the precipitating pathology during the immediate presentation. Further, these multidisciplinary teams should be experts in managing the physical and psychosocial aspects of medium- and long-term recovery to optimize outcome.

This chapter will focus on key aspects of prehospital and early hospital care in the cardiac arrest patient, with focused sections on each critical aspect of care.

53.2.1 Prehospital Care

Resuscitation of patients with out-of-hospital cardiac arrest (OOHCA) is based on the "chain of survival" concept, with links of early activation of EMS, early CPR, early defibrillation, advanced cardiac life support, and post-resuscitation care [17]. Optimal treatment of OOHCA in the prehospital setting is complex and requires time-sensitive, coordinated actions involving multiple groups, such as lay persons who can perform bystander CPR and use community-based AEDs and EMS providers to ensure high-quality CPR, early defibrillation, and initiation of ACLS, and transport to hospitals which can provide comprehensive post-resuscitation care including acute coronary interventions, therapeutic hypothermia, neurological care, and goal-directed critical care.

The importance of early CPR on survival in OOHCA has been well established, and early CPR is considered to double or even triple the survival rate [18–20]. In addition, a growing body of data points to the importance of high-quality CPR in achieving return of spontaneous circulation (ROSC) and improving outcomes [20, 21]. As such, public health initiatives have focused on educating the lay public about the importance and mechanics of CPR. As discussed above, compression-only CPR is now recommended for bystanders, with the intent of simplifying and removing barriers to its initiation. International guidelines endorse CPR with minimized interruptions, compressions of adequate depth (>5 cm) and rate (>100/min), and full release of pressure between compressions, as well as avoidance of excessive ventilation [22].

Defibrillation for ventricular tachycardia/ventricular fibrillation is another critical prehospital intervention for OOHCA. Despite an increased presence of AEDs in public places like airports and shopping malls, a minority of patients with OOHCA receive AED defibrillation prior to EMS arrival, suggesting that further expansion of public access defibrillation programs would be beneficial [23, 24].

The final component of the prehospital management of OOCHA is transfer to an appropriate facility. With increased recognition that aggressive, comprehensive post-cardiac arrest care improves outcomes, guidelines recommend that field providers should bypass local hospitals and go directly to a hospital capable of providing angiography within 90 min and helicopter transport for patients when anticipated time to angiography exceeds 90 min [25].

53.2.2 Early Hospital Care

While prehospital interventions like defibrillation and high-quality compressions are critical in achieving ROSC, increased attention has been focused on the role of in-hospital post-resuscitation care to help improve survival rates following cardiac arrest [12]. Epidemiological data on patients resuscitated from OOHCA suggest there is a wide variation in regional and institutional treatments as well as survival rates [26]. Accordingly, there have been increased efforts to define and characterize how elements of post-resuscitation care contribute to increased survival. Data suggests that hospitals that provide an integrated team approach to post-resuscitation care report improved survival rates [27].

The AHA's 2010 guidelines for postarrest care list the following priorities [12]:

1. Therapeutic hypothermia to optimize survival.
2. Identify and treat acute coronary syndrome.
3. Optimize mechanical ventilation to minimize lung injury.
4. Support organ function to reduce risk of multiorgan failure.
5. Assess prognosis for recovery.
6. Assist survivors with rehabilitation services when needed.

53.3 Post-cardiac Arrest Syndrome

Post-cardiac arrest syndrome describes the global ischemic injury and reperfusion injury characterizing patients resuscitated from cardiac arrest. This complex pathophysiological state includes brain injury, myocardial dysfunction, and systemic ischemia/reperfusion response induced by the arrest event as well as underlying pathology which led to the arrest [26].

The brain is particularly vulnerable to injury in cardiac arrest due to its limited tolerance for ischemia as well as its unique response to reperfusion, which includes excitotoxicity, impaired calcium homeostasis, and activation of protease cascades and cell death signaling pathways [28, 29]. Furthermore, postarrest hypoxemia, hypotension, and impaired cerebral autoregulation can lead to secondary neurologic injury. Clinical manifestations of postarrest brain injury include coma, seizures, cognitive dysfunction, and death [30, 31]. Thus, strategies to reduce brain injury,

such as therapeutic cooling and hemodynamic optimization, are core treatment elements following cardiac arrest.

Post-cardiac arrest myocardial dysfunction also contributes to the high mortality rate following cardiac arrest [26]. Importantly, data suggests that myocardial dysfunction, also known as "myocardial stunning," is both responsive to therapy and reversible, again underscoring the need for aggressive postarrest care [32, 33].

53.4 Therapeutic Hypothermia

Therapeutic hypothermia, also known as targeted temperature management, is a mainstay of treatment to minimize postischemic brain injury in the patient who remains comatose after cardiac arrest. In 2002, two landmark randomized controlled trials (RCTs) demonstrated improved survival in adults with OOHCA from ventricular fibrillation (VF) treated with therapeutic hypothermia. The first study, a large European multicenter trial, reported a 16 % absolute improvement in outcomes in patients with VT/VF arrest cooled to a range of 32–34 °C, and the second study, performed in Australia, reported a 23 % improvement in patients randomized to cooling to 33 °C [34, 35]. In addition, more than 40 nonrandomized trials have reported improved outcomes with therapeutic hypothermia [36]. On the basis of this evidence, professional societies have been advocating therapeutic hypothermia in patients resuscitated after VT/VF cardiac arrest.

A recent international study comparing cooling temperatures has challenged the long-held dogma of therapeutic hypothermia's benefits. Nielsen et al. randomized 950 patients with OOHCA of presumed cardiac cause to targeted temperature management of 33 °C versus 36 °C and found no difference in outcomes among the two groups [37]. This study has generated intense debate and raised numerous questions about therapeutic hypothermia, including its potential benefit, what the optimal temperature and timing of cooling is, whether avoidance of fever is the beneficial mechanism, or whether the rapid rewarming in the study negated any benefits of therapeutic hypothermia [38, 39]. Further research is needed to clarify optimal parameters for therapeutic hypothermia, which as yet remain undefined.

While no randomized controlled trials have compared hypothermia versus normothermia in patients with non-VT/VF cardiac arrest, observational studies suggest a possible benefit, and therapeutic hypothermia is often used as a treatment for cardiac arrest from non-shockable rhythms as well [40, 41]. Current guidelines recommend cooling comatose patients after VF cardiac arrest to 32–34 °C for 12–24 h (Class I, level of evidence B), with consideration for patients with cardiac arrest from non-shockable rhythms (Class IIb, level of evidence B) [12].

Therapeutic hypothermia can be divided into three phases: induction, maintenance, and rewarming. Induction can be initiated with intravenous ice-cold fluids (0.9 % saline or Ringer's lactate 30 mL/kg), or ice packs placed on the groin, armpits, and around the head and neck [42–44]. This can be easily started in the prehospital setting. Once the patient arrives in the hospital, internal cooling devices, such

as intravascular cooling catheters, are inserted into the femoral or subclavian veins and provide controlled temperature maintenance.

The goal of the maintenance phase is to maintain temperature at 32–34 °C and prevent significant temperature fluctuations, which is best achieved with internal cooling devices [26]. Neuromuscular blockade with sedation may be required to prevent shivering and its associated heat generation. While the optimal rewarming rate has not been defined, the current consensus is to warm at 0.25–0.5 °C per hour [41].

Complications of hypothermia include shivering, increased systemic vascular resistance which can reduce cardiac output, and arrhythmias, particularly bradycardia [40]. In addition, hypothermia triggers a cold diuresis, which can lead to hypovolemia and electrolyte disturbances, such as hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia, all of which can worsen arrhythmias. Electrolytes should be checked frequently and repleted if necessary. Finally, cold-induced impairment of platelets and clotting function can lead to coagulopathy and bleeding problems [26].

53.5 Early Cardiac Catheterization

Coronary artery disease (CAD) is present in the majority of patients with out-of-hospital cardiac arrest, and acute coronary syndrome (ACS) is the leading cause of sudden cardiac death [45]. A recent review showed acute coronary plaque disruptions in 40–86 % of cardiac arrest survivors and in 15–64 % of autopsy studies [46]. This research, along with similar work, suggests that patients resuscitated from VF arrest are likely to have an acute coronary occlusion, and has prompted investigation into early percutaneous coronary intervention (PCI) as a treatment for out-of-hospital arrest (Chap. 7) [25].

The efficacy of early PCI after OOHCA is well established [47, 48]. Studies of post-cardiac arrest patients with ST segment elevation myocardial infarction report angiographic success rates from 78 to 95 % and in-hospital mortality rates of 25–56 %, lower than typical cardiac arrest mortality rates [26]. In addition, studies with broader inclusion criteria, including cardiac arrest patients without ST elevation on EKG, also show promising results and suggest a mortality benefit to early PCI [47]. Many of these studies combine early PCI with therapeutic hypothermia and provide support of the feasibility and benefit of a combined approach [26].

Current guidelines endorse emergent PCI on patients with ROSC after cardiac arrest for patients who have ST segment elevation on EKG (Class I, level of evidence B). However, given the high prevalence of CAD in this population and the unreliability of initial EKG for the diagnosis of ACS, emergent PCI should be considered for patients with a presumed cardiac cause even in the absence of ST elevation on EKG [25]. Therapeutic hypothermia can be safely combined with emergent PCI. If no facility with PCI capability is available, consideration should be given for thrombolytics in patients with ST elevation myocardial infarction, although there is a paucity of data on thrombolytics in the post-cardiac arrest population [25].

53.6 Goal-Directed Therapy and Management of Cardiogenic Shock

Early hemodynamic optimization, or early goal-directed therapy, refers to an algorithmic approach which aims to restore and maintain the balance between systemic oxygen delivery and demands. While early goal-directed approaches have been shown to improve survival in septic shock, there is little data from randomized controlled trials of post-cardiac arrest patients [49]. However, there are numerous physiologic similarities between the postarrest and sepsis states, and current guidelines support a similar resuscitation strategy, consisting of targeting physiologic parameters with a priority on early initiation.

Based on available evidence, resuscitation targets in post-cardiac arrest patients include mean arterial pressure (MAP) of 65–100 mmHg, central venous pressure of 8–12 mmHg, and mixed venous O_2 ($ScvO_2$) >70 %, urine output >1 mL/kg/h, and a normal or decreasing serum lactate level [49, 50]. The optimal hemoglobin level has yet to be defined.

53.6.1 Mechanical Ventilation Strategies

A growing body of evidence points to the detrimental effect of hyperoxia in the post-resuscitation period, with a proposed mechanism of increased oxidative stress to vulnerable postischemic neurons [51, 52]. A recent study revealed that ventilation with 100 % oxygen in the first hour post-ROSC contributed to worse outcomes than titration of FiO_2 (fraction of inspired oxygen) to maintain oxygen saturation of 94–96 % [53]. Therefore, current guidelines advocate an FiO_2 of 100 % during CPR, but rapid titration of oxygen to maintain saturations of 94–96 % once ROSC has been achieved.

Another priority endorsed by the AHA for post-resuscitation care is optimization of ventilation. High tidal volumes can cause barotrauma and volutrauma in patients with acute lung injury [54, 55]. In addition, hyperventilation should be avoided as it can lead to cerebral vasoconstriction with resultant worsening of cerebral ischemia [56]. Likewise, hypoventilation with its associated hypoxia and hypercapnia can increase intracerebral pressure and compound preexisting metabolic acidosis in the postarrest state. Therefore, ventilation should be adjusted to avoid high volumes and to maintain normocarbia, with frequent arterial blood gas measurements to guide optimization of ventilatory parameters.

53.7 Circulatory Support

Hemodynamic instability is common in postarrest period due to a combination of factors including transient myocardial dysfunction, intravascular volume depletion, and impaired vasoregulation [33]. Clinical manifestations may include

dysrhythmias, hypotension, and low cardiac index. Goals of resuscitation include circulatory support to help balance systemic oxygen delivery with demands, maintaining adequate end-organ perfusion.

Hypotensive patients should first be treated with intravenous fluids to optimize right heart filling pressures. There is no evidence to support invasive hemodynamic monitoring over noninvasive monitoring. Inotropes and vasopressors should be added if hemodynamic goals are not achieved once preload has been optimized. While post-cardiac arrest global myocardial dysfunction is generally reversible and responds well to inotropes, the severity of myocardial dysfunction may impact survival [33]. If volume expansion and use of vasoactive and inotropic drugs fail to restore adequate organ perfusion, mechanical circulatory support should be considered. First line for fluid- and pressor-refractory hypotension is the intra-aortic balloon pump, followed by more invasive options like percutaneous cardiopulmonary bypass, extracorporeal membrane oxygenation (ECMO), or ventricular assist devices.

53.8 Seizure Monitoring and Control

Seizures, myoclonus, or both occurs in 5–15 % of patients with ROSC after cardiac arrest and in up to 40 % of patients who remain comatose [30, 57]. Prompt treatment of seizures is important as prolonged seizures increase cerebral metabolism and may cause cerebral injury in the vulnerable postischemic brain [58]. Electroencephalographic (EEG) monitoring should be performed in comatose patients after ROSC (Class I, level of evidence C). Guidelines recommend treatment of seizures with benzodiazepines, phenytoin, sodium valproate, propofol, or a barbiturate, though data showing benefit is lacking (Class IIb, level of evidence B) [12].

53.9 Organ Donation

Despite aggressive management, the mortality rate for out-of-hospital cardiac arrest remains high. Data suggests similar outcomes when organs are transplanted from patients with brain death from cardiac arrest compared to brain death from other causes [59]. Current guidelines recommend adult patients with cardiac arrest who progress to brain death should be considered for organ donation (Class I, level of evidence B) [12].

53.10 Concluding Remarks

Cardiac arrest is a highly complex and time-sensitive process. This, coupled with marked patient heterogeneity, makes cardiac arrest very challenging to manage. However, incremental improvements in outcome can be achieved through

implementation of research-proven interventions. For example, we know that early interventions from lay people, early activation of the EMS system, and provision of meticulous postarrest care that includes therapeutic hypothermia, early cardiac catheterization, seizure control, and goal-directed care improve outcomes. The next steps forward are to continue to support cardiac arrest research to identify interventions that will impact outcomes and to promote regionalized systems where patients are directed to centers that are skilled in optimum treatment strategies, mirroring the regionalized systems that have been implemented for stroke, ST segment elevation myocardial infarction, and trauma care.

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Part VII
Valvular Heart Disease

Chapter 54
Valvular Heart Disease: Introduction, Clinical Pathogenesis, and Management

Siri Kunchakarra, Jyothy Puthumana, and Kameswari Maganti

Abstract Valvular heart disease (VHD) is a common cardiac condition with a big impact on healthcare economics. The incidence of VHD had been increasing over the past few decades, likely due to aging population [1]; improved mortality outcomes with increased survival in patients with conditions such as ischemic heart disease, chronic kidney disease, inflammatory disease states, and oncologic patients; earlier diagnoses due to technologic advances in imaging tools; and iatrogenic valve disease such as prosthetic valve dysfunction [2]. It is important to have an in-depth understanding of the different types of VHD; the natural history; interplay between anatomic, genetic, and molecular mechanisms of specific VHD; impact of VHD on other organ systems; and advances in diagnostic and therapeutic options that will translate to improved patient outcomes [3].

Keywords Valvular heart disease • Aortic valve disease • Mitral valve disease • Tricuspid valve disease • Pathogenesis • Rheumatic heart disease • Aortic stenosis • Aortic regurgitation • Mitral stenosis

54.1 Introduction

The incidence of VHD had certainly changed within the last few decades. Rheumatic heart disease (RHD) is still a major etiologic factor for the development of VHD worldwide, whereas degenerative valve disease is likely the most common etiology of VHD in developed countries [3]. The prevalence of the VHD increases from 0.7 % in people <45 years to 13 % in people over 75 years [4]. This translates to a significant public health burden. Thus, a physician should be well versed in obtaining a thorough history and performing a complete physical examination, understand the appropriate diagnostic testing to accurately diagnose the severity of valve disease, and apply timely therapeutic options that are available with a clear understanding of their effect on morbidity and mortality. In this chapter, we present

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fundamental information on valvular heart disease that is important and useful to a physician because the initial presentation of such patients often occurs in the primary care or emergency room settings. Prompt diagnosis and treatment are essential to minimize high morbidity and mortality.

54.2 Aortic Stenosis (See Also Chap. 57)

54.2.1 Etiology

Aortic stenosis (AS) is the third most common form of cardiovascular disease after hypertension and coronary artery disease. The most common cause of aortic obstruction is valvular AS. However, supravalvular AS and subvalvular AS can occur but are much less common than valvular AS. The overall prevalence of AS is estimated at 2.8 % in people above the age of 75 years. The incidence increases with age with a prevalence of 9.8 % in octogenarians [5, 6]. AS in developed countries is often caused by calcification of either a congenitally bicuspid aortic valve or a normal trileaflet aortic valve. However, rheumatic heart disease continues to be the most common etiology worldwide. In one US series with 932 patients aged 26–91 years undergoing aortic valve replacement for AS, 54 % of patients had congenitally malformed (mostly bicuspid) valves and 45 % had trileaflet valves [7]. Bicuspid aortic valve disease is responsible for 60 % of aortic valve replacements in people younger than 70 years and 40 % of patients above the age of 70 years [8]. A genetic component is thought to be responsible for calcific AS in patients with bicuspid aortic valves (BAV). Epidemiologic studies suggest that BAV is heritable, and follows an autosomal dominant mode of transmission with variable expressivity. The molecular basis of BAV is incompletely understood, at least 2 pathways seem critical for normal tricuspid aortic valve formation, namely, Notch and Nos3. [9, 10]. The risk factors for development of degenerative AS are similar to those of atherosclerotic vascular disease such as older age, male gender, smoking, hypertension, hyperlipidemia with high LDL and lipoprotein(a), diabetes, and metabolic syndrome [11, 12]. There is an increased risk of AS in patients with a history of mediastinal irradiation, renal disease, dialysis state, abnormal calcium metabolism, and familial hyperlipidemia [13].

54.2.2 Pathophysiology

Calcific aortic stenosis is thought to be an active process that begins at molecular and cellular levels, and then becomes a systemic disease as disease progresses [14, 15]. Calcific changes of the aortic valve leaflets that occur with aging, formerly called degenerative changes, are characterized by increased leaflet thickening, stiffening,

and calcification without commissural fusion. Aortic valve sclerosis is the initial stage of calcific disease and even in the absence of stenosis has been shown to be associated with increased risk of myocardial infarction and cardiovascular death [22]. Aortic valve sclerosis is common, and currently about 25 % of people aged 65–74 years and about 48 % of people older than 84 years have aortic valve sclerosis. Progression to aortic stenosis has been reported in about 15 % of patients [16].

A bicuspid aortic valve is the most common congenital cardiovascular malformation and occurs in up to 2 % of the general population [5]. The bicuspid valve has only two functional cusps, usually of unequal size, with the larger cusp having a midline raphe, resulting from incomplete commissural separation during development. Cusp fusion patterns differ in patients with bicuspid aortic valve. Most commonly, fusion of the right and left cusps is seen in 70–80 % and, less commonly, fusion of the right and noncoronary cusps is seen in 20–30 % [17, 18]. The midline raphe and the base of the cusp are often sites for calcific deposits and once stenosis occurs, the pathophysiology and clinical course is similar to that of calcific aortic stenosis. However, bicuspid valves incur greater mechanical stress and can get stenotic in an accelerated manner compared to normal tricuspid aortic valves [18, 19]. Typically, the calcification of degenerative AS begins at the bases of the cusps and progresses to the apices.

In developed countries, rheumatic fever is a very rare cause of aortic stenosis, though it continues to remain a significant problem worldwide [20]. When the aortic valve is affected by rheumatic heart disease, the mitral valve is almost always affected as well. In rheumatic AS, the commissures are fused, forming a conjoined cusp due to endocardial inflammation and valve fibrosis, unlike calcific aortic stenosis [20, 21].

Similar to atherosclerosis, the pathogenesis of calcific aortic valve disease involves an active process of inflammation with lipid deposition, macrophage infiltration, and osteopontin deposition, a protein needed for bone formation. The histological changes seen in aortic sclerosis with lipoprotein accumulation, cellular infiltration, and extracellular matrix formation eventually result in a macroscopic, progressive valve thickening. The characteristic of severe AS is the increased calcification that leads to leaflet immobility and the outflow tract obstruction [16, 22, 23].

Progression from mild AS to severe AS is nearly always seen, with a vast majority needing aortic valve replacement [24–29]. The rate of progression of AS is widely variable among individuals. On an average, there is an increase in peak jet velocity between 0.1 and 0.3 m/s with a mean gradient increase between 3 and 10 mmHg per year and a decrease in aortic valve area by 0.1 cm^2 per year [30].

In patients with AS, the valvular stenosis progressively worsens with time. The outflow tract obstruction leads to chronic pressure overload that results in concentric left ventricular hypertrophy (LVH). The development of hypertrophy is a compensatory mechanism that works to normalize left ventricular (LV) wall stress, helping to preserve LV systolic function and maintain normal cardiac output for many years. With time, systolic function can decline as a result of pressure overload. Increased myocardial cell mass can also be a maladaptive response and cause increased LV stiffness and diastolic dysfunction. Left atrial enlargement is often seen, due to elevated left ventricular filling pressures. In addition, there is calcification of mitral annulus as well as ascending aorta. LV systolic and diastolic

dysfunction will often improve after aortic valve replacement (AVR), but systolic dysfunction may not improve if the contractile dysfunction is irreversible and some degree of diastolic dysfunction may persist [31, 32]. Increased LV mass requires increased oxygen but also reduces coronary perfusion gradient between the aorta and the myocardium, which can lead to angina even in the absence of epicardial coronary disease. There is an increased incidence of aortic dilatation noted in patients with AS, more often in bicuspid as compared to tricuspid aortic valves [33] which can result in aortic dissection [34, 35].

54.2.3 Diagnosis

54.2.3.1 Symptoms and Physical Exam

The physical examination findings in patients with AS vary with the degree of valve stenosis, LV function, and forward stroke volume. The symptoms of AS are angina (due to reduced coronary flow reserve and increased myocardial demand by high afterload), syncope (related to exertion and caused by arrhythmias, hypotension, or decreased cerebral perfusion resulting from increased blood flow to exercising muscles without compensatory increase in cardiac output), and congestive heart failure. About 75 % of patients with symptomatic AS will die 3 years after onset of symptoms unless the aortic valve is replaced. Heart failure carries the worst prognosis. The severity of aortic stenosis is progressive and gradually gets worse over the course of 10–15 years. During this time, medical surveillance and patient education regarding disease course are essential [36]. Even when moderate-to-severe AS develops, the prognosis is excellent as long as the patient is asymptomatic. In asymptomatic patients with severe AS, the likelihood of developing cardiac symptoms within 5 years is also very high. Aortic valve area and LVH may be predictive of development of symptoms [37]. Regardless of the etiology of AS, once symptoms of angina (35 %), syncope (15 %), or heart failure (50 %) develop, survival decreases precipitously, with average survival of about 2–3 years and an increased risk of sudden cardiac death [36–40] (Fig. 54.1). Among symptomatic patients with severe AS, those with a failed left ventricle do poorly. Once symptoms develop, the mortality is quite high, which can be mitigated by prompt aortic valve replacement [40, 41]. In some patients with AS, gastrointestinal bleeding due to angiodysplasia is seen. This is typically associated with a deficiency on von Willebrand factor multimers, a condition termed Heyde's syndrome [42]. This reverses once the AS is corrected.

The four key features of the physical exam include palpation of carotid upstroke, auscultation of the systolic murmur, assessment of the splitting of the second heart sound, and examination for signs of heart failure. In severe AS, ventricular systole becomes prolonged and the carotid upstroke is slow rising and late peaking (*pulsus parvus et tardus*). Rarely, a systolic thrill in carotid pulse may be appreciated. A sustained bifid left ventricular impulse indicates concomitant left ventricular hypertrophy. The classic murmur of AS is a crescendo-decrescendo systolic murmur heard best at the cardiac base (right upper sternal border) radiating to the carotids.

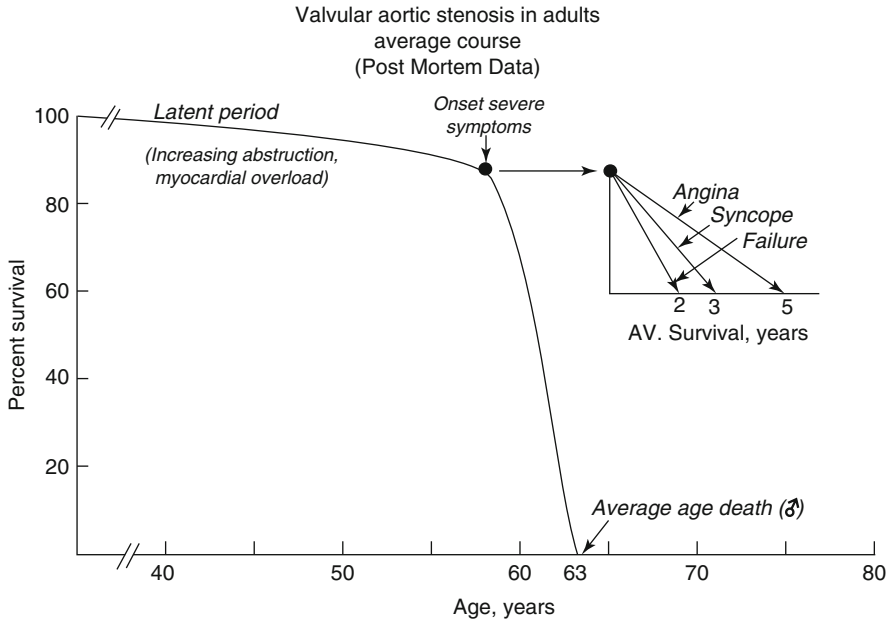

Fig. 54.1 Natural history in untreated severe AS

The intensity of the murmur does not correlate with the severity of AS. However, as the severity of AS increases, the duration of the murmur may increase, with a peak in mid to late systole. The murmur may rarely be heard in the LV apex area, mimicking mitral regurgitation (Gallavardin's phenomenon). A diastolic murmur may be heard, if coexistent aortic regurgitation (AR) is present. With severe AS, the physiologic splitting of S2 may be absent as a result of calcification and immobility of aortic valve leading to an inaudible A2. The vigorous atrial contraction may give rise to an S4. Presence of S4 in a young patient with AS is usually consistent with a significant aortic stenosis. Systolic clicks are often heard before the onset of murmur in young patients with bicuspid aortic valves. If heart failure results from severe AS, the systolic murmur may get softer or even be absent due to a low-flow state. Other signs of heart failure such as lateral displacement of the apical impulse, third heart sound, or an elevated jugular venous pressure may be seen on exam [5, 43].

54.2.3.2 Diagnostic Testing

The electrocardiogram (ECG) is typically nondiagnostic in patients with AS. About 85 % of patients with severe AS have LVH with repolarization. Other ECG abnormalities include left atrial abnormality, left or right axis deviation, left bundle branch block, or atrial fibrillation. The chest radiograph is nonspecific in patients with AS. There is rounding of the LV borders and apex consistent with LVH. There may be aortic valve and aortic root calcifications, best appreciated in the lateral projections or fluoroscopy. Dilatation of aorta is sometimes seen.

Table 54.1 Recommendations for classification of aortic stenosis severity by echocardiography

	Aortic sclerosis	Mild AS	Moderate AS	Severe AS
Aortic jet velocity	≤2.5 m/s	2.6–2.9	3.0–4.0	≥4.0
Mean gradient		<20	20–40	>40
AVA (cm^2)		>1.5	1.0–1.5	<1.0
Indexed AVA (cm^2/m^2)		>0.85	0.60–0.85	<0.6
Velocity ratio		0.50	0.25–0.50	<0.25

Echocardiography with Doppler evaluation is the imaging test of choice to diagnose and to estimate the severity of AS. This will help assess the LV dimensions, extent of LVH, LV systolic function, LA dimensions, diastolic function, aortic root dimensions, anatomy of the aortic valve to delineate if the valve is bicuspid or tricuspid, amount of aortic valve calcification, transvalvular pressure gradient, aortic valve area, and associated mitral valve disease. In patients with bicuspid aortic valves, doming of the aortic valve due to asymmetric size of leaflets as well as ascending aortic dilatation is often seen [44]. Table 54.1 delineates the echocardiographic measures used to determine the severity of AS [45].

Exercise stress testing is absolutely contraindicated in symptomatic patients with severe AS. However, there is a role in testing asymptomatic patients with severe AS to provoke symptoms, to ensure that there is an appropriate increase in blood pressure with exercise, and to evaluate exercise capacity [46, 47]. In patients with low cardiac output (ejection fraction, EF <50 %), the calculated gradient and the aortic area may be underestimated due to low aortic flow. In cases of "low-flow, low-gradient" cases of AS, low-dose dobutamine may be necessary to assess the true severity of AS [48, 49]. Diagnosis of low-flow, low-gradient severe AS with a normal ejection fraction is extremely challenging. This is often seen in elderly women with small LV dimensions, LVH, and diastolic dysfunction. In this population, the stroke volume index is <35 ml/m^2 with an indexed aortic valve area of <0.6 cm^2 [50].

Because of the accuracy of echocardiography in detecting and determining the severity of AS, invasive methods such as cardiac catheterization are seldom necessary in the evaluation of AS. However, it may be helpful in patients in whom the noninvasive tests are inconclusive or if there is a discrepancy in assessing the severity of AS. Coronary angiography is used to determine concomitant coronary heart disease (CHD) prior to surgical aortic valve replacement.

54.2.4 Treatment

Treatment decisions are based on symptoms, severity of valve obstruction, and presence of LV adaptation to pressure overload. The presence of symptoms drives the treatment in patients with AS. Figure 54.2 delineates the treatment algorithm for patients with severe AS [1].

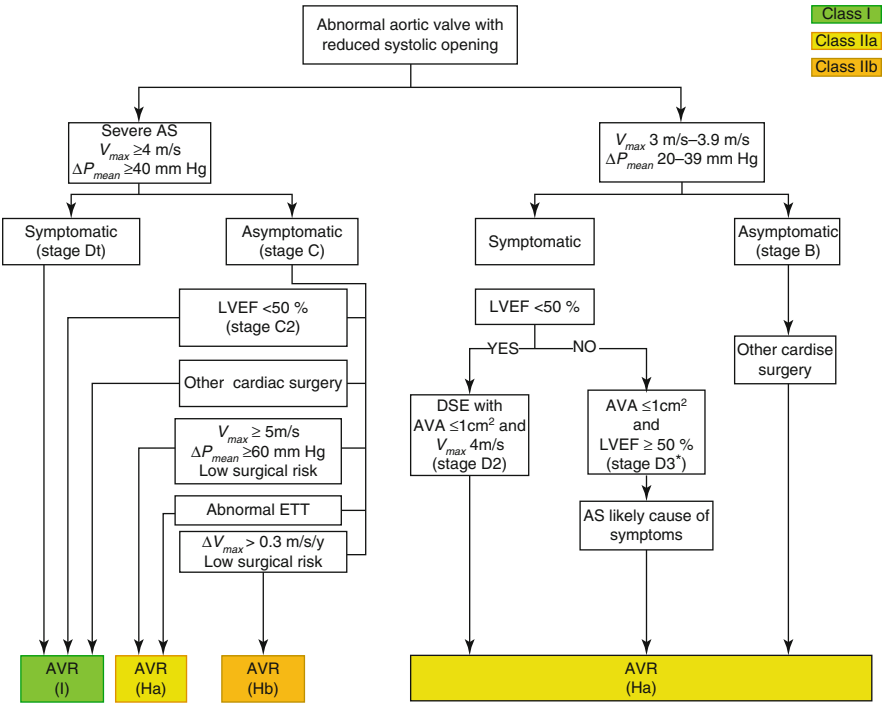

Fig. 54.2 Indications for AVR in patients with AS. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. *AVR should be considered with stage D3. AS only if valve obstruction is the most likely cause of symptoms, stroke volume index is <35 ml/m^2, indexed AVA is ≤0.6 cm^2/m^2, and data are recorded when the patient is normotensive (systolic BP <140 mmHg). *AS* indicates aortic stenosis, *AVA* aortic valve area, *AVR* aortic valve replacement by either surgical or transcatheter approach, *BP* blood pressure, *DSE* dobutamine stress echocardiography, *ETT* exercise treadmill test, *LVEF* left ventricular ejection fraction, *ΔPmean* mean pressure gradient, and *Vmax* maximum velocity (Adapted with permission from Ref. [1])

54.2.4.1 Medical Treatment

There are no medical treatments that have shown to delay the progression of AS. Due to the known association between AS and other CHD risk factors, statin therapy has been studied as a potential therapeutic intervention to slow the progression of AS. However, statins have not been shown to delay progression, improve mortality, or delay time to surgery in AS [25, 51, 52]. Diuretics may be useful when symptoms of heart failure have developed, although should be used cautiously as hypovolemia may lower cardiac output and LV end-diastolic pressure and cause orthostatic hypotension. Beta-adrenergic blockers can depress myocardial function and should be avoided in patients with severe AS.

54.2.4.2 Aortic Valve Replacement (AVR)

Calcific AS is now the leading indication for AVR in North America and Europe. There is overwhelming data to indicate that AVR is indicated for patients with symptomatic severe AS [40, 41, 53, 54]. Typical initial symptoms appear to be decreased exercise tolerance and exertional dyspnea. The classic triad of angina, syncope and heart failure are typically symptoms suggestive of advanced AS. Class I indications for AVR are severe symptomatic AS, asymptomatic patients with severe AS and LVEF <50 %, and patients with severe AS undergoing cardiac surgery for other indications [1]. Additionally, AVR could be considered in asymptomatic patients with severe AS when exercise testing provokes symptoms or causes a fall in systolic blood pressure or when markers of rapid progression are present (such as severe valve calcification or increase in aortic velocity of ≥0.3 m/s per year). AVR is also reasonable in asymptomatic patients with very severe AS (Vm ≥5 m/s or mean gradient ≥60 mmHg) who are at a low surgical risk and low-flow low-gradient severe AS with reduced EF [1, 55].

Surgical AVR is considered to be the treatment of choice except in cases of high surgical mortality or inoperable cases. Overall, 30-day surgical mortality is less than 3 % for isolated AVR and approximately 4.5 % for AVR with coronary artery bypass grafting performed at the same time as AVR. Surgical mortality for AVR rises to 10 % in individuals older than the age of 75.

Percutaneous balloon valvulotomy may be considered in children and adolescents with noncalcified aortic valves. Given the high rate of restenosis and failure to improve long-term survival, this is not the procedure of choice in adults who are suitable for AVR. However, it can be occasionally considered for patients who are highly symptomatic as a bridge to surgery in critically ill patients with advanced AS or as palliative procedure when surgery is too high risk.

Transcatheter aortic valve replacement (TAVR) by percutaneous transfemoral or transapical approach is an alternative in selected patient populations who are considered to be at a prohibitive risk for surgical aortic valve replacement. In patients with severe AS, who are poor surgical candidates, and with a predicted post-procedure survival of greater than 12 months, TAVR is a class I recommendation according to the ACC/AHA guidelines. It is also a reasonable alternative to surgical AVR in patients who have high surgical risk and meet an indication for AVR [1, 54]. However, these decisions are made by a Heart Valve Team consisting of an integrated, multidisciplinary, collaborative group of healthcare professionals with expertise in valvular heart disease, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery.

Long-term anticoagulation is necessary for mechanical aortic valve prostheses, but not necessary with bioprostheses. Short duration of anticoagulation up to 3 months following a bioprosthetic aortic valve implantation is frequently utilized. Adjunctive pharmacologic therapy with TAVR primarily consists of heparin during the procedure and dual-antiplatelet therapy with aspirin and clopidogrel for 6 months after implantation.

Table 54.2 Etiologies of aortic regurgitation

Aortic leaflet abnormalities	Aortic annulus or root abnormalities
• Congenital abnormalities include bicuspid, unicuspid, or quadricuspid valves • Rupture of a congenitally fenestrated valve • Subaortic membranes • Structural deterioration of bioprosthetic aortic valve	Idiopathic aortic root dilatation, degeneration of the extracellular matrix due to • Isolated condition • Related to Marfan syndrome • Related to congenitally bicuspid aortic valves • Ehlers-Danlos syndrome • Osteogenesis imperfecta • Syphilitic aortitis
• Rheumatic heart disease with fusion of the commissures and retraction of the aortic valve leaflets due to scarring and fibrosis • Myxomatous infiltration of the aortic valve; tumors • Infective endocarditis • Atherosclerotic degeneration • Connective tissue disorders such as Marfan syndrome • Ingestion of ergot-derived compounds • Inflammatory diseases such as aortitis • Antiphospholipid syndrome • Use of anorectic drugs	Aortitis noted with other connective tissue diseases such as • Ankylosing spondylitis • Giant cell arteritis • Behçet syndrome • Psoriatic arthritis
Systemic disorders that may affect the aortic valve include • Lupus erythematosus • Giant cell arteritis • Takayasu arteritis • Ankylosing spondylitis • Jaccoud arthropathy • Whipple disease • Crohn's disease	Other forms of arthritis associated with • Ulcerative colitis • Relapsing polychondritis • Reiter syndrome

54.3 Aortic Regurgitation (AR) (See Also Chap. 57)

54.3.1 Etiology

The etiology of AR can be divided into two major categories: abnormalities of the aortic leaflets and abnormalities of the supporting structures such as the aortic root and the annulus that prevent proper coaptation of aortic leaflets. In the developing world, rheumatic disease is the most common cause of AR. In the western world, severe AR is most often caused by congenital or degenerative causes. The causes of AR are listed in Table 54.2 [1, 3, 56].

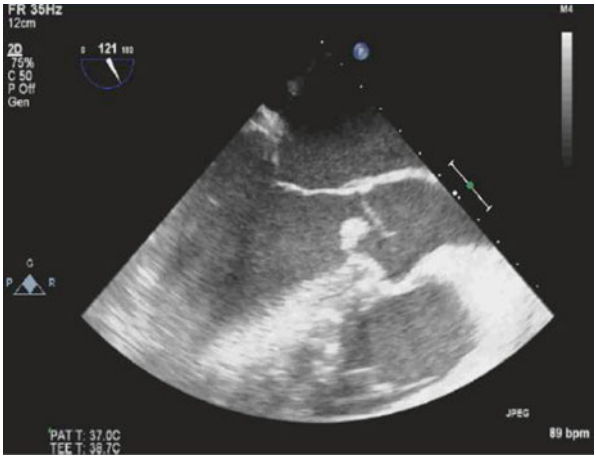

Fig. 54.3 Aortic valve vegetation (group B Streptococcus) causing leaflet prolapse

With leaflet causes such as bicuspid valves, rheumatic fever, or infective endocarditis, there may be a loss of proper coaptation of the cusps, prolapse of the aortic cusp, or incomplete closure of the valve leading to AR (Fig. 54.3). In aortic root enlargement, aortic annulus becomes dilated causing the aortic leaflets to separate and can cause tension and bowing of the cusps, leading to AR.

The overall prevalence of AR is estimated to be between 4.9 % and 10 % [58, 59], with prevalence increasing with age and with more severe AR seen in men [60]. AR due to aortic root disease may be more common than due to valvular disease. In one study that looked at US patients who underwent aortic valve replacement for AR, the cause of AR was valvular in 46 % and aortic root in 54 % of the patients [61].

54.3.2 Pathophysiology and Natural History

AR creates both a volume and pressure overload on the LV. In AR, the LV stroke volume is a combination of forward stroke volume and the regurgitant volume. Although the regurgitant volume empties back into LV during diastole, a large total ejected stroke volume during systole creates a wide pulse pressure and systolic hypertension.

Normal LV forward stroke volume is maintained by increasing the total stroke volume (hence increasing preload) corresponding to the severity of regurgitation. This increase in stroke volume is possible because of increased end-systolic and end-diastolic volumes. Elevated end-diastolic volume increases LV wall stress, thereby increasing LV afterload. In addition, the large total ejected stroke volume that results in systolic hypertension can further increase afterload. In fact, the wall stress in AR is as much as the wall stress noted with AS which is a pure pressure overload condition [62, 63]. This combination of preload and afterload increase eventually results in LV dilation with resultant systolic dysfunction [56, 64]. Volume overload (preload) leads to compensatory eccentric hypertrophy (with replication of sarcomeres in series), while pressure overload (afterload) leads to superimposed compensatory

concentric hypertrophy. These mechanisms help to maintain normal wall stress and LV ejection fraction, and patients can remain asymptomatic for a number of years.

With progressive LV dilatation, preload reserves may exhaust or compensatory hypertrophy may be insufficient resulting in afterload mismatch and LV dysfunction. This process can be initially reversible with the correction of the valve disorder but, if left untreated, can lead to irreversible LV dysfunction. In later stages, right-sided pressures can also increase. As heart failure develops, a common initial symptom is shortness of breath, which first develops with exercise and can later occur at rest. Anginal chest pain can also occur due to decreased diastolic perfusion pressure and increased LV oxygen demand due to hypertrophy [56, 64].

Asymptomatic mild, moderate, or even severe AR has a favorable prognosis, with quantitative measurements of AR severity, LV size, and systolic function being predictors of poor outcome. In one study, patients with mild AR had a 10-year survival of 95 ± 4 %, while those with severe AR had a 10-year survival of 69 ± 9 % [65]. Patients with severe chronic AR have an increased risk of morbidity and mortality. Within 10 years of diagnosis of severe AR, heart failure can occur in almost half the patients and most surviving patients require AVR. Once symptoms develop, disease course rapidly worsens. Death may occur within 4 years of onset of angina and within 2 years of onset of heart failure [60].

Unlike chronic AR, acute AR is often a catastrophic illness as the LV has not had the time to develop the compensatory mechanisms described above. Thus, the large total stroke volume and the attendant wide pulse pressure responsible for most of the signs of chronic AR are absent [66]. Compensatory tachycardia attempts to maintain cardiac output [17]. Patients with severe acute AR have a high mortality when treated medically. Rapid diagnosis and prompt surgical intervention are important.

54.3.3 Diagnosis

54.3.3.1 Symptoms and Physical Examination

The presenting symptoms of AR generally are determined by the rapidity with which the regurgitation develops. In chronic AR, exertional dyspnea and fatigue are the most common symptoms. Patients with chronic AR may remain asymptomatic for many years. LV failure is a late event and may be sudden in onset. Patients with acute AR, on the other hand, may present with tachypnea, tachycardia, and dyspnea due to pulmonary congestion/pulmonary edema or may present with cardiogenic shock in severe acute AR.

In patients with chronic AR, findings on physical examination are related to increased stroke volume and widened pulse pressure. The augmented stroke volume can create a hyperdynamic apical impulse and an audible systolic thrill at the cardiac base or carotid arteries. In chronic AR, a patient's head may bob with each heartbeat (de Musset sign), nail beds may pulsate with minimal pressure (Quincke's pulse), diastolic bruit may be heard over the femoral artery (Duroziez's sign), and systolic pulsations of the patient's uvula may be seen (Muller sign). The peripheral pulses can

demonstrate an abrupt rise in upstroke with a quick collapse (water hammer or Corrigan pulse), bisferiens pulse may be palpable, and "pistol shot" sounds may be heard over the femoral artery. The systolic blood pressure may be ≥30 mmHg higher in the leg than in the arm (Hill sign). The heart sounds are usually altered in patients with chronic AR. Although S1 is often normal, S2 is loud or soft depending on the etiology of the AR. A loud closure sound is associated with a dilated aortic root. A soft S2 is found when the AR is due to abnormally thickened and retracted leaflets [57]. Ejection clicks can be heard in young patients with bicuspid valves. The presence of an S3 may signify a failing left ventricle. The classic murmur of AR is a high-pitched, blowing, decrescendo diastolic murmur heard best at the aortic region. In mild AR, murmur is only in early diastole, but as severity of AR worsens, the murmur can become more holodiastolic. In severe AR, a second low-pitched diastolic murmur can be heard at the apex (Austin Flint murmur), which is thought to represent physiologic mitral stenosis (MS) murmur caused by a rapid increase in LV diastolic pressure.

The physical examination findings in acute AR may be quite difficult to elucidate since the ventricle has not had time to compensate. Thus, the large stroke volume and wide pulse pressure, which are responsible for the physical exam findings of chronic AR, are not present. With the sudden decrease in forward stoke volume, the cardiac output can only be maintained by an increase in heart rate. The physical exam is of a quiet precordium, a soft first heart sound, and a short diastolic murmur. The soft S1 is due to tricuspid valve contribution as there is early closure of the mitral valve due to a rapid increase in the LV filling pressure resulting from the large regurgitant volume entering the normal-size LV. Thus, early closure of the mitral valve noted on echo is a poor prognostic sign and should prompt rapid surgical correction.

54.3.3.2 Diagnostic Testing

In patients with chronic AR, signs of left ventricular hypertrophy can be seen on an electrocardiogram. Chronic AR can also lead to left axis deviation, a pattern of LV volume overload with an increase in initial forces, prominent Q waves in leads I, aVL, and V3–V6. With time, these forces diminish with an increase in QRS voltage. A chest radiograph may demonstrate an enlarged cardiac silhouette and enlarged aorta, if present.

Echocardiography is the most useful diagnostic tool in helping to identify both the cause as well as the severity of AR. It allows for the anatomic evaluation of the aortic valve, such as detecting congenital abnormalities (e.g., bicuspid valve), determining if there is a thickening of the valve cusps, or identifying a flail leaflet or vegetation. It is also useful in the measurement of LV end-diastolic and end-systolic dimensions and volumes, LV ejection fraction, and LV mass. Doppler echocardiography is used for the assessment of severity of AR. It is possible to quantify the effective regurgitant orifice and regurgitant volume. The classification of severity of AR using Doppler echocardiography is described in Table 54.3. If the patient has a poor acoustic window, alternative diagnostic methods such as transesophageal echocardiography may be considered.

Cardiac catheterization is mostly used as a preoperative tool to identify preexisting coronary artery disease or to evaluate the coronary and aortic root

Table 54.3 Classification or the severity of aortic regurgitation by echocardiography

Variable	Mild	Mild to moderate	Moderate to severe	Severe
Width of vena contracta (mm)	<3.0	3.0–5.9	3.0–5.9	≥6
Ratio of width of aortic regurgitant jet to LV outflow (%)	<25	25–44	45–64	≥65
Regurgitant volume (ml per beat)	<30	30–44	45–59	≥60
Regurgitant fraction (%)	<30	30–39	40–49	≥50
Effective regurgitant orifice (mm^2)	<10	10–19	20–29	≥30

anatomy. Invasive assessment of LV function and severity of AR is only used in those patients whose noninvasive measurements are inconclusive [1, 56]. Cardiac MRI provides highly accurate measurements of LV volumes, mass, and ejection fraction and allows for a thorough visualization of the aortic root. It also gives information on regurgitant volumes and flow [54, 56, 67, 68].

54.3.4 Treatment

54.3.4.1 Medical

In patients with chronic AR, no medical therapy has been proven to slow progression of disease. Treatment for hypertension is recommended in patients with chronic AR with dihydropyridine calcium channel blockers (Chap. 37) or ACE inhibitors/ARBs (Chap. 36) [1]. Vasodilators such as hydralazine, ACE inhibitors, and calcium channel blockers have been studied given their potential to reduce afterload in patients with chronic AR, theoretically increasing forward flow, decreasing wall stress, and limiting LV dilation and hypertrophy. Long-term studies have not shown consistent improvements in blood pressure, LVEF, LV end-systolic or diastolic dimensions, or other hemodynamic or structural parameters [69]. However, there is a role for medical therapy with vasodilators in symptomatic patients who are not candidates for surgery to help alleviate symptoms. Patients should be referred for surgery when symptoms or LV dysfunction develop.

54.3.4.2 Surgical

Patients with chronic AR can remain asymptomatic for years with normal LV systolic function. Asymptomatic patients with normal LV systolic function have a favorable prognosis. However, once symptoms develop in patients with chronic severe AR, mortality significantly increases without AVR. In a series of 246 patients with severe AR treated only medically, those with NYHA class III–IV had a mortality rate of 24.6 % per year. Even those with class II symptoms had a mortality rate of 6.3 % per year [1, 60] (Fig. 54.4). Symptoms are a major predictor of survival and a class I indication to pursue AVR, regardless of LV function in chronic severe AR. Besides symptoms, resting LV dysfunction (EF <50 %) in the absence

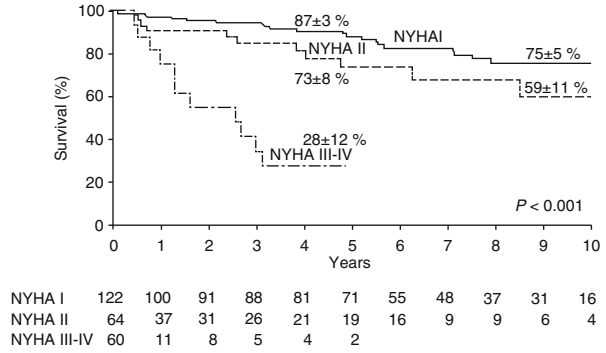

Fig. 54.4 Survival in patients with severe AR stratified according to NYHA class at baseline (Adapted with permission from Ref. [60])

of other causes for systolic dysfunction is also a class I indication for surgical AVR. When patients develop asymptomatic LV dysfunction, most will become symptomatic and require AVR within 2–3 years. Outcomes of surgery are better when AVR is performed before the onset of LV systolic dysfunction. Similarly, AVR is a class I indication for patients with severe AR while undergoing cardiac surgery for other indications [1]. Figure 54.5 outlines management algorithm for chronic AR.

54.4 Mitral Stenosis (MS)

54.4.1 Prevalence and Causes

The most common cause of mitral stenosis (MS) worldwide is rheumatic fever, though its prevalence is decreased in industrialized countries [70–72]. Isolated MS is more common in women than in men, with a ratio of 2:1 [72–74]. Other less common causes of MS include congenital anomalies such as parachute mitral valve or double-orifice mitral valve, prior chest radiation exposure, severe mitral annular calcification, mucopolysaccharidoses, and inflammatory diseases such as systemic lupus erythematosus [75], and conditions that mimic mitral stenosis such as left atrial myxoma and cortriatratum.

54.4.2 Pathophysiology and Natural History

Normal mitral leaflets are thin and very mobile. Rheumatic fever is a hypersensitivity reaction induced by group A streptococci in which antibodies directed against the M proteins of certain strains of streptococci cross-react with tissue glycoproteins in the valves. This chronic inflammation results in fibrous thickening and calcification of the valve leaflets, fusion of the commissures, and subvalvular chordal apparatus resulting in chordal thickening, shortening, and fibrosis, all resulting in narrowing of the mitral valve orifice leading to mitral stenosis. The stenotic valve

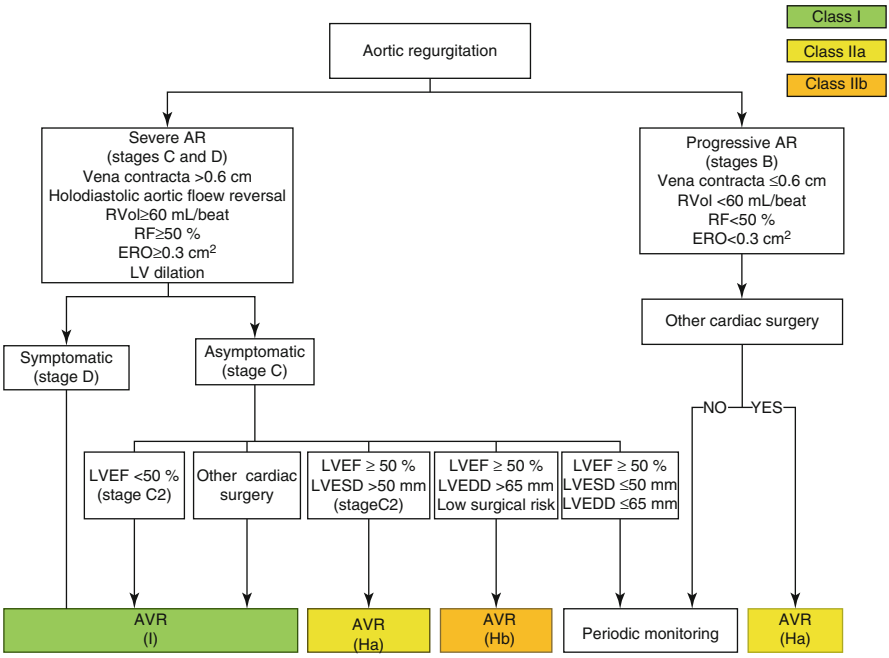

Fig. 54.5 Indications for AVR in chronic AR. *AR* aortic regurgitation, *AVR* aortic valve replacement (valve repair may be appropriate in selected patients), *ERO* effective regurgitant orifice, *LV* left ventricular, *LVEDD* left ventricular end-diastolic dimension, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic dimension, *RF* regurgitant fraction, *RVol* regurgitant volume (Adapted with permission from Ref. [1])

poses obstruction to left atrial emptying, leading to pulmonary hypertension and compromised right ventricular function.

A normal mitral valve (MV) area is 4.0–6.0 cm^2. A gradient across the MV is rare unless the valve is less than 2 cm^2. Exertional symptoms usually develop when the valve area decreases below 2.0–2.5 cm^2. Transmitral gradients that result in symptoms are typically based on the MV area, cardiac output, and duration of diastole. Atrial contraction helps maintain flow across the stenotic MV. Atrial fibrillation therefore has an adverse effect and precipitate dyspnea and heart failure.

Pulmonary hypertension (PH) is the result of backward pressure that is transmitted from the left atrium and pulmonary arteriolar vasoconstriction due to intimal hyperplasia and medial hypertrophy. In some patients, a secondary obstruction may also develop at the level of the pulmonary veins. Once these changes occur, despite correction of MS, at least a part of PH becomes irreversible (Chap. 45).

Resting symptoms can develop when the valve area is less than 1.5 cm^2. However, symptoms occur in patients with large valve areas if conditions arise that decrease diastolic filling or increase transmitral flow. Such conditions commonly include atrial fibrillation, pregnancy, exercise, infection, or emotional stress. Once significant symptoms develop, however, survival decreases to 0–15 % at 10 years [76]. If marked pulmonary hypertension develops, the average survival is less than 3 years [77]. The severity of MS is defined in Table 54.4 [1, 45].

Table 54.4 Grading mitral stenosis severity

	Mild	Moderate	Severe
Mean gradient (mm Hg)	<5	5–10	>10
Pulmonary artery systolic pressure (mm Hg)	<30	30–50	>50
Valve area (sq.cm.)	>1.5	1.0–1.5	<1

54.4.3 Diagnosis

54.4.3.1 Symptoms and Physical Examination

Patients with MS often are asymptomatic until the onset of atrial fibrillation or during pregnancy when they experience dyspnea and orthopnea. Symptoms of MS are usually related to the elevated left atrial pressure and reduced cardiac output due to a fixed obstruction to the filling of left ventricle. The first symptoms of MS are usually exertional dyspnea and fatigue. However, patients may also present with hemoptysis, chest pain due to pulmonary hypertension, pulmonary edema, endocarditis, atrial fibrillation, or an embolic event. Rarely patients may present with hoarseness due to compression of recurrent laryngeal nerve from left atrial enlargement (Ortner's syndrome), hemoptysis, or dysphagia. Survival is good (80 % in 10 years) in patients who are symptomatic or minimally symptomatic.

The classic physical examination in patients with MS includes a normal apical LV impulse as left ventricle is not affected in isolated or pure MS. However, a right ventricular heave may be present due to right ventricular hypertrophy. Auscultation reveals an accentuated first heart sound (S1) in patients with a mobile but thickened valve, an opening snap (OS) followed by a mid-diastolic murmur, and a presystolic murmur heard best at the apex in the left lateral decubitus position. These findings, however, may not be present in patients with severe pulmonary hypertension, with low cardiac output, or with a heavily calcified and immobile valve. The mid-diastolic, low-frequency murmur of MS is heard best with the bell of the stethoscope with the patient in the left lateral decubitus position. The second sound can also be loud because of an increased P_2 component thought to result from pulmonary hypertension, with resultant right ventricular overload. In severe MS with low flow across the mitral valve, the murmur may be soft and difficult to hear, especially in patients with atrial fibrillation. "Mitral facies" may manifest as purple-pink patches on the cheeks as a result of systemic vasoconstriction from the low cardiac output state of mitral stenosis.

54.4.3.2 Diagnostic Testing

The electrocardiogram can be completely normal especially in patients with mild MS. Patients in sinus rhythm show evidence of left atrial enlargement. Atrial fibrillation is also a common finding. ECG evidence of right axis deviation, right ventricular hypertrophy, and right atrial enlargement can be seen in individuals with pulmonary hypertension. The most common chest x-ray finding in patients with significant MS is that of left atrial enlargement. Enlargement of the right atrium, right ventricle, and the pulmonary artery can also be seen on chest x-rays of patients with advanced MS with pulmonary hypertension.

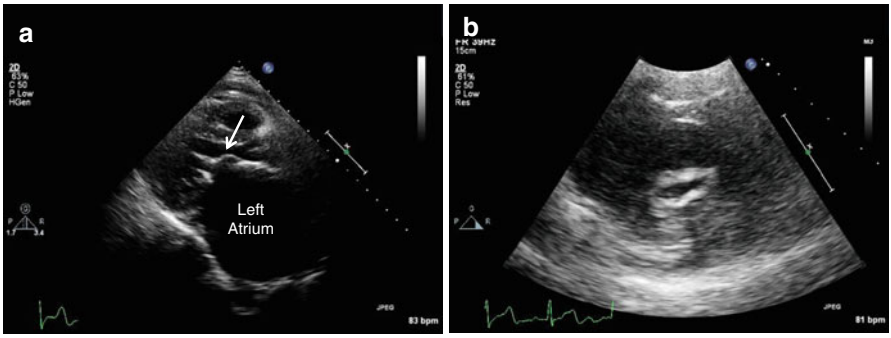

Fig. 54.6 Rheumatic mitral stenosis. Note the thickening of mitral leaflets with "hockey-stick" appearance of anterior mitral leaflet (*arrow*) and an enlarged left atrium (L). The short-axis image of mitral valve demonstrates a "fishmouth" appearance with valve area of 0.9 cm^2 (R)

Echocardiogram is the primary imaging tool used to assess a patient with MS. The anterior leaflet generally shows a "hockey-stick" or "bent-knee" deformity since restricted motion of the valve most commonly involves the leaflet tips. The posterior leaflet is often restricted in both systole and diastole. The echo also provides information about the size of the left atrium and the size and function of the left ventricle and the right-sided chambers (Figs. 54.6 and 54.7). Doppler examination provides information about the severity of MS by assessment of transvalvular pressure gradient, mitral valve area, the presence of other associated valve lesions, and the degree of pulmonary hypertension [78–82]. Echocardiography is also helpful to diagnose atrial myxomas that can have physical findings similar to those with MS. Transesophageal echocardiogram is more sensitive than transthoracic echocardiogram to assess left atrial appendage thrombi. Wilkins scoring system is a simple echocardiographic scoring system that takes into account the amount of leaflet thickening, the degree of leaflet mobility, the involvement of subvalvular apparatus, and the degree of calcification to decide whether a valve is suitable for percutaneous balloon valvuloplasty [83]. A Wilkins score less than 8 predicts a good result following an intervention and improved survival [84].

Routine diagnostic cardiac catheterization is no longer performed in patients with MS since accurate hemodynamic information is usually obtainable using echo. Diagnostic cardiac catheterization is only necessary when echo is nondiagnostic or results are discrepant with clinical findings. Catheterization-based hemodynamic assessment is also performed before, during, and after percutaneous balloon valvotomy [85]. Coronary angiography is performed in patients scheduled to undergo valve replacement surgery if there is a risk of coronary artery disease.

54.4.4 Treatment

Patients with MS caused by rheumatic heart disease should receive penicillin prophylaxis for beta-hemolytic streptococcal infections to prevent recurrent rheumatic fever [86]. Prophylaxis for infective endocarditis is no longer recommended unless the patient has a prior history of endocarditis or a prosthetic valve. Anticoagulant

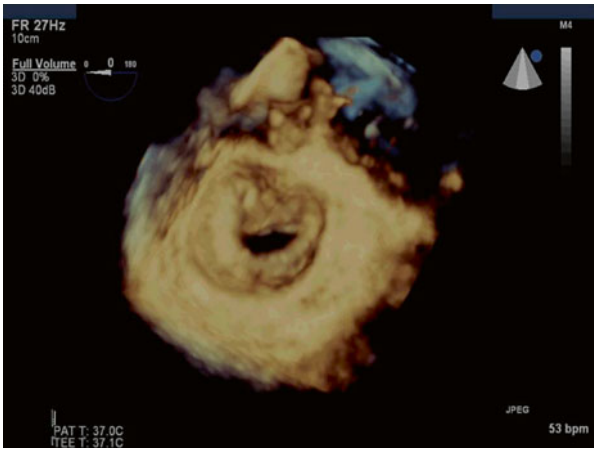

Fig. 54.7 3D Echo image of rheumatic MS with a valve area of 0.8 cm^2

therapy is indicated for prevention of systemic embolism in patients with atrial fibrillation (persistent or paroxysmal), any prior embolic events (even if in sinus rhythm), and in those with documented left atrial thrombus. When mild symptoms appear, diuretics have been shown to be effective in lowering left atrial pressure and reducing symptoms.

Mitral stenosis is generally associated with a long asymptomatic phase, followed by subtle limitation of activity. Asymptomatic patients with mild-to-moderate rheumatic mitral valve disease should have a history and yearly physical examination, chest x-ray, and ECG. No specific medical therapy is indicated. Echocardiogram should be performed if there is a change in clinical status or if severe MS is suspected. All patients with significant MS should be advised to avoid occupations requiring strenuous exertion [87].

The onset of atrial fibrillation often precipitates more severe symptoms. Conversion to sinus rhythm or ventricular rate control may be necessary to provide symptom relief. At the onset of atrial fibrillation, the patient should receive warfarin anticoagulation even if sinus rhythm is restored because 20–30 % of these patients have systemic embolization if untreated.

Symptomatic MS has a very poor prognosis, with probability of survival being inversely proportional to NYHA functional class. Symptomatic patients with severe MS or those with significant pulmonary hypertension (greater than 50 mmHg at rest) should be considered for percutaneous balloon valvuloplasty (PBV). Symptoms may be difficult to ascertain in patients who are sedentary. In such individuals, exercise testing with the assessment of the mitral valve gradient and pulmonary artery pressures before and after exercise may be useful [1]. PBV has become the mainstay of treatment for MS and is as effective as open surgical valvotomy unless in anatomically unsuitable valves, with reduced morbidity and cost.

Typically following successful percutaneous balloon mitral valvuloplasty (PBMV), there is doubling of the valve area with a 50 % reduction in mitral valve

gradient [88]. Patients typically note a rapid improvement in shortness of breath, though improvement in exercise tolerance takes a much longer time [89]. Initial success rates of PBMV are high especially if valve calcification is not excessive. However, if there is significant valvular calcification and severe distortion of valvular components or more than moderate mitral regurgitation exists, then open commissurotomy, valve reconstruction, or mitral valve replacement will be necessary. Figure 54.8 provides indications for intervention in rheumatic MS. Table 54.5 outlines the ACC/AHA class 1 indications for intervention in patients with MS.

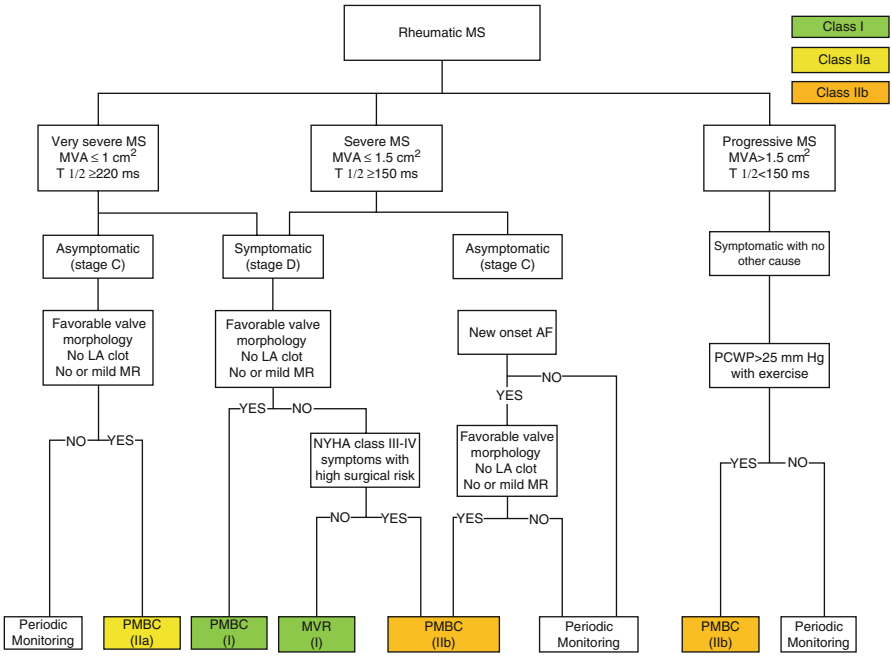

Fig. 54.8 Indications for intervention in rheumatic MS. *AF* atrial fibrillation, *LA* left atrial, *MR* mitral regurgitation, *MS* mitral stenosis, *MVA* mitral valve area, *MVR* mitral valve surgery (repair or replacement), *NYHA* New York Heart Association, *PCWP* pulmonary capillary wedge pressure, *PMBC* percutaneous mitral balloon commissurotomy, *T ½* pressure half time (Adapted with permission from Ref. [1])

Table 54.5 ACC/AHA class I recommendations for intervention in MS

PMBC is recommended for symptomatic patients with severe MS (MVA 1.5 cm^2, stage D) and favorable valve morphology in the absence of contraindications
Mitral valve surgery is indicated in severely symptomatic patients (NYHA class III/IV) with severe MS (MVA 1.5 cm^2, stage D) who are not high risk for surgery and who are not candidates for or failed previous PMBC
Concomitant mitral valve surgery is indicated for patients with severe MS (MVA 1.5 cm^2, stage C or D) undergoing other cardiac surgery

54.4.5 Pregnancy

MS can affect women in their childbearing years; MS poses a hemodynamic challenge during pregnancy and labor. Rheumatic MS is responsible for 90 % of cardiac disease in pregnancy and responsible for 33 % of maternal deaths [73, 90–92]. The increased intravascular volume increased cardiac output, and tachycardia may result in symptoms of dyspnea and heart failure. PBMV can be performed safely in the second trimester with excellent results. Patients with moderate-to-severe MS should be referred to a cardiovascular specialist for assistance in the care of the patient during the pregnancy and delivery.

Mitral restenosis following PBMV or previous surgical commissurotomy can be retreated with a repeat balloon valvotomy. If this is technically difficult or the results are unfavorable, surgical treatment should be considered.

54.5 Mitral Regurgitation (See Also Chap. 55)

54.5.1 Prevalence and Causes

Mitral regurgitation (MR) is the second most common valvular heart disease in clinical practice, affecting 3–5 % of the population in the USA. The mitral valve is a complex structure that comprises of mitral annulus, anterior and posterior mitral leaflets, papillary muscles with chordae tendineae, and the adjacent supporting left ventricular wall (Fig. 54.9). Abnormalities in any of these components can result in mitral regurgitation [93, 94]. In developing areas of the world, rheumatic heart disease is the leading cause of MR and can lead to MR both in the acute and chronic phases of the disease [95–97]. Mitral valve prolapse can affect approximately 2 % of general population and can result in mitral regurgitation [98–100]. Other conditions include infective endocarditis, mitral annular calcification, and congenital anomalies such as cleft mitral valves (Chap. 59), and rare causes such as endomyocardial fibrosis, carcinoid disease with right to left shunt, ergotamine toxicity (Chap. 58), radiation therapy, systemic lupus erythematosus, and diet-drug toxicity. MR can also result from dilatation of the mitral valve annulus or from myocardial infarction. In particular, infarctions involving the inferolateral wall and the posteromedial papillary muscle produce tethering of the mitral leaflets so that they cannot provide normal coaptation, leading to "functional" MR even though the valve leaflets themselves are normal [101, 102].

54.5.2 Pathophysiology

In mitral valve prolapse, the valve leaflets, particularly the posterior leaflet, are enlarged and the normal dense collagen and elastin matrix of the valvular fibrosa is fragmented and replaced with loose, myxomatous connective tissue. If the leaflets are excessively redundant or there is significant chordal elongation or rupture, MR

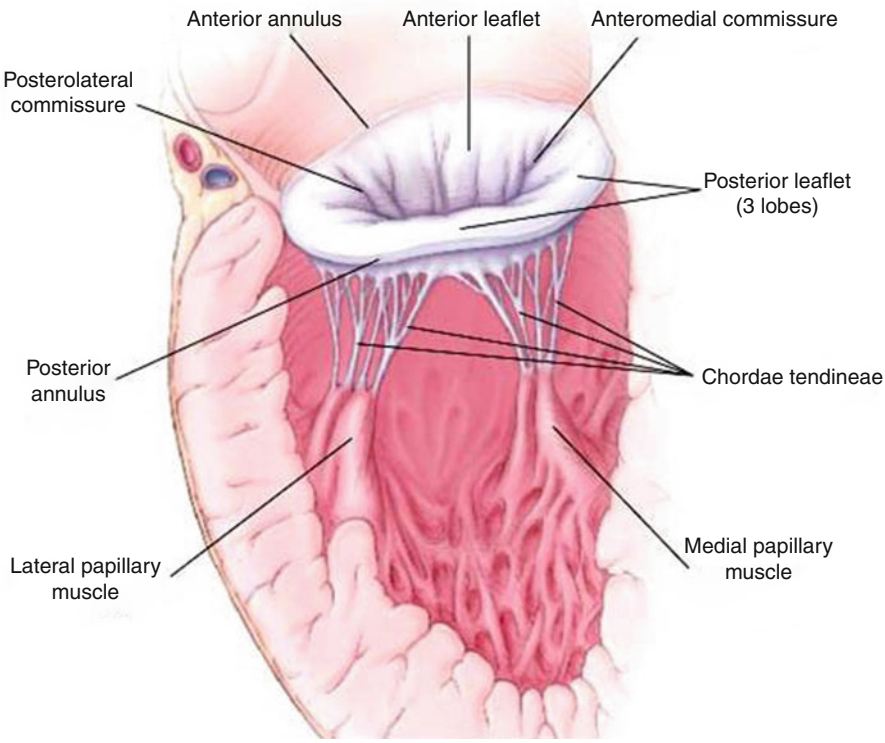

Fig. 54.9 Components of mitral valve apparatus

of varying degrees occurs. Severe MR can result from papillary muscle dysfunction and rupture which may occur 2–7 days following an acute myocardial infarction. This is rare, often seen with inferior myocardial infarction, and is a life-threatening surgical emergency that can lead to sudden death.

Patients with coronary heart disease may also have stable ischemic papillary muscle dysfunction leading to MR that can be mild at rest but worsens during exercise due to ischemic dysfunction. In patients with long-standing LV failure, functional MR may result from the malfunctioning of the mitral valve apparatus or dilation of the mitral annulus. Infective endocarditis can also lead to acute MR due to disruption of the mitral valve apparatus.

Patients who develop acute severe MR usually present with symptomatic heart failure since the left ventricle is ill prepared to accept the sudden increase in volume load. However, if the patient survives the acute episode or has gradually progressive MR, the LV is able to adapt, and compensatory changes are seen. Symptoms are therefore either absent or progress slowly over many years. The compensatory changes of the ventricle to the volume overload include LV dilatation and eccentric hypertrophy. The left atrium also enlarges, thus allowing accommodation of the regurgitant volume at a low pressure [1, 3, 17, 102].

Although patients with compensated, chronic MR may remain asymptomatic for many years, decompensation may eventually develop if the regurgitation is severe enough. The LV ejection fraction in chronic MR may be greater than normal due to an increase in preload as well as the afterload-reducing effect of ejection into the low-impedance left atrium. Therefore, LV ejection fraction can be misleading as a measure of compensation. Advanced myocardial dysfunction may occur, while LV ejection fraction is still well within the normal range. Thus, outcome following mitral valve surgery is poor in patients with low-normal ejection fractions compared to those with ejection fractions in the higher normal range [1, 103–105]. In patients with functional MR, the risk of death in subjects aged >70 years old with moderate or severe MR has been shown to be more than fourfold higher than that of age- and sex-matched subjects with absent or mild MR [106]. As the severity of mitral regurgitation increases over time, LV systolic function decreases due to the inability of LV to augment systolic function with resultant heart failure.

54.5.3 Diagnosis

54.5.3.1 Symptoms and Physical Examination

The clinical presentation of MR depends on the rapidity with which the valvular incompetence develops. In the case of acute MR, the left atrial pressure rises abruptly which is transmitted to the pulmonary circulation, resulting in pulmonary congestion. If the onset of MR is more gradual, the left atrium enlarges progressively and the pressure in the pulmonary veins and capillaries rises only transiently during exertion; in these patients, exertional dyspnea and fatigue progress over several years.

Like those with MS, patients with MR are predisposed to atrial fibrillation; however, atrial fibrillation is less likely to provoke acute pulmonary congestion, and <5 % of patients with MR have peripheral arterial emboli. MR also predisposes to infective endocarditis.

The examination of the patient with chronic, severe MR varies according to the degree of decompensation. The carotid upstroke is sharp in patients with compensated MR, but the volume of the carotid pulse is reduced in the presence of advanced heart failure. The apical impulse is usually brisk and hyperdynamic; in those with severe MR, it may be enlarged and displaced laterally. S1 is usually soft. A widely split S2 is common. A diastolic murmur or third heart sound may be present and does not necessarily indicate LV dysfunction. The systolic murmur of MR varies according to the etiology of the regurgitation. The murmur is usually heard best at the apex in the left lateral decubitus position. With severe degenerative MR, the murmur is holosystolic and radiates either to the axilla or the entire precordium. Early systolic murmurs are typical for acute MR. Late systolic murmurs are typical of mitral valve prolapse or papillary muscle dysfunction. Signs of pulmonary hypertension, such as a loud P2, are usually ominous and represent advanced disease. A third heart sound may be auscultated in patients with LV failure in the setting of severe MR.

54.5.3.2 Diagnostic Testing

Left atrial enlargement and atrial fibrillation are the most common ECG findings in patients with MR. Chest radiography typically demonstrates cardiomegaly due to LV and left atrial enlargement in patients with chronic, severe MR. Enlargement of the right ventricle is also a common finding in patients with pulmonary hypertension. Kerley-B lines and interstitial edema can be seen on the chest x-rays of patients with acute MR or progressive LV failure.

The echocardiogram is the diagnostic tool of choice to evaluate a patient with MR. The echocardiogram provides information about the anatomy of the mitral apparatus, mechanism and severity of MR, size and function of the left and right ventricles, left atrial size, severity of pulmonary hypertension, and the presence of other associated valve lesions. Doppler evaluation provides quantitative measures of severity of MR, an important predictor of outcome. Table 54.6 delineates echocardiographic grading of MR.

Table 54.6 Grading mitral regurgitation severity by echocardiography

	Mild	Moderate	Severe
Specific signs	Small central jet <4 cm^2 or <10 % of LA VCW <0.3 cm No or minimum flow convergence	MR more than mild, but without any criteria for severe MR	VCM ≥0.7 cm with a large central MR jet (area >40 % of LA) Wall impinging jet of any size Large flow convergence Systolic flow reversal in pulmonary veins Prominent flail leaflet or ruptured chord
Supportive signs	Systolic dominant flow in pulmonary veins A-wave dominant flow in mitral inflow Low density Doppler MR signal Normal LV size	MR more than mild, but without any criteria for severe MR	Dense, triangular MR signal E-wave dominant mitral inflow (>1.2 m/s) Enlarged LV and LA (particularly with normal or hyperdynamic LV function)
Quantitative variables			
Regurgitant volume (ml per beat)	<30	30–44 (mild–moderate) 45–59 (moderate–severe)	≥60
Regurgitant fraction	<30 %	30–39 % (mild–moderate) 40–49 % (moderate–severe)	≥50
ERO area (cm^2)	<0.20	0.20–0.29 (mild–moderate) 0.30–0.39 (moderate–severe)	≥0.40

Cardiac catheterization is generally performed to assess the hemodynamic severity of MR when noninvasive testing is inconclusive or there is a discrepancy between clinical and noninvasive findings. Cardiac catheterization allows accurate assessment of regurgitation, LV function, and pulmonary artery pressure. Coronary angiography is indicated for patients who are planning to undergo surgery and are at risk for CHD [1].

54.5.4 Treatment

For patients with asymptomatic organic MR, there is no accepted medical therapy, which could delay the need for surgical intervention. However, it is important to treat systemic hypertension, as hypertension aggravates MR and it affects the left ventricular, left atrial, and pulmonary venous pressures. In patients with functional MR associated with LV dysfunction, angiotensin-converting enzyme inhibitors, beta-blockers, and biventricular pacing have been shown to produce beneficial reverse remodeling and reduction in LV end-diastolic and end-systolic volumes, which in turn decrease severity of MR [107].

Patients with chronic MR can remain asymptomatic for years. However, serial clinical evaluations and noninvasive tests are necessary, since LV dysfunction can develop in the absence of symptoms. Patients with mild MR and an otherwise normal heart may be followed with yearly clinical examinations; echocardiograms should be done only if there has been a change in clinical status. In patients with moderate MR, clinical examination and echocardiography should be performed yearly or sooner if symptoms develop. Asymptomatic patients with severe MR should be considered for surgical correction, especially if the valve can be repaired, as noted below, after discussions regarding the benefit of early referral for surgery. If such patients decline surgery, they should be followed with clinical examinations and echocardiograms every 6–12 months and should be referred for surgery promptly if they develop symptoms, atrial fibrillation, pulmonary hypertension, or LV systolic dysfunction. Because progressive and irreversible deterioration of LV function may occur before the onset of symptoms, early operation is indicated in asymptomatic patients with a declining ejection fraction (LV systolic dysfunction in severe MR is defined as an ejection fraction less than 60 %) or marked left ventricular dilation (end-systolic LV dimension greater than 40 mm) on echocardiography [1].

The timing of surgical correction is significantly related to whether the patient is a candidate for mitral valve repair or will require mitral valve replacement (MVR). Valve repair is associated with a low surgical risk, improved survival and LV function, excellent long-term durability, and absence of risks associated with long-term anticoagulation [103]. It is therefore critical that patients with severe MR who may require surgery are referred to experienced surgical centers where the chances of a successful repair are high. The indications for surgery in severe MR are listed in Fig. 54.10. A number of transcatheter MV therapies are currently being applied to patients at high risk for surgery due to coexisting comorbidities [108]. MitraClip is one such device that is being used in this population.

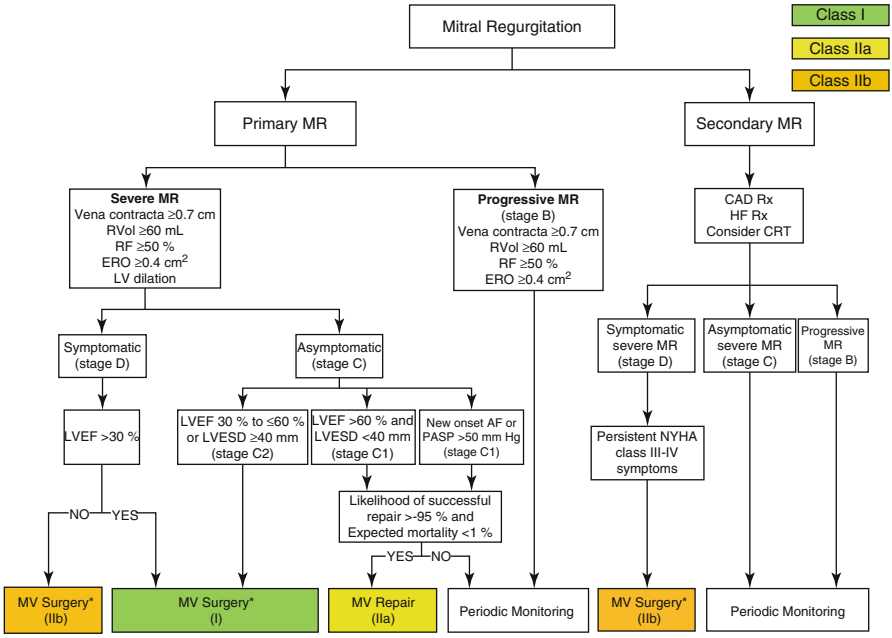

Fig. 54.10 Indications for surgery for MR *AF* atrial fibrillation, *CAD* coronary artery disease, *CRT* cardiac resynchronization therapy, *ERO* effective regurgitant orifice, *HF* heart failure, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *LVESD* left ventricular end-systolic dimension, *MR* mitral regurgitation, *MV* mitral valve, *MVR* mitral valve replacement, *NYHA* New York Heart Association, *PASP* pulmonary artery systolic pressure, *RF* regurgitant fraction, *RVol* regurgitant volume, *Rx* therapy. *Mitral valve repair is preferred over MVR when possible (Adapted with permission from Ref. [1])

Acute MR caused by endocarditis, myocardial infarction, and ruptured chordae tendineae often warrants emergency surgery. Some patients can be stabilized with vasodilators (e.g., nitroprusside) or the use of an intra-aortic balloon pump, both of which reduce regurgitant flow by lowering systemic vascular resistance. Note that while vasodilators are used successfully to increase forward output and decrease LV filling pressure in patients with acute MR, there are no data to suggest long-term benefit from their use.

54.6 Tricuspid Regurgitation (See Also Chap. 56)

54.6.1 Prevalence and Causes

Tricuspid regurgitation (TR) occurs commonly in the healthy general population. Primary TR is due to intrinsic tricuspid valve disease seen in 15–30 % of all TR cases. Secondary or functional TR is much more common, seen in the absence of structural

abnormalities of tricuspid valve which accounts for 70–85 % of all TR cases [109]. Overall, the prevalence of significant TR was 4.3 times higher in women than in men. TR due to primary valve lesions is rare in the western world. Worldwide, rheumatic heart disease is the most common etiology among the organic causes and can lead to tricuspid valve dysfunction with combined tricuspid stenosis and tricuspid regurgitation due to retracted leaflets and/or thickening with shortening of subvalvular apparatus of tricuspid valve. Myxomatous tricuspid valve degeneration with prolapse is characterized by tricuspid annular dilatation with redundancy of tricuspid leaflets. Congenital heart disease such as Ebstein's anomaly, tricuspid valve hypoplasia, or dysplasia also results in TR. Infective endocarditis of tricuspid valve, endomyocardial fibrosis, and carcinoid disease are other etiologies. Right ventricular myocardial infarction with papillary muscle rupture can result in significant TR. Blunt chest trauma or iatrogenic causes such as pacemaker/defibrillator leads, endomyocardial biopsy, drugs such as methysergide or phen-fen, and radiation can also result in TR (Chap. 58).

Secondary or functional TR due to either left heart disease or pulmonary hypertension is the most common etiology encountered in clinical practice [110]. In these patients, moderate-to-severe or severe TR is associated with heart failure, reduced functional capacity, and death. If TR is not addressed at the time of left heart valve surgery, this results in significant morbidity and mortality [111, 112]. Several studies have demonstrated that a more proactive approach to TV repair in patients with moderate-to-severe TR and TV annular dilation results in improved outcomes [113–115].

54.6.2 Pathophysiology

The most common etiology of secondary TR is left heart dysfunction leading to right ventricular dilatation and dysfunction. The pathophysiology of TR is divided into three phases [115, 116]. In the first phase, there is tricuspid annular dilatation predominantly affecting the anterior and posterior portions of the annulus as there is tethering effect of fibrous skeleton on the septal portion of annulus that limits its dilatation. The severity of TR during this phase is dependent upon the degree of annular dilatation. During the second phase, there is a significant TR due to progressive right ventricular and tricuspid annular dilatation leading to poor coaptation of tricuspid leaflets. During the third phase, continued right ventricular and tricuspid annular dilatation result in right ventricular distortion and eccentricity with tethering and fibrotic changes of the tricuspid leaflets [117].

54.6.3 Diagnosis

54.6.3.1 Symptoms and Physical Examination

In the early stages of disease, patients remain completely asymptomatic or present with fatigue and shortness of breath. Reduced exercise tolerance is a result of decreased cardiac output. Overtime, progressive symptoms of right heart failure

develops. With severe right heart failure, patients typically develop severe TR and may present with weight loss and cachexia, cyanosis, and jaundice. Lower extremity edema, abdominal discomfort due to hepatomegaly, ascites, and even anasarca are usually from elevated right atrial pressures. Rarely, a patient may initially present to gastroenterology clinic due to hepatic cirrhosis. Atrial arrhythmias secondary to pathological dilatation of right atrium may be seen. These arrhythmias are notoriously difficult to treat even with surgical management and can contribute to worsening of TR. Symptoms and features of advanced cardiac cachexia and anasarca and signs of low cardiac output and cardiac cirrhosis are usually associated with end-stage RV failure with severe TR and typically portend a very poor prognosis.

Physical Examination Findings

Physical examination signs are consistent with RV pressure and/or volume overload and, at a later time, right-sided heart failure. Jugular venous distension is often present marked by a prominent systolic "v" wave. Pulsatile, tender hepatomegaly can be noted with severe TR.

Palpation of the abdomen is, therefore, an important feature of the physical examination. The murmur of TR is inconsistent. In severe TR, the holosystolic murmur increasing with inspiration is audible in <20 % of all patients likely because of equalization of RA and RV pressures and laminar regurgitant jet blood flow. Lesser grades of TR are often accompanied by a holosystolic murmur best heard over the lower left sternal border. When present, the murmur of TR is best auscultated along either side of the lower sternal border and radiates toward the liver. It can be augmented with maneuvers that increase systemic venous return such as inspiration or kneeling. Carvallo sign is commonly appreciated and is a detectable increase in the TR murmur intensity because of increased RV preload during inspiration.

54.6.3.2 Diagnostic Testing

Right atrial and right ventricular enlargement, and evidence for right heart strain are the most common electrocardiographic findings in patients with severe TR. Chest radiography may demonstrate cardiomegaly with enlarged right ventricular and right atrial contours. Echocardiography is the diagnostic tool of choice. The echocardiogram provides information about the anatomy of the tricuspid apparatus, mechanism and severity of TR, size and function of the left and right ventricles, left and right atrial size, severity of pulmonary hypertension, and the presence of other associated valve lesions. Doppler evaluation provides quantitative measures of severity of TR, an important predictor of outcome. Functional TR is characterized by tricuspid annular dilatation (>40 mm) and may also reveal tethering of tricuspid leaflets. Cardiac magnetic resonance (CMR) is not limited by acoustic window and can image the whole heart in any plane providing excellent myocardial definition. CMR

is currently the gold standard for the assessment of RV morphology and function, and accurate assessment of the RV is crucial to understand the underlying mechanisms and address management in patients with TR. At present, diagnostic left cardiac catheterization should rarely, if ever, be undertaken for the diagnosis or quantitation of TV disease alone. However, a right heart catheterization accurately measures the right heart pressures and pulmonary vascular resistance.

54.6.3.3 Treatment

Conservative management of secondary tricuspid regurgitation includes optimization of right ventricular preload and afterload. Right ventricular overload may benefit from progressive use of diuretics and angiotensin-converting enzyme inhibitors. However, an excessive reduction in central venous pressure may result in worsening of tricuspid regurgitation severity. Sustained high systemic venous and intra-abdominal pressures may induce a cardiorenal syndrome and diuretic resistance. The use of angiotensin-converting enzyme inhibitors is supported by evidence that chronic right ventricular pressure overload activates the renin-angiotensin-aldosterone system, which may contribute to fluid retention and ventricular remodeling. Atrial arrhythmias are often difficult to treat because of the positive feedback cycle of progressive TR resulting in greater atrial hypertension and distension and more difficult to control atrial arrhythmias.

Severe secondary tricuspid regurgitation should always be corrected at the time of left-heart surgery. In less than severe functional tricuspid regurgitation, the diameter of the tricuspid annulus (rather than the grade of regurgitation) should be the criterion to indicate the need for concomitant tricuspid valve repair. If the tricuspid annulus is dilated, tricuspid annuloplasty should be performed during left-sided valve surgery. A ring annuloplasty represents a more durable solution than suture annuloplasty. When the dilatation of the tricuspid annulus is combined with significant leaflet tethering, adjunctive surgical techniques should be added to tricuspid annuloplasty or valve replacement should be performed [1, 116–119]. A more aggressive management of secondary tricuspid regurgitation such as this could hopefully decrease the occurrence of late tricuspid regurgitation following previous mitral valve surgery. This remains a challenging problem for those whose surgical treatment is associated with high hospital mortality and poor postoperative outcome. The indications for surgery in TR are listed in Fig. 54.11.

In patients with persistent or recurrent tricuspid regurgitation after left-sided surgery, earlier intervention should be recommended before the occurrence of right ventricular dysfunction. A better understanding of functional TR and anatomy of tricuspid valvular apparatus will provide basis for percutaneous tricuspid valve technologies in the future for those patients with high surgical risk.

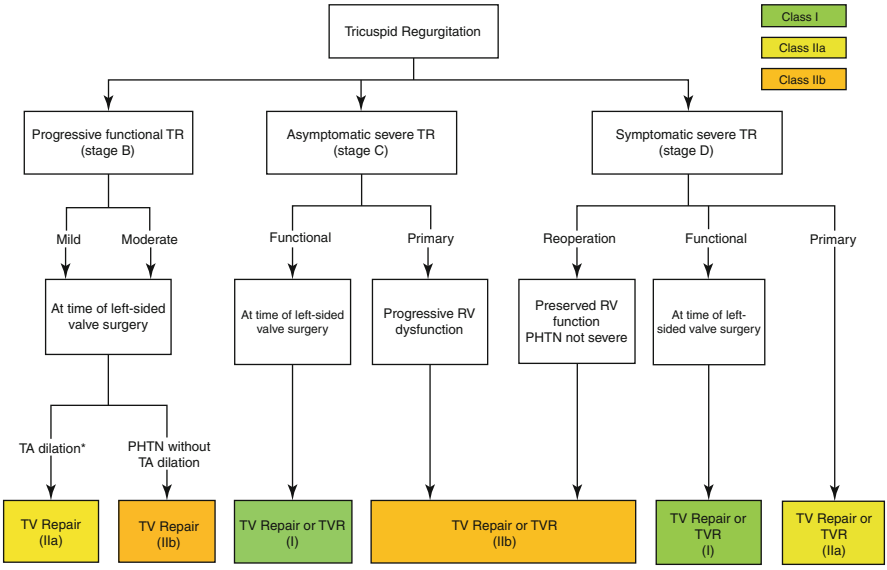

Fig. 54.11 Indications for surgery in TR. TA dilation is defined by >40 mm on TTE (>21 mm/m^2) or >70 mm on direct intraoperative measurement. *LV* indicates left ventricular, *PHTN* pulmonary hypertension, *RV* right ventricular, *TA* tricuspid annular, *TR* tricuspid regurgitation, *TTE* transthoracic echocardiogram, *TV* tricuspid valve, and *TVR* tricuspid valve replacement (Adapted with permission from Ref. [1])

54.7 Concluding Remarks

The incidence of valvular heart disease is on the increase, owing to an increase in aging population. Valvular heart disease when severe and untreated creates a hemodynamic overload, eventually causing myocardial damage with ventricular dysfunction, heart failure, and death. Appropriate diagnosis, management, and follow-up of these patients are imperative to reduce long-term morbidity and mortality. With recent availability of multiple therapeutic options using percutaneous devices, referral of patients with significant valve abnormalities to a Heart Valve Center is recommended where a multidisciplinary team approach is utilized to select the most appropriate therapeutic option, thereby avoiding expensive, high-risk, and ultimately futile procedures in patients who will derive little symptomatic benefit or improvement in quality of life. A fundamental knowledge of valve disease is important for the primary care physician because the initial presentation of such patients often occurs in the primary care setting.

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Chapter 55
Mitral Regurgitation in Heart Failure: Mechanisms and Therapeutic Options

Michael Huntgeburth and Volker Rudolph

Abstract Mitral regurgitation (MR) is commonly encountered in congestive heart failure (CHF) patients and is known to complicate the clinical course of this disease. While MR in general is most often a consequence of degenerative changes of the mitral valve apparatus (primary MR), MR in CHF patients is typically caused by alterations of left ventricular geometry, whereas the structural integrity of the valve apparatus is not affected (secondary MR, SMR). In this chapter, we focus on the diverse mechanisms of SMR in heart failure patients and elucidate the different therapeutic options spanning from medical approaches over implantable devices to improve heart function to established surgical and evolving interventional therapeutic options for mitral valve repair.

Keywords Mitral regurgitation • Functional mitral regurgitation • Heart failure • Percutaneous valve repair

Abbreviations

CAD	Coronary artery disease
CHF	Congestive heart failure
CRT	Cardiac resynchronization therapy
EF	Ejection fraction
HF	Heart failure
IE	Infective endocarditis
IHF	Ischemic heart failure
IMR	Ischemic mitral regurgitation
LV	Left ventricle/left ventricular

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LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MR	Mitral regurgitation
MV	Mitral valve
MVP	Mitral valve prolapse
NYHA	New York Heart Association
PM	Papillary muscle
RCT	Randomized controlled trial
SMR	Secondary mitral regurgitation

55.1 Introduction

Mitral regurgitation (MR) occurs in almost two thirds of patients with a left ventricular ejection fraction below 40 % [1] and is associated with a dramatic worsening of heart failure symptoms and prognosis in patients suffering from congestive heart failure (CHF) [2–5]. Due to the increasing prevalence of heart failure and demographic changes, MR also poses an increasing burden to healthcare systems [6, 7]. Pathophysiologically, the regurgitant volume is lost for systemic perfusion and poses a volume overload for the left heart, aggravating pulmonary congestion as well as pulmonary hypertension and predisposing to atrial fibrillation. Future-directed optimal treatment of MR in heart failure involves an individualized approach that incorporates optimal medical and resynchronization therapy of primary heart failure as the basis of therapy, as well as options to improve valve function by surgical and percutaneous techniques, as the majority of patients are considered not suitable for operation due to the high perioperative risk [8–10]. In this chapter, we focus on the diverse mechanisms of functional MR in heart failure patients and elucidate the different therapeutic options spanning from medical approaches over implantable devices to improve heart function to established surgical and evolving interventional therapeutic options for mitral valve repair (Chaps. 3, 8, and 54).

55.2 Mechanisms of Mitral Regurgitation in Heart Failure

A more detailed analysis of ventricular remodeling and the underlying mechanistic features of the mitral valve causing MR has led to the recognition of diverse and complex entities of MR. Currently, out of the different classifications suggested for MR, the basic differentiation between primary and secondary MR has emerged as the most widely used (Fig. 55.1) [9].

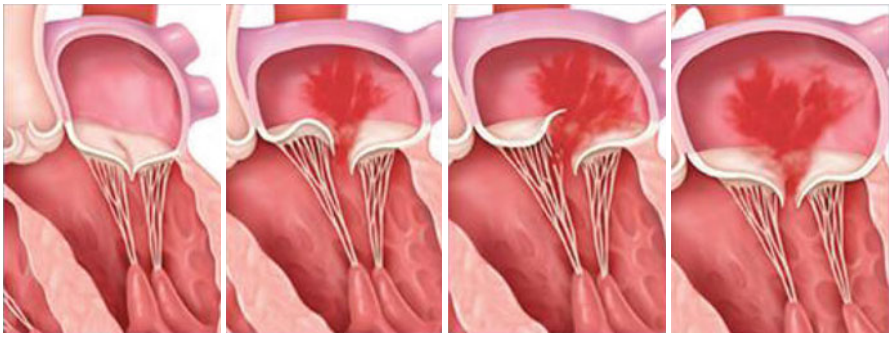

Fig. 55.1 Different etiologies of mitral regurgitation. Schematic illustration of a normal mitral valve closure, degenerative MR with mitral valve prolapse, degenerative MR caused by flail leaflet, and functional MR (from *left* to *right*). Note the central MR in functional MR and pronounced excentric jet caused by the flail leaflet (Images courtesy of Abbott Vascular)

55.2.1 Primary MR

In primary (also termed organic or degenerative) MR, components of the valvular apparatus are directly affected. These can span from isolated destructive alterations of single components such as leaflet prolapse, leaflet perforation, and chordal or papillary muscle (PM) rupture (e.g., mitral valve prolapse in connective tissue abnormalities, endocarditis, ischemia, rheumatic disease) or other rare congenital causes to the co-occurrence of several of these pathologies. Primary MR is the most common cause for MR in the industrialized world [7, 9, 11]. It is described to develop and progress in stages. Initially, a condition with a risk of MR, such as a mild mitral valve prolapse (MVP) with normal coaptation or mild leaflet thickening and leaflet restriction represents a predisposing state for primary MR (stage A, Fig. 55.1). This state can decline into progressive MR (stage B, e.g., severe MP, rheumatic disease, or prior infective endocarditis (IE)) and asymptomatic severe MR (state C, e.g., loss of coaptation or flail leaflet), and finally, into stage with symptomatic severe MR (stage D, Fig. 55.1) [12]. As most patients with primary MR present with a normal left ventricular function and an otherwise unaffected heart, correction of primary MR in these patients is considered to be curative [12]. However, in some cases, primary MR can be encountered in CHF patients, who develop left heart dysfunction as a result of long-standing volume overload because timely treatment of primary MR has been missed. In other patients, mixed primary and secondary MR can be encountered. These patients initially exhibit mild primary MR and develop left ventricular dysfunction due to another underlying disease, such as myocardial ischemia, which then aggravates the already present primary MR.

55.2.2 Secondary MR

In heart failure patients, secondary MR (SMR) is more prevalent. In SMR, the structural integrity of the components of the valvular apparatus per se is preserved. Several mechanisms can contribute to the presence of SMR. One of the most commonly encountered mechanisms is MV leaflet tethering arising from displacement of the papillary muscles, either occurring as a consequence of regional wall motion abnormalities, particularly after an inferior or posterior myocardial ischemic event or as consequence of global LV dilatation and dysfunction (e.g., dilative cardiomyopathy or adverse remodeling after a large anterior myocardial infarction, Fig. 55.2). Further mechanisms include reduced closing forces due to LV dysfunction and functional (reduced contraction) and geometrical (flattening, dilation) changes of the MV annulus, which are in part only incompletely understood [1, 13].

Based on the underlying etiologies of heart failure, functional MR can be divided further into two subgroups, ischemic and nonischemic MR. Ischemic mitral regurgitation (IMR) is defined as functional MR caused by ischemic wall motion abnormalities or ischemic LV remodeling. Chronic IMR occurs after the healing phase of MI with an estimated prevalence of 20–50 % [3, 14]. The presence of IMR, even if it is clinically insignificant, represents an independent prognostic factor for worse outcome with a stepwise decline of survival as grade of IMR increases [3].

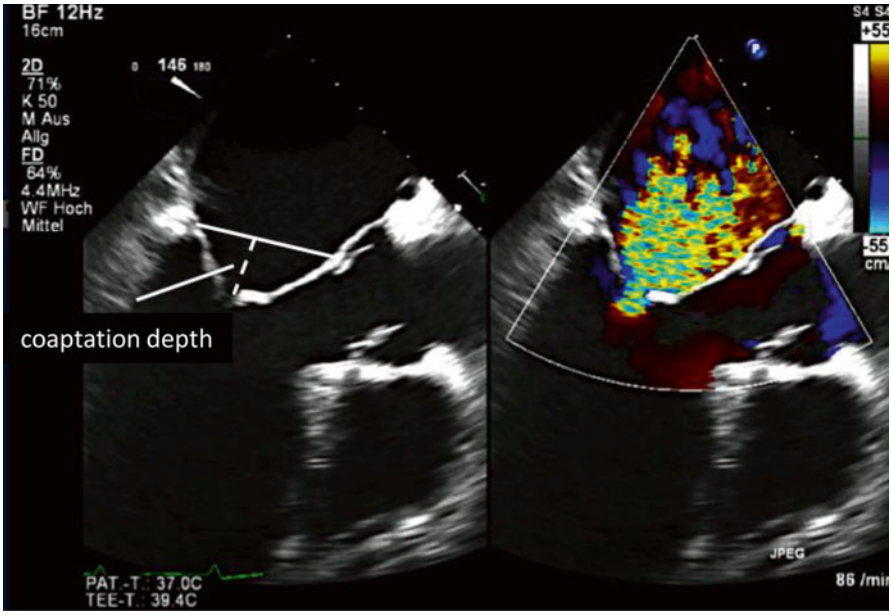

Fig. 55.2 Secondary mitral regurgitation. Transesophageal long axis view showing the mechanism of secondary mitral regurgitation with LV dilation, tethering of both leaflets, and increased coaptation depth. MR results due to decreased or absent coaptation (Image courtesy of Abbott Vascular)

As described for primary MR, secondary MR also progresses in stages (stage A–D). In patients with CAD or cardiomyopathy, the valvular apparatus is initially not relevantly affected, therefore posing a risk for secondary MR (stage A). As LV geometry changes, regional wall motion abnormalities with mild leaflet tethering or annular dilation with decreased central coaptation induce progressive MR (stage B). This proceeds to severe but asymptomatic MR (stage C) and can ultimately result in severe tethering and relevant annular plane dilation with loss of central coaptation (stage D) [12]. As secondary MR is caused by left ventricular disease and by itself aggravates left ventricular disease due to the imposed volume overload, it is part of a self-perpetuating process, which accelerates functional and clinical deterioration.

Due to the complexity and dynamic nature of its underlying mechanisms, determination of MR severity by echocardiography requires some special considerations [12]. Thus, in contrast to primary MR, where the regurgitant jet has a circular cross-sectional area, the cross-sectional area of secondary MR typically is crescent shaped, which has important implications when assessing regurgitation severity with two-dimensional imaging techniques. Current guidelines therefore propose evaluation of the regurgitant jet in more than one plane, and three-dimensional techniques are rapidly evolving [15]. Additionally, dynamic changes due to exercise and loading conditions have a significant impact on severity of SMR. An exercise-induced increase of afterload has been proposed to increase displacement of papillary muscles away from the annular plane, thereby worsening MR by increasing tethering forces [16]. Grade of MR greatly depends on pre- and afterload conditions, explaining the effectiveness of diuretic and afterload-decreasing medication [17]. Likewise, volume status, systemic blood pressure, or anesthesia decisively effect severity of MR and might lead to significant misjudgment. In cases of uncertainty, exercise-stress echocardiography is warranted when a relevant MR is suspected [18]. The complex interplay between LV geometry and function, the mitral valve apparatus, and ultimately, the hemodynamics of the systemic circulation contributing to SMR make therapeutic decision-making a difficult task and explains why treatment strategies are not as clear-cut as for other valvular disorders [12].

55.3 Therapeutic Options

55.3.1 Medical Therapy

In primary MR or in the case of a relevant degenerative component of MR, medical therapy will only be of limited efficiency. Thus, ACE inhibitors (Chap. 36) and beta-blockers (Chaps. 5 and 8) can be used with the aim to reduce adverse LV remodeling in patients without an indication for valve intervention, although convincing evidence for slowing of MR progression or improved outcomes does not exist [19]. Administration of diuretics (Chap. 38) or vasodilators (Chap. 40), although potentially very effective, particularly in the symptomatic treatment of acutely decompensated patients, should not unduly delay valve repair or replacement once indicated. In

Table 55.1 Recommendations for medical treatment in chronic severe secondary MR

1. Patients with chronic secondary MR (stages B–D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACE inhibitors, ARBs, beta-blockers, and/or aldosterone antagonists as indicated (level of evidence: A)
2. Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B–D) who meet the indications for device therapy (level of evidence: A)

According to the AHA/ACC Valvular Heart Disease Guidelines [12]

contrast, the potential of medical therapy to positively influence secondary MR is better established [20–23]. On the one hand, it is based on unloading of the LV mainly by diuretics. On the other hand, more sustainable effects can be achieved by drugs targeting adverse LV remodeling, as they have the potential to interrupt the above described vicious circle between secondary MR and left ventricular dysfunction. Human and animal studies provide evidence that ACE inhibitors and beta-adrenergic blockade are capable of reducing MR by reverse remodeling and improving LV function [24–26]. Accordingly, the current AHA guidelines of valvular heart disease recommend optimized medical treatment in patients with reduced LV function and chronic secondary MR (stages B–D) including ACE inhibitors, ARBs, beta-blockers, and/or aldosterone antagonists (Class I, level of evidence: A) as an inalienable basis of heart failure therapy in patients with secondary MR and LV dysfunction (Table 55.1) [12]. In patients with ongoing symptoms and severe MR cardiac resynchronization, therapy is an option if general criteria are met (Table 55.1), and a surgical or interventional approach to correct valve function should be strongly considered (also see Chap. 54) [12].

55.3.2 Cardiac Resynchronization Therapy (CRT)

It is generally recognized that CRT can reduce severity of SMR in heart failure patients by restoring a more physiological timing of processes involved in mitral valve closure. Acutely, CRT was able to significantly reduce MR by optimizing timing of papillary muscle contraction in patients with left bundle branch block and dyssynchrony [27]. Moreover, CRT was shown to positively affect LV shape and functional parameters and reduce apical leaflet tethering, thereby significantly reducing MR [28, 29]. According to a small study involving 98 patients with severe secondary MR, 49 % of patients showed a reduction in MR grade that was associated with an improvement in survival compared to patients without a reduction in MR grade [30, 31]. According to current guidelines, CRT is indicated for symptomatic patients with chronic severe functional MR, if general criteria for resynchronization therapy are met (Class I, level of evidence: A) [12, 30, 32].

55.3.3 Surgery

In the absence of a high perioperative risk, reconstructive mitral valve surgery clearly is the gold standard of therapy in primary MR. In contrast, for secondary MR, the benefit of surgery is less well established as no prospective studies comparing

surgery to conservative heart failure therapy exist, and observational data did not show a benefit for MV surgery over medical therapy in regard to survival [10], despite reverse LV remodeling and functional improvement [33]. However, there is an agreement that MV surgery is recommended for severe secondary MR when aortocoronary bypass surgery is indicated and that it should be considered when there is an option for revascularization [9]. The conventional approach for reconstructive surgery is restrictive mitral annuloplasty to decrease the anterior-posterior dimension of the MV annulus [34]. However, further techniques such as chord transection and methods for PM repositioning are critically debated. The complex nature of functional MR becomes evident by the fact that recurrence rates of relevant MR are around 30 % after MV reconstruction even in contemporary reports [34, 35]. One important aspect for recurrence of MR is believed to be a progression of ventricular disease particularly in patients with already severely dilated left ventricles [36]. In the future, scientific efforts are necessary to understand the influence of ongoing LV dysfunction and remodeling in order to be able to eliminate the factors causing high rate of recurrent MR.

Current guidelines recommend MV surgery in symptomatic patients with severe secondary MR (stages C and D) and who are undergoing coronary revascularization or aortic valve replacement (Class IIa, level of evidence C), patients who are considered severely symptomatic (NYHA III–IV) due to chronic MR (stage D, Class IIb, level of evidence B), or in patients with chronic moderate MR (stage B) who are undergoing cardiac surgery for other reasons (Class IIb, level of evidence C). In general, MV repair is recommended over MV replacement [12], although this concept has been challenged by a recent randomized trial failing to demonstrate a difference between both treatment with regard to LV remodeling or survival.

55.3.4 Interventional Approaches

An increasing number of interventional, catheter-based treatment options have been developed and are being tested in humans. Interventional approaches are designed primarily to reduce annular ring dilation or directly act on the leaflets, thereby increasing coaptation area.

55.3.4.1 Percutaneous Edge-to-Edge Repair with the MitraClip System

The MitraClip is a percutaneous transvenous procedure that aims to create an edge-to-edge repair of the MV resulting in a double orifice mitral valve mimicking the Alfieri surgical technique [37]. The procedure is performed under general anesthesia in the cath lab with a transvenous access usually via the right femoral vein. After transseptal puncture in the area of the fossa ovalis, a steerable guiding sheath (size 24 French) is placed in the left atrium. The inner lumen allows advancing the steerable clip delivery system toward the MV. After choosing an appropriate position (in most cases, the area of the greatest coaptation defect), the clip arms are opened and adjusted perpendicularly to the edge of the leaflets. Guiding of the procedure is performed mainly by transesophageal echocardiography (TEE, 2- and 3-dimensional)

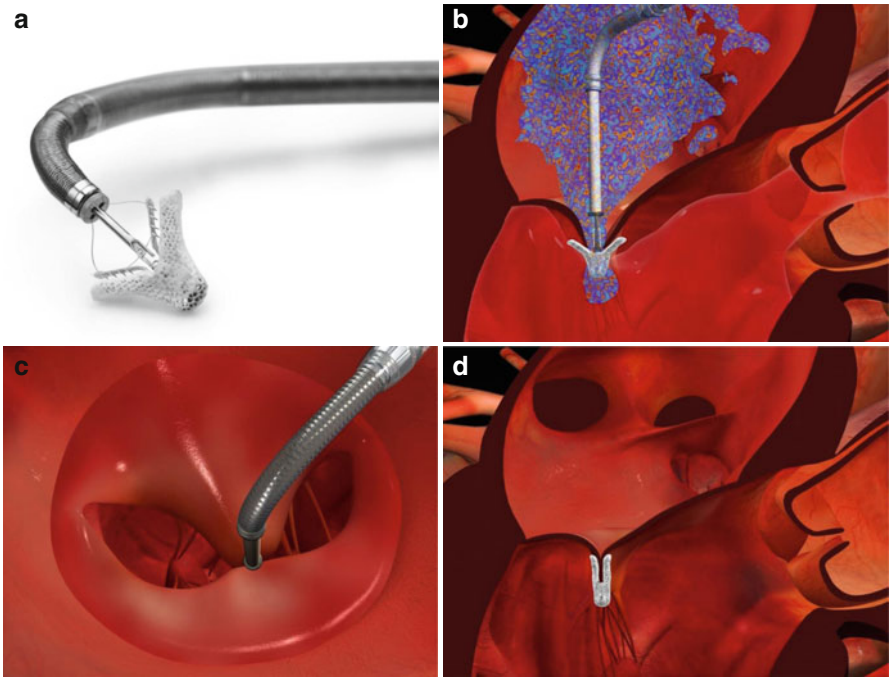

Fig. 55.3 MitraClip device and procedure. (**a**) Photograph of the MitraClip device attached to its delivery system. Leaflets are grasped between the clip arms and gripper arms. (**b**) Schematic illustrating leaflet grasping at the site of maximal mitral regurgitation. (**c**) Created double orifice mitral valve after grasping viewed from left atrium before final clip deployment. (**d**) Schematic of left ventricular outflow tract view after clip deployment (Images courtesy of Abbott Vascular)

and by fluoroscopy. The clip is advanced from the LA, through the MV orifice to the LV side. Care has to be taken to avoid entangling in the chordae. After adjusting for the right position and angulation, the anterior and posterior leaflets of the mitral valve are grasped between the "gripper arms" and the "clip arms" (Fig. 55.3). By closing the clip, the leaflets are firmly gripped, forming a double orifice with approximated leaflet edges. Depending on the resulting MR reduction, the clip can be repositioned as long as the clip is attached to the delivery catheter. Once a satisfying result is obtained, the clip is released from the delivery system.

In the only available RCT to date, the EVEREST II trial, 279 patients with moderate to severe or severe MR who were good candidates for MV surgery were randomized in a 2-to-1 fashion to percutaneous therapy or surgery. This study showed superiority for surgery, as freedom of the primary efficacy end point (death, surgery for mitral-valve dysfunction, or MR grade 3+ to 4+) at 12 months was significantly lower in the interventional than in the surgical group (55 % vs. 73 %, $p=0.007$) [38], which was driven by a high rate of surgery for MV dysfunction in the interventional group. Reduction in MR and LV end-diastolic volume was higher in the surgical group than in the interventional group; however, surgical patients also

exhibited a strong reduction in LVEF. In contrast, reduction in NYHA functional class was high in patients treated with the MitraClip [38]. After 4 years of follow-up, the difference with regard to the primary end point was no longer significant, and survival was identical in both groups [39]. It is of relevance to note that this trial predominantly included patients with primary MR (73 % of patients), whereas in the "real world," more than two thirds of patients treated with the MitraClip have secondary MR. Importantly, a post hoc analysis of the EVEREST II trial revealed that effectiveness of the percutaneous approach was not inferior to surgery in patients with impaired left ventricular function and those with functional MR [38]. Moreover, a series of observational studies shows that MitraClip therapy is feasible and safe, even in high-risk patients with severely impaired LV function and that it is associated with symptomatic improvement [40–43]. Prospective, randomized trials comparing the MitraClip to optimized medical therapy for SMR are currently ongoing in Europe and the USA, and studies comparing the MitraClip with MV surgery are planned.

55.3.4.2 Percutaneous Annuloplasty

Devices aiming to adapt the mitral leaflets by reducing the diameter of the mitral annulus can be separated into *indirect* annuloplasty devices, which are positioned in the coronary sinus thereby secondarily acting on the valve and *direct* annuloplasty devices, which are directly addressing the mitral annulus.

Indirect Annuloplasty The only currently available device for indirect annuloplasty is the Carillon system (Cardiac Dimensions, USA). It consists of a distal and proximal anchor connected by a nitinol bridge and is advanced into the coronary sinus via the right jugular vein. Due to the proximity of the coronary sinus to the mitral annulus, it is able to reduce the diameter of the mitral annulus thereby improving leaflet coaptation. Despite a low procedural success rate (e.g., due to interference with the circumflex artery), a significant functional improvement, as well as reverse LV was observed in successfully treated patients [44].

Direct Annuloplasty Different devices have been developed for reducing annular size by direct annuloplasty. The Mitralign system (Mitralign, USA) advanced retrogradely through the aorta and approaches the ventricular side of the posterior annulus of the MV via the aortic valve. After penetration of the annulus with radiofrequency wires, two pairs of pledges are positioned on the atrial side of the mitral annulus, which are connected with a string. By pulling the strings, the pledges are drawn together, plicating the annulus and reducing the mitral annulus plane. Results of implants in humans are not yet available. The Accucinch system (Guided Delivery Systems, USA) is also advanced retrogradely to the left ventricle, aiming to implant 12 nitinol anchors interlinked with an adjustable cable to the ventricular site of the mitral annulus. Cinching of the device leads to narrowing of the mitral annulus and reduction of MR. Again, technical feasibility has been demonstrated in humans' CHF and secondary MR but outcome data are still missing. Currently, under

investigation is the percutaneous mitral ring system named Cardioband (Valtech), which, like the MitraClip, uses a transfemoral vein access and approaches the left atrial side of the annulus by transseptal puncture. Under careful positioning mainly by 3D-TEE, anchors within a Teflon band are screwed into the annulus thereby fixating the Teflon annuloplasty band. By tightening the band, a plication (sewing) of the annulus can be achieved thereby reducing mainly a centrally secondary MR. All of these devices are currently tested in feasibility and safety studies, whereas there efficacy remains to be proven.

55.3.4.3 Percutaneous Mitral Valve Replacement

Percutaneous replacement of the mitral valve is an obviously attractive concept, but in contrast to transcatheter aortic valve, replacement is complicated by the fact that the mitral valve annulus is more complex and dynamic compared to the aortic annulus. Several models using a transapical retrograde access have been developed and tested in first-in-man studies but definitive feasibility remains to be confirmed.

55.4 Concluding Remarks

Secondary mitral regurgitation in heart failure is a complex and multifactorial condition that is not yet fully understood. Although profound clinical data are missing, it seems to be favorable to eliminate or reduce functional MR, as its presence is associated with adverse outcome. Medical therapy, supplemented with cardiac resynchronization therapy, as recommended for the treatment of chronic heart failure, is the cornerstone of therapy for secondary MR. In patients with ongoing symptoms despite these therapies, MV surgery and percutaneous mitral valve repair should be considered for symptomatic improvement, while their impact on clinical outcome remains to be proven.

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Chapter 56
Pathophysiology and Management of Functional Tricuspid Regurgitation

Jason H. Rogers and Steven F. Bolling

Abstract Functional tricuspid regurgitation (FTR) is an increasingly recognized cause of morbidity and mortality. This clinical entity is most frequently encountered during operations for left-sided heart valve disease, particularly in the setting of functional mitral regurgitation (FMR). Failure to recognize the importance of FTR correction during mitral valve surgery often leads to poor early and late outcomes due to progression of tricuspid regurgitation (TR) and subsequent right heart failure. Consequently, the 2012 ESC/EACTS and 2014 ACC/AHA valvular heart disease guidelines favor a proactive approach to TR correction and highlight the shifting consensus towards more liberal application of surgical therapy. Randomized trials are needed to bolster guideline recommendations further, which are based entirely on retrospective studies. Rigid annuloplasty rings have superior durability and should be used in favor of flexible bands or DeVega-style repairs. Preoperative determinants of clinical outcomes now include echocardiographic parameters of tricuspid valve tenting area and associated right ventricular size and function. Newer percutaneous therapies for FTR may allow less invasive management at the time of percutaneous mitral valve repair or in patients who develop TR late and are at high risk for reoperation. The purpose of this chapter is to review the pathophysiology and current surgical management of functional tricuspid regurgitation, as well as emerging transcatheter therapies.

Keywords Tricuspid regurgitation • Surgery • Outcomes • Annuloplasty • Transcatheter tricuspid valve repair

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
EACTS	European Association for Cardiothoracic Surgery
ESC	European Society of Cardiology
FTR	Functional tricuspid regurgitation
STS	Society of Thoracic Surgeons

56.1 Introduction

Functional tricuspid regurgitation (FTR) results from malcoaptation of the tricuspid valve leaflets in the setting of right ventricular enlargement and tricuspid annular dilation. The onset of FTR can be insidious, with patients having only mild or moderate tricuspid regurgitation (TR) for many years, only to subsequently develop worsening TR which can accelerate underlying right-sided heart failure. Patients with significant FTR suffer from reduced cardiac output, congestive hepatopathy and cardiac cirrhosis, ascites, peripheral edema, and a general failure to thrive. Functional TR is often encountered during surgical correction of functional mitral regurgitation (FMR) in the setting of left ventricular heart failure, which results in secondary right ventricular enlargement, unfavorable geometric remodeling, and tricuspid annular dilation. Despite the fact that surgical FTR correction has risen and operative mortality has decreased over the last decade, surgical correction of TR remains underutilized. Aggressive treatment of FTR at the time of initial surgery is important, since reoperation for recurrent TR carries an inhospital mortality of up to 37 % [1, 2]. The 2012 guidelines from the ESC/EACTS have raised the level of indication to Class I for many situations of FTR, and these recommendations have been mirrored in the 2014 ACC/AHA guidelines. Tricuspid valve repair is preferred to replacement for FTR, and this should be performed with a rigid annuloplasty ring, which is more durable than flexible bands or suture-based annuloplasty. Finally, emerging minimally invasive and transcatheter methods of FTR correction will expand therapeutic options and improve safety. The purpose of this chapter is to review the pathophysiology and current surgical management of functional tricuspid regurgitation, as well as emerging transcatheter therapies.

56.2 Pathophysiology of Functional Tricuspid Regurgitation

Like the mitral valve, the tricuspid valve is an apparatus that depends on the coordinated interaction of its components for proper function (Fig. 56.1). The tricuspid apparatus consists of three valve leaflets (anterior, posterior, and septal), which are attached at their bases to the semi-fibrous tricuspid valve annulus. Tricuspid

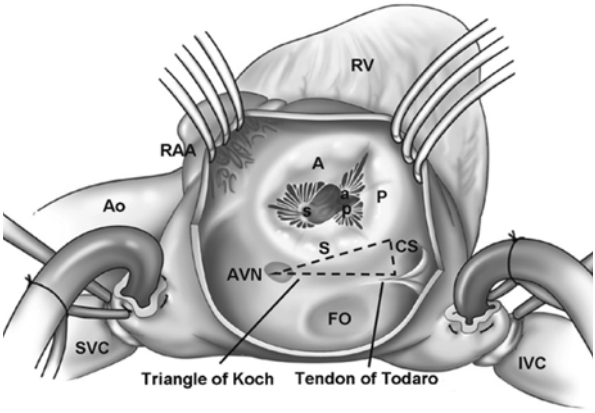

Fig. 56.1 Anatomy and surgical perspective of the tricuspid valve complex. The tricuspid valve consists of three leaflets: anterior (*A*), posterior (*P*), and septal (*S*). There are two main papillary muscles, anterior (*a*) and posterior (*p*). The septal papillary muscle(s) is rudimentary and chordae tendinae arise directly from the interventricular septum. Important adjacent structures include the atrioventricular node (*AVN*), coronary sinus ostium (*CS*), and the tendon of Todaro, which form the triangle of Koch. *Ao* aorta, *FO* foramen ovale, *IVC* inferior vena cava, *SVC* superior vena cava, *RAA* right atrial appendage, *RV* right ventricle (Reproduced with permission from Rogers and Bolling [6])

regurgitation can arise from structural leaflet changes (primary TR) due to a variety of causes. More commonly, TR is secondary (functional) and related to structural changes in the heart that lead to right ventricular and tricuspid annular dilation (Table 56.1). Unlike the mitral valve, where the primary chordae tendinae attached to the leaflet edges are connected directly to the left ventricular papillary muscles, the free edges of the tricuspid valve leaflets are tethered not only to the anterior and posterior right ventricular papillary muscles, but also directly to the right ventricular myocardium and interventricular septum. This direct continuity with the right ventricle exacerbates FTR in the setting of right heart failure. Dilation of the tricuspid annulus along the anterior portion coincident with a dilating right ventricular (RV) free wall is the primary mediator of functional TR [3] (Fig. 56.2). The tricuspid annulus has a unique saddle-shaped structure, and it has been demonstrated by 3D-echocardiography that patients with FTR develop a more planar annulus, which dilates primarily in the septal-lateral direction [4]. Other mechanistic contributors to FTR include right ventricular enlargement with papillary muscle tethering and adverse interactions between LV and RV myofibrils. Experimental models have shown that 20–40 % of RV systolic pressure and volume outflow results from left ventricular contraction [5]. In addition, the left and right ventricles may share a common biochemical responsiveness, whereby improvements in systemic and local neurohormonal parameters may result in improvements in biventricular function. Importantly, left-sided heart failure with chamber enlargement and mitral regurgitation can result in right-sided pressure overload, right ventricular chamber enlargement, tricuspid annular dilation, and resultant FTR. In severe FTR, chronic elevation

Table 56.1 Etiologies of tricuspid regurgitation

Primary (*structural*)
Rheumatic
Myxomatous
Ebstein's anomaly
Endomyocardial fibrosis
Endocarditis
Carcinoid disease
Traumatic (blunt chest injury)
Iatrogenic (pacemaker/defibrillator leads)
Right ventricular biopsy
Drugs (fenfluramine-phentermine or methysergide)
Radiation
Secondary (*functional*)
Left heart disease (LV dysfunction or aortic/mitral valve disease)
Any cause of pulmonary hypertension (idiopathic, pulmonary thromboembolism, left to right shunt)
Any cause of RV dysfunction (myocardial disease, RV ischemia/infarction, chronic volume overload, e.g., from dialysis)
Atrial fibrillation resulting in RA and tricuspid annular enlargement

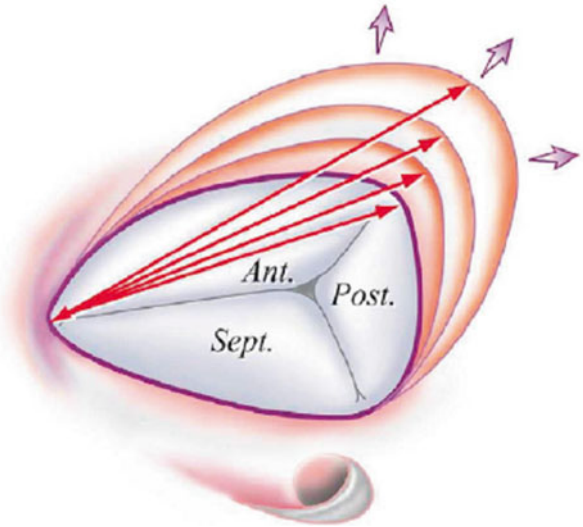

Fig. 56.2 Predominant mechanism of tricuspid annular dilation. Note that in functional tricuspid regurgitation, dilation occurs primarily along the mural portion of the tricuspid annulus, above the right ventricular free wall. Note the shape of the tricuspid annulus is similar to the letter "D," with the base of the septal leaflet forming the straight portion of the annulus. *Arrows* designate the intercommissural distance that increases with progressive annular dilation (Reproduced with permission from Dreyfus et al. [11])

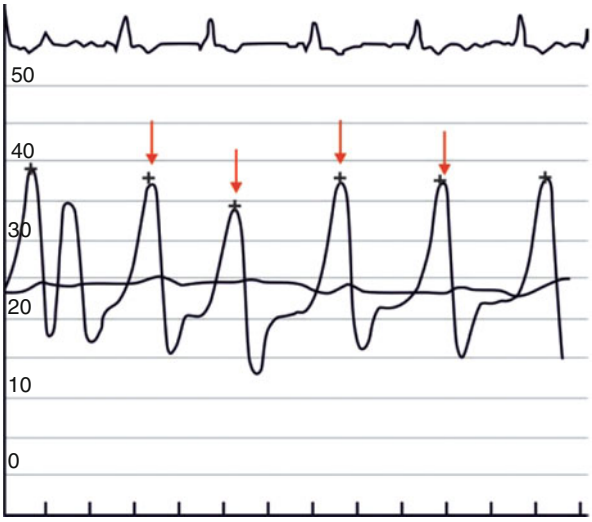

Fig. 56.3 CV Merger waves. Right atrial (*RA*) pressure waveform shows giant CV merger waves in the presence of severe functional TR with marked elevation in the mean and peak RA pressure (Image courtesy of Jaypee Medical Publishers)

in right atrial pressure with giant CV waves (Fig. 56.3) elevates the hepatic venous pressure, which over time can lead to hepatocyte dysfunction, atrophy, and eventually cardiac cirrhosis (fibrosis). The development of liver dysfunction in patients with heart failure and TR can also occur from an ischemic hepatopathy secondary to decreased cardiac output. In general, most patients with cardiac cirrhosis present late in the disease state, at which time correction of TR may not be helpful.

There are often multiple contributors to FTR in a given patient, and the initial management should be targeted at these factors, such as volume overload, left-sided heart failure, and pulmonary hypertension [6].

56.2.1 Natural History of Functional Tricuspid Regurgitation After Mitral Valve Surgery

The primary mechanistic goal of surgery for functional TR should be the application of a rigid annular ring to reduce annular diameter and circumference and thereby leaflet coaptation. Some reports have described that benign neglect of mild-moderate TR at the time of mitral valve surgery may be acceptable since TR is unlikely to progress after MV repair. The fate of TR at the time of mitral valve surgery appears to depend on the etiology of mitral valve disease undergoing correction, and patients with functional MR are at a higher risk for progression of TR after MV surgery (Chap. 55).

For degenerative MR, the fate of TR may be more benign based on some reports. Yilmaz et al. from the Mayo Clinic described 699 patients who underwent mitral valve repair for severe degenerative MR. At the time of surgery, 84 % had TR grade <3+, and 16 % had TR ≥3+. These patients were younger (mean, 60 years) and

had preserved LVEF (mean, 65 %), and 68 % were NYHA Class ≤2. The mean TR grade at discharge was 1.79 and progressed to 2.11 in those patients with >5-year follow-up. Only one patient required tricuspid reoperation 4.5 years after mitral repair [7]. Matsuyama et al. reported in a study of 174 patients that only 16 % of patients who underwent nonischemic (i.e., degenerative) mitral valve surgery without tricuspid valve surgery developed 3–4+ TR at 8-year follow-up [8]. Other reports do not describe such a benign course for TR after surgery for degenerative MR. Desai et al. studied 1,833 patients with degenerative MR who underwent surgical mitral valve repair. These patients also had a structurally normal tricuspid valve, and 67 with significant TR (almost entirely grade 3–4+) underwent concomitant TV repair. The findings were notable in that all patients undergoing mitral valve repair alone had improvements in TR grade and RV function after surgery; however, these improvements were temporary and by 3 years returned to preoperative levels. In contrast, concomitant TV repair in patients with 3–4+ TR durably eliminated severe TR and improved RV function at up to 3 years. These results support a more aggressive use of surgical TR correction in patients undergoing degenerative MV repair with at least 3–4+ TR at the time of surgery [9].

In contrast, patients with functional MR with TR appear to be at higher risk for progression of FTR over time, and more liberal application of TR correction appears warranted in these patients (Fig. 56.4). Matsunaga et al. described 70 patients undergoing MV repair for functional ischemic mitral regurgitation. Approximately one-third (21/70) of patients had at least moderate TR before surgery. In the postoperative period, the prevalence of at least moderate TR increased over time from 25 % at less than 1 year, 53 % at 1–3 year, and 74 % at greater than 3-year follow-up [10]. For patients with dilated cardiomyopathies (mean LVEF 31 %), DeBonis et al. reported that in 91 patients undergoing MV repair for FMR with varying degrees of preoperative TR, 13 patients (14.2 %) underwent concomitant tricuspid annuloplasty for TR ≥3+, whereas the remaining 78 (with preoperative TR ≤2+) did not. At a mean of 1.8 years of follow-up, 12 % of patients had ≥3+ TR, mostly in those patients who did not undergo tricuspid repair. Based on these findings, the authors argue for more aggressive and effective treatment of functional TR during the initial operation.

It has been proposed by Dreyfus et al. that at the time of MV repair, the presence of tricuspid annular dilation (≥70 mm measured intraoperatively in a flaccid heart by deforming the annulus to its maximal diameter), even in the absence of significant TR, should be an indication for TV annuloplasty. The authors described that TR increased by at least two grades in 45 % of the patients who received isolated MV repair, but TR increased in only 2 % of patients undergoing tricuspid annuloplasty based on their ≥70 mm measurement, supporting the notion that tricuspid dilation is an ongoing, progressive process that often warrants preemptive surgical treatment. Based on their findings, any patient with greater than 2+ TR or a tricuspid annular diameter ≥35–40 mm in any echocardiographic view should be considered for repair of TR during any left-sided valve surgery [11]. Other authors have also reported that preemptive surgical annuloplasty in the presence of tricuspid annular dilation ≥40 mm or ≥21 mm/m^2 can stabilize TR grade at a lower level and prevent an increase in RV size over time [12, 13].

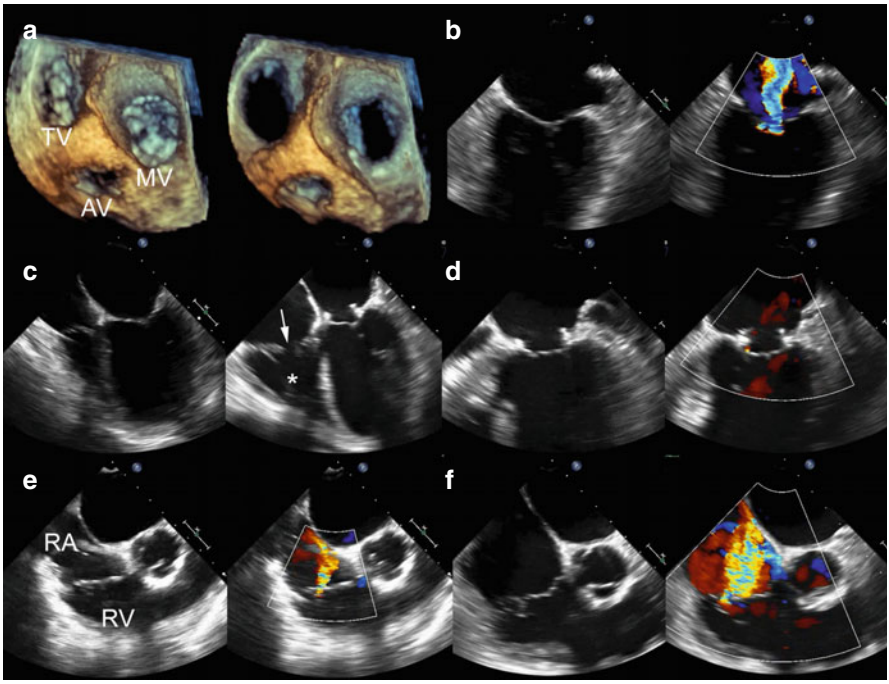

Fig. 56.4 Worsening functional tricuspid regurgitation after surgical mitral valve annuloplasty. (**a**) 3-dimensional transesophageal echocardiography showing the relationships of the mitral valve (*MV*), tricuspid valve (*TV*), and aortic valve (*AV*) in systole and diastole. (**b**) Baseline functional mitral regurgitation due to LV enlargement and annular dilation. (**c**) 14 months after mitral valve annuloplasty showing progressive RV enlargement (*asterisk*) and tricuspid valve malcoaptation (*arrow*) due to underlying pulmonary hypertension and chronic systolic heart failure despite MR correction. (**d**) Continued resolution of MR after mitral annuloplasty with trace MR 14 months after initial operation. (**e**) Baseline mild TR. *RA* right atrium, *RV* right ventricle. (**f**) 14 months after mitral annuloplasty, severe functional TR is now present, and the patient has symptoms of right heart failure with edema, ascites, and fatigue

56.3 Surgical Approach to Functional Tricuspid Regurgitation

Surgical correction of FTR typically consists of downsizing the tricuspid annular area with ring or suture annuloplasty to move the leaflets closer together. Suture annuloplasty techniques were first described by DeVega and Kay almost 50 years ago [14, 15]. However, despite studies showing more stable and durable outcomes with rigid ring annuloplasties, suture and rigid annuloplasties are still both employed in the surgical treatment of TR [16, 17]. Many of the repair techniques used for the tricuspid annulus were originally described for the mitral valve, which were then translated to the tricuspid valve. Carpentier et al. introduced the concept of rigid ring annuloplasty, which has been applied to the mitral and tricuspid valves [18]. Examples of surgical repair techniques are shown in Fig. 56.5. Newer rigid

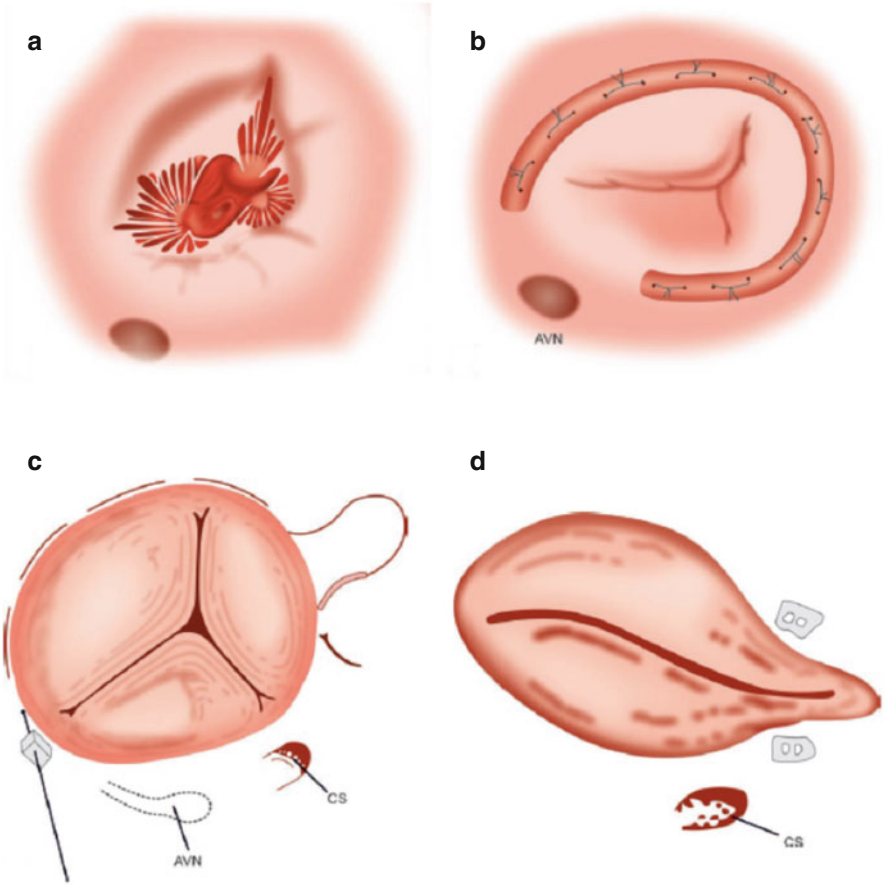

Fig. 56.5 Surgical tricuspid annuloplasty techniques. (**a**) Dilated tricuspid valve annulus with functional tricuspid regurgitation. (**b**) Rigid planar annuloplasty ring. Note that the ring is open to prevent damage to the atrioventricular node leading to heart block. (**c**) DeVega suture repair technique. (**d**) Kay annuloplasty leading to a bicuspidalized valve (Image courtesy of Jaypee Medical Publishers)

annuloplasty rings (e.g., MC3 Tricuspid Annuloplasty Ring, Edwards Lifesciences, Irvine California) are shaped to conform to the complex contours of the tricuspid valve annulus.

Rigid annuloplasty rings are more durable than suture-based or flexible band annuloplasty for the treatment of FTR. McCarthy et al. reported 790 subjects undergoing TV annuloplasty for FTR using four annular approaches: Carpentier-Edwards semirigid ring, Cosgrove-Edwards flexible band, DeVega procedure, and customized semicircular Peri-Guard annuloplasty. Regurgitation severity increased more rapidly over time with the DeVega and Peri-Guard procedures at up to 8-year follow-up, whereas regurgitation severity was relatively stable across time with

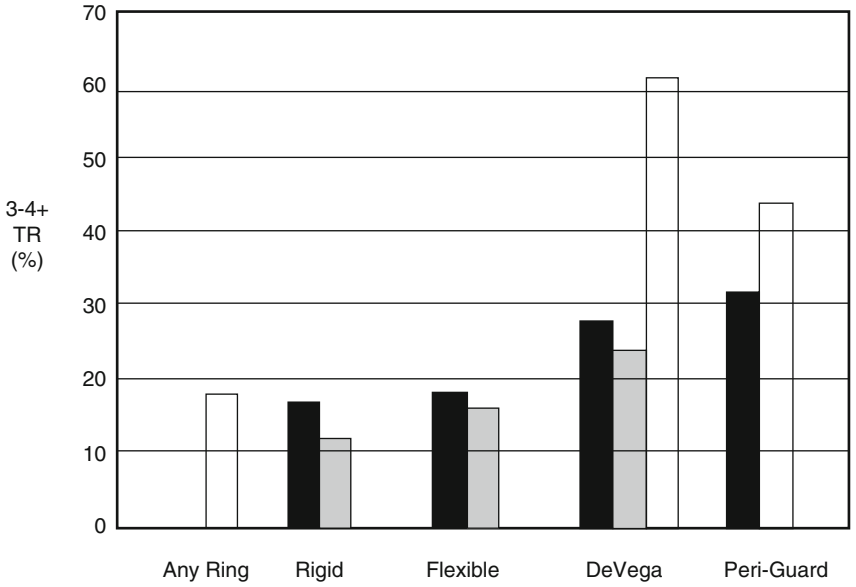

Fig. 56.6 Recurrence of tricuspid regurgitation after ring and non-ring annuloplasty. Reported rates for the recurrence of grade 3 or 4+ TR after initial tricuspid valve annuloplasty by technique. *Dark bars*, McCarthy et al. 5-year follow-up; *gray bars* Navia et al. 5-year follow-up; *open bars* Tang et al. mean 5.9-year follow-up (Reproduced with permission from Rogers and Bolling [36])

the Carpentier-Edwards ring and Cosgrove-Edwards band [16]. Tang et al. have described 702 subjects undergoing TV repair predominantly in the setting of MV surgery, of which 493 had predominantly DeVega repair and 209 had an annuloplasty ring (54 % Carpentier-Edwards, 25 % Duran, and 21 % Cosgrove-Edwards). At up to 21-year follow-up (mean 5.9 years), long-term survival, event-free survival, and freedom from recurrent TR were superior in the ring group. Finally, Navia et al. reported on 2,277 patients who underwent TV procedures during primarily mitral and aortic operations in whom a rigid tricuspid annular ring was used in 26 %, flexible ring in 46 %, DeVega in 5.7 %, Peri-Guard in 8.1 %, Kay procedure in 11 %, and edge-to edge leaflet suture in 3.5 %. By 5 years, TR had increased only slightly to 12 % for isolated rigid prosthesis annuloplasty but was progressively greater for all other annular procedures (flexible prosthesis 16 %, DeVega 24 %, Peri-Guard 44 %, and 19 % for the Kay procedure) [17]. A summary from these comparative reports is shown in Fig. 56.6.

Tricuspid valve repair is preferred over replacement. If replacement is required, a bioprosthesis is generally preferred to avoid the bleeding complications associated with anticoagulation for mechanical valves. Despite the common perception, it is not proven that tricuspid valve replacements are at a higher risk for thrombosis than mitral valve replacements. Tricuspid valve repair appears to result in improved midterm survival (up to 10 years after surgery) as compared with TV replacement, although there is no significant difference in valve-related mortality or

need for TV reoperation [1]. Although the mechanisms for this difference are not fully understood, it is hypothesized that a rigid object (TV valve) in a deformable low-pressure cavity (right ventricle) may result in RV dysfunction and perioperative low output state. Replacements also complicate the need for right ventricular pacemaker leads. These leads are placed epicardial since this is preferred to leads being placed across the bioprosthesis.

Recently, investigators have examined echocardiographic predictors of adverse outcomes after annuloplasty for FTR. Yiu et al. recently studied 74 patients (age 58 ± 10 years; men 27 %) with significant tricuspid regurgitation who consequently underwent TV annuloplasty during left heart valve surgery [19]. RV mid-cavity diameter, RV longitudinal dimension, and tricuspid valve (TV) tethering area were independently associated with adverse events after adjustment with age and New York Heart Association Class III/IV. Receiver-operator characteristic curve demonstrated that RV mid-cavity diameter (area under curve [AUC] = 0.74, $P < 0.01$) and TV tethering area (AUC = 0.70, $P = 0.04$) were most associated with adverse events at 1-year follow-up after TA. Topilsky et al. have shown that the right index of myocardial performance (RIMP) ratio, an echocardiographic global estimate of RV systolic and diastolic function, was a significant predictor of mortality after isolated tricuspid valve replacement [20]. Preoperative assessment of RV function, TV morphology, and the relation of these variables to clinical outcomes remains an understudied area.

Given the data favoring more aggressive treatment of FTR at the time of mitral valve surgery and the superiority of repair over replacement, it is encouraging that several large registry reports have described increased utilization of tricuspid valve repair with annuloplasty and decreased TV replacements. In addition, despite increasing comorbidities and surgical risk, 30-day mortality has decreased perhaps reflecting improved surgical techniques.

Kilic et al. recently reported on 54,375 patients undergoing TV surgery from 2000 to 2010 in the Society of Thoracic Surgeons (STS) National Database [21]. The majority of cases were repairs (89 %) and were performed concomitant with another major procedure (86 %), presumably for predominantly FTR. The most common concomitant procedure was mitral valve surgery alone (47.6 %), followed by CABG with mitral valve (19.6 %) and triple valve surgery with concomitant aortic and mitral valve surgery (12.2 %). The proportion of tricuspid valve repairs increased from 84.6 % in 2000 to 89.8 % in 2010 ($P = 0.01$). The most common type of repair was tricuspid valve annuloplasty only (75.5 %)—the annuloplasty technique used was not reported. Most of the tricuspid valve replacements were performed using bioprostheses (81.5 %), with the rate increasing from 77.4 % in 2000 to 86.6 % in 2010 ($P = 0.001$). Despite increased age, comorbidity burden, and more emergency cases over the time period, unadjusted 30-day operative mortality for TV surgery declined from 10.6 % in 2000 to 8.2 % in 2010 ($P < 0.001$), and this trend persisted after risk adjustment (Fig. 56.7).

Marquis-Gravel et al. reported on a retrospective cohort study of 926 consecutive cases of TV surgery (792 repairs and 134 replacements) performed at a single center from 1977 to 2008 [22]. Operative mortality decreased over time (20 % from

1977 to 1998, 7 % from 1999 to 2008, $P<0.001$). Ten-year survival was 49 ± 2 % and 38 ± 5 % in the repair and replacement groups, respectively ($P=0.012$). At discharge, severity of TR was ≥3/4 in 13 % of repair and in and 2 % of replacement groups ($P=0.01$). Propensity score analysis showed that tricuspid repair was associated with higher rates of TR ≥3/4 at follow-up compared with replacement (hazard ratio 2.15, $P=0.02$). Importantly, the use of rigid annuloplasty rings (such as Carpentier-Edwards, Contour, Tri-AD, and MC3) was the predominant repair technique used in the latter part of this series, and the use of a rigid ring resulted in less TR ≥3/4 recurrence at follow-up compared with patients who underwent Bex or DeVega procedures (HR 0.56, $P=0.001$). Forty-eight reoperations (7 % of patients at risk) were performed during follow-up (repair group, 6 %; replacement

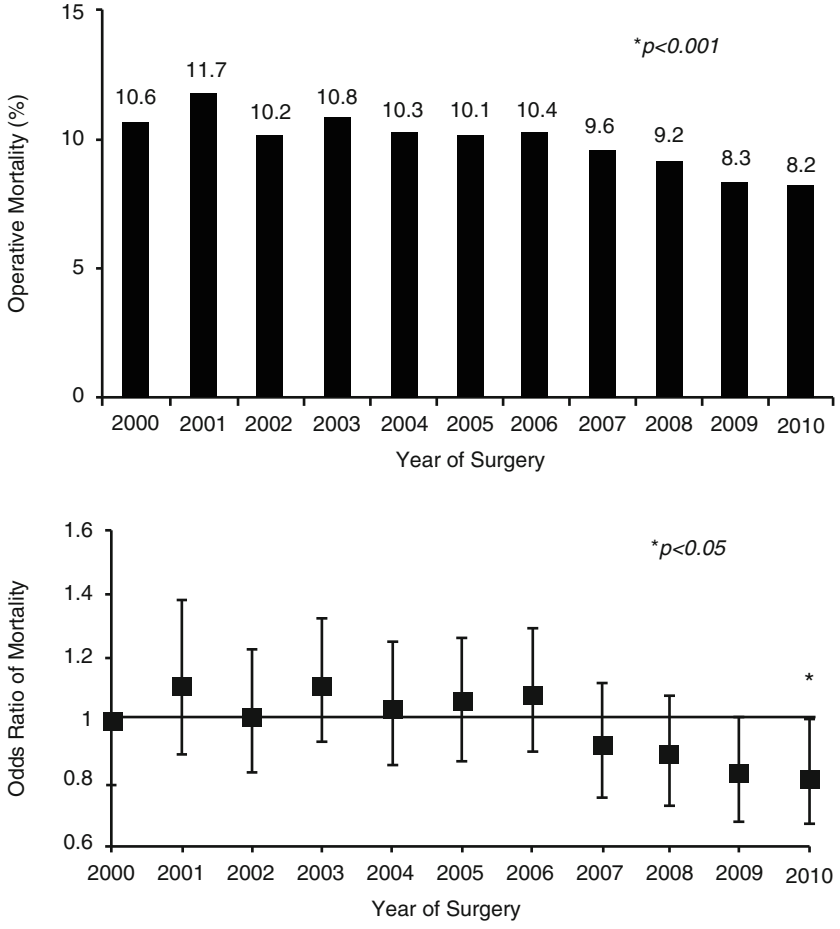

Fig. 56.7 Trends in tricuspid valve surgery in 54,375 patients from STS database 2000–2010. Annual unadjusted (*top panel*) and risk-adjusted (*lower panel*) operative mortality rates during the study period (Reproduced with permission from Kilic et al. [21])

group, 15 %; $P=0.01$). At last follow-up, New York Heart Association functional class was improved compared with baseline in both groups ($P<0.001$). The authors conclude that tricuspid valve surgery is associated with substantial early and late mortalities but with significant functional improvement [22]. Replacement is more effective in early and late corrections of regurgitation, but it did not translate into better survival outcomes.

Despite these and other data that encourage a proactive and aggressive approach to surgical TR correction, others have reported that a concomitant TV operation at the time of MV surgery is a proxy for more advanced valve disease, and that compared with MV operations alone, combined mitral and tricuspid operations are associated with increased morbidity and mortality even after risk adjustment. LaPar reported on a registry from Virginia over a 6-year period with 5,495 MV operations (approximately half replacements and half repairs), of which 433 had a concomitant TV procedure (25 replacements, 408 repairs). The etiology of mitral valve disease was not described in this registry. Those undergoing the combined valve surgery were more frequently women, had heart failure, required reoperations, and had higher unadjusted operative mortality (6.0 % MV only vs. 10.4 % MV+TV, $p=0.001$). Risk adjustment showed that the performance of concomitant TV procedures was an independent predictor of operative death (odds ratio, 1.50; $p=0.03$) and major complications (odds ratio, 1.39; $p=0.004$) [23] (Chaps. 54 and 55).

Debate remains on the fate of mild-moderate FTR. A Korean group reported retrospectively on 959 subjects with mild-to-moderate functional TR who underwent mitral valve surgery with (repair group $n=431$) or without (control group $n=528$) concomitant TV repair from 1994 to 2010. The decision for FTR repair was left to the surgeon's discretion, and no systematic criteria were applied. At a median follow-up of 64.8 months, there were no significant differences in early mortality, major morbidity rates, TV reoperation, and congestive heart failure in the TR repair group as compared with the control group. Of 144 propensity-matched pairs of patients that had echocardiographic follow-up, patients with greater than moderate TR at latest follow-up were significantly less common in the repair group compared with those in the control group (10.4 % vs. 13.9 %; $P=0.023$). On multivariate Cox-regression analysis, preoperative clinical risk profile and the performance of a Maze procedure for atrial fibrillation seemed to be more important than TV repair in overall clinical outcomes [24].

In a recent observational report by Teman et al., patients with FTR repaired as a redo operation between 2004 and 2012 were identified. These patients were propensity-matched 1:2 with contemporaneous patients with FTR or tricuspid dilatation who underwent tricuspid repair at the same time as mitral valve repair. The authors described 21 patients treated with redo tricuspid valve repair that were matched with 42 patients treated prophylactically. There were three deaths at 30 days in the redo group (14 %), compared with zero in the prophylactic group ($P=0.03$). Long-term mortality in the redo group was 29 % at a mean 31-month follow-up but was less at 14 % (6 of 42) in the prophylactic group at a mean 25 months follow-up. Kaplan-Meier long-term survival analysis did not reveal a difference between groups (log-rank $p=0.37$) once the perioperative period was survived [25].

In summary, whereas there is clear indication for correction of ≥3+ FTR at the time of mitral valve surgery, a randomized, controlled trial of prophylactic tricuspid operation for mild-moderate FTR at the time of the mitral operation is needed to solidify the evidence to date.

56.4 Guidelines for the Surgical Management of Functional Tricuspid Regurgitation

Current guidelines mirror the increasingly proactive and prophylactic approach to FTR correction that are described in the literature (Table 56.2). The 2014 ACC/AHA Valvular Heart Disease Guidelines give a Class I indication for tricuspid valve repair in any patient with severe TR undergoing mitral valve surgery [26]. The guidelines generally favor prophylactic FTR correction for any patient with tricuspid annular dilation or evidence of right-sided heart failure. The 2012 Joint ESC/EACTS recommendations are similarly aggressive, with all scenarios achieving either a Class I or IIa recommendation [27]. Despite the ACC/AHA and ESC/EACTS guidelines that support surgical repair of TR at the time of mitral valve surgery in many patients, tricuspid valve repair currently is still underutilized. The current surgical volume of tricuspid valve repair represents only approximately one-tenth of the greater than 50,000 mitral valve operations performed yearly in the United States [28].

56.5 Transcatheter Tricuspid Valve Repair

Tricuspid valve repair adds operative time and complexity. Efforts to decrease surgical risk for correction of FTR are important if adoption is to continue to increase. Lee et al. have described minimally invasive tricuspid valve surgery in a series of 141 consecutive patients undergoing tricuspid valve operation using mini-thoracotomy with the heart unclamped and the heart either beating or fibrillating. The repair rate was encouraging at 61 % and 30-day mortality was low at 2.1 % [29].

There have not yet been human reports of transcatheter valve implantations in native degenerated tricuspid valves. However, transcatheter tricuspid valve therapies have been used for treating degenerated surgical bioprosthesis as "valve-in-valve" (VIV) therapies (Fig. 56.8). In the global valve-in-valve registry, tricuspid VIV therapies are much less commonly performed ($n = 12$) when compared to aortic or mitral VIV procedures ($n = 574$) [30].

The majority of the reported tricuspid VIV procedures are case reports with a few case series with short to intermediate follow-up from 5 days to 22 months. These patients tend to be younger (mean age 43 years) with severe right-sided heart failure either due to congenital heart disease, acquired heart disease, or rarely due to the sequelae of carcinoid syndrome. Current methods of valve implantation include

Table 56.2 (A) 2012 Joint European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines pertaining to the surgical management of tricuspid valve regurgitation. (B) 2014 American College of Cardiology/American Heart Association (ACC/AHA) valvular heart disease guidelines regarding tricuspid regurgitation

(**A**) **2012 ESC/EACTS guidelines**
Class I
1. Surgery is indicated in patients with severe primary or secondary TR undergoing left-sided valve surgery (*level of evidence*: *C*)
2. Surgery is indicated in symptomatic patients with severe isolated primary TR without severe right ventricular dysfunction (*level of evidence*: *C*)
Class IIa
1. Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery (*level of evidence*: *C*)
2. Surgery should be considered in patients with mild or moderate secondary TR with dilated annulus (≥40 mm or >21 mm/m^2) undergoing left-sided valve surgery (*level of evidence*: *C*)
3. Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive right ventricular dilatation or deterioration of right ventricular function (*level of evidence*: *C*)
4. After left-sided valve surgery, surgery should be considered in patients with severe TR who are symptomatic or have progressive right ventricular dilatation/dysfunction, in the absence of left-sided valve dysfunction, severe right or left ventricular dysfunction, and severe pulmonary vascular disease (*level of evidence*: *C*)
(**B**) **2014 ACC/AHA guidelines**
Class I
Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery (*level of evidence*: *C*)
Class IIa
1. Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at the time of left-sided valve surgery with either (1) tricuspid annular dilation or (2) prior evidence of right HF (*level of evidence*: *B*)
2. Tricuspid valve surgery can be beneficial for patients with symptoms due to severe primary TR that are unresponsive to medical therapy (stage D) (*level of evidence*: *C*)
Class IIb
1. Tricuspid valve repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery (*level of evidence*: *C*)
2. Tricuspid valve surgery may be considered for asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater RV dilation and/or systolic dysfunction (*level of evidence*: *C*)
3. Reoperation for isolated tricuspid valve repair or replacement may be considered for persistent symptoms due to severe TR (stage D) in patients who have undergone previous left-sided valve surgery and who do not have severe pulmonary hypertension or significant RV systolic dysfunction (*level of evidence*: *C*)

The level of evidence (LOE, where LOE = A denotes a recommendation derived from multiple randomized clinical trials or meta-analyses, LOE = B denotes a recommendation derived from a single randomized clinical trial or large nonrandomized studies, and LOE = C denotes a recommendation based on consensus of expert opinion or based on small studies, retrospective studies, or registries) supporting the recommendation is given in parenthesis

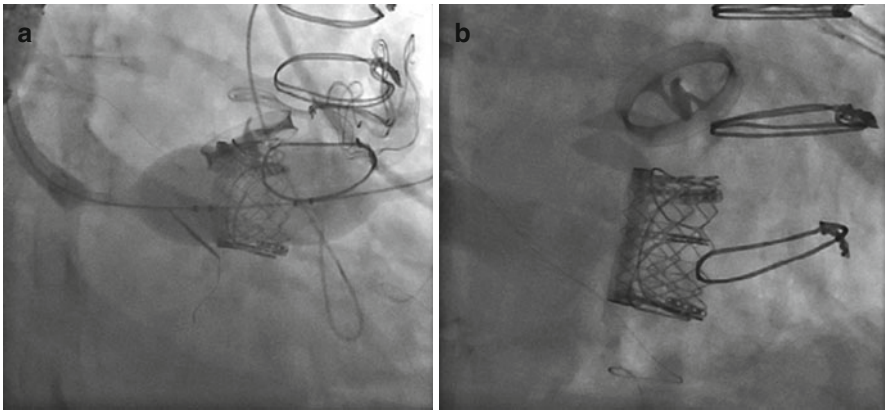

Fig. 56.8 Tricuspid valve-in-valve therapy. (**a**) Transcatheter tricuspid valve-in-valve replacement performed jugular from the right internal using a balloon-expandable Edwards Sapien 26 mm valve (Edwards Lifesciences, Irvine, California). The patient has mechanical aortic and mitral valves. (**b**) Final appearance of transcatheter valve within the tricuspid with bioprosthesis (Reproduced permission from Daneault et al. [37])

a right trans-atrial approach (via a thoracotomy) or transvenous approach using either the right internal jugular or femoral vein. The most commonly used devices are the Melody valve (Medtronic Inc., Fridley, MN), Edwards SAPIEN, or Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) valves. The SAPIEN XT valves are available in larger diameter sizes and are also shorter in length as compared with the Melody Valve. Both valves have comparable efficacy and safety in the short term but longer-term data are limited [31–33].

Investigators have reported placing transcatheter valves in the inferior vena cava (IVC) (and in some cases, the superior vena cava) for the treatment of TR. The rationale behind this approach is to reduce the regurgitant volume and pressure from TR that refluxes back into the IVC. This regurgitant volume leads to symptoms of advanced right heart failure such as hepatic congestion/cirrhosis, ascites, and lower extremity edema refractory to diuretic therapy. Transcatheter placement of a custom stented valve in the inferior vena cava in a patient with severely symptomatic FTR with right heart failure resulted in dramatic clinical improvement in congestive symptoms [34] (Fig. 56.9). The Sapien XT valve has also been used in the IVC and SVC position with clinical success to reduce the systemic hemodynamic effects of severe TR [35]. Technical challenges to this approach include the very large diameter of the inferior vena cava, a short landing zone between the right atrium and hepatic vein, and the presence of pacing leads in the SVC. The long-term effects of this caval stenting approach on right atrial size and right ventricular function are not known, and long-term anticoagulation is currently recommended.

There are numerous other transcatheter therapies for FTR currently in development (Fig. 56.10). Some of these technologies have been translated mechanistically from the experiences with transcatheter mitral valve repair. Transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) is a novel transcatheter technique to treat

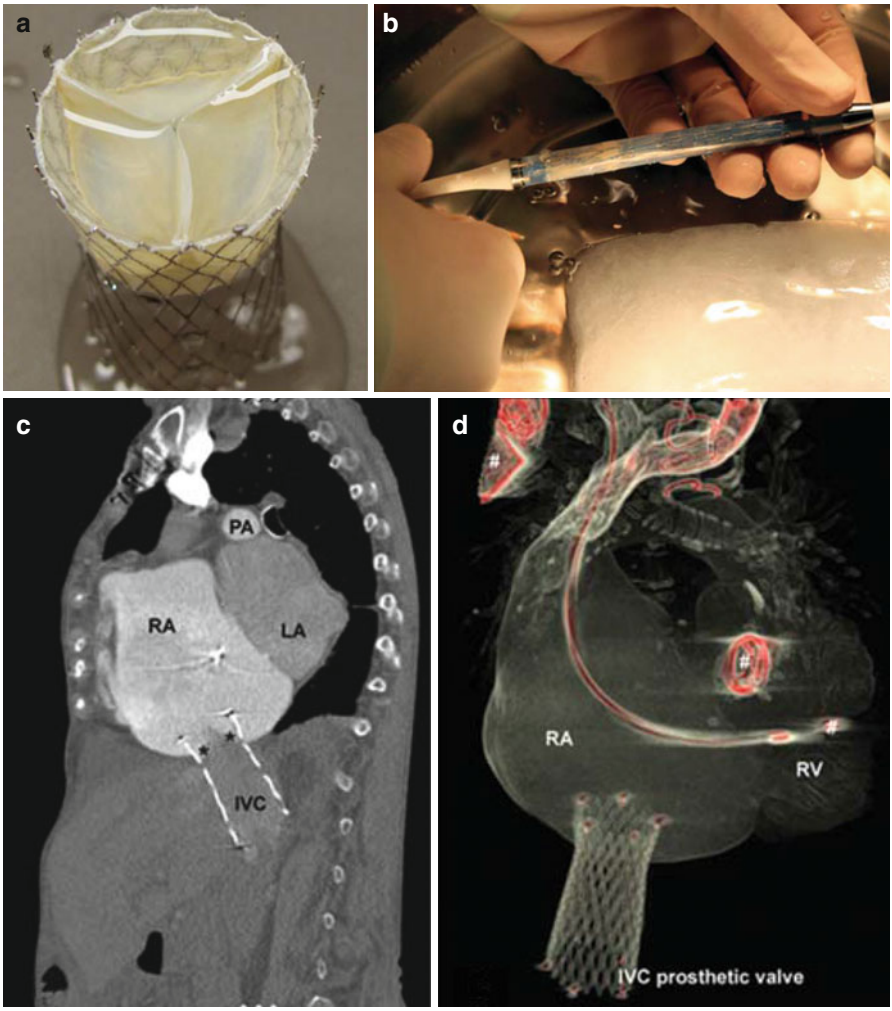

Fig. 56.9 (**a**) A custom self-expanding percutaneous heart valve for inferior vena cava implantation. This device was designed with a shorter upper valved segment protruding into the right atrium and a longer lower segment for anchoring in the inferior vena cava. (**b**) The valve is self-expanding and is loaded into a 27 Fr catheter for implantation. (**c**) A computed tomographic angiogram 8 weeks after implantation with contrast injected in superior vena cava visualizes proper valve function without regurgitation into the IVC. The level of the leaflets (*asterisks*) is aligned with the cavoatrial junction, thus protecting of the hepatic vein from elevated right atrium pressure. (**d**) Three-dimensional reconstruction confirms the forward-tilted position of the valve in the inferior vena cava. A prosthetic mitral valve (*#* on the *right side*) and RV pacing lead are also seen (Reproduced with permission from Lauten et al. [34])

functional tricuspid regurgitation developed by Rogers and Lederman at the NIH. This procedure has been studied in a porcine model and utilizes the right atrial appendage to achieve pericardial access with a sheath, through which an encircling

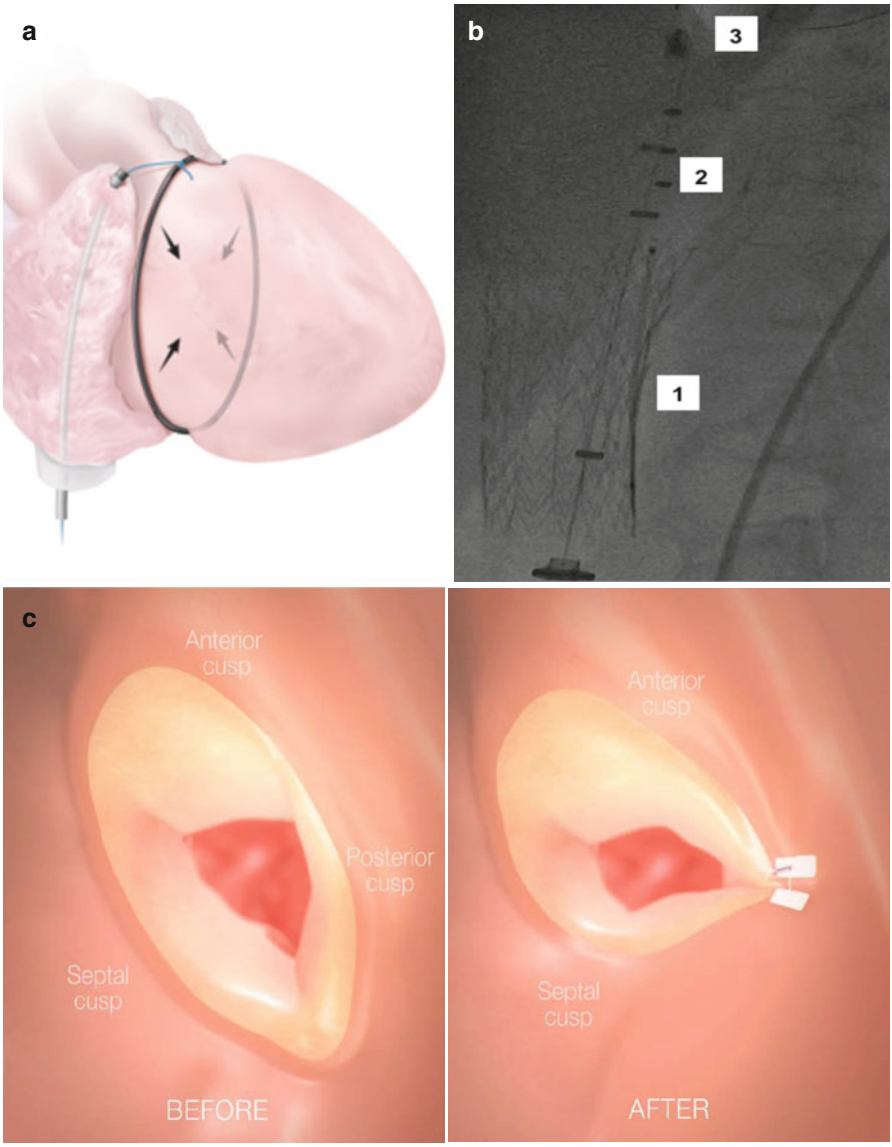

Fig. 56.10 Emerging transcatheter technologies for functional tricuspid regurgitation. (**a**) The transatrial intrapericardial tricuspid annuloplasty (TRAIPTA) device is delivered through the right atrial appendage, opens inside the pericardial space, loops around the whole heart, and is positioned along the atrioventricular groove. The device is tensioned to reduce tricuspid annular size and thereby ameliorate TR (Figure courtesy of Robert Lederman). (**b**) The 4Tech TriCinch Gen 1 System consists of (*1*) an anchor attached to the tricuspid annulus and (*2*) a Dacron band which connects the tricuspid anchor to (*3*) a nitinol stent anchor in the IVC. By tensioning the band, the annulus is reshaped. (**c**) Mitralign Tricuspid Annuloplasty. Two pledgeted anchors are delivered to the posterior tricuspid annulus via the right internal jugular vein under fluoroscopic and transesophageal echocardiographic guidance. Once the pledgets have been delivered, they are plicated or pulled together and locked in place and suture cut. The resulting posterior annuloplasty creates a bicuspidization of the tricuspid valve

device is positioned around the heart and tensioned, resulting decreased tricuspid annular diameter, thereby reducing TR. The TriCinch™ Gen 1 System (4 Tech, Dublin, Ireland) is a percutaneous approach in which anchors are placed in the IVC and on the tricuspid valve annulus. Tension is then applied between the two points with a Dacron band leading to a reduction of the tricuspid valve area and decreased FTR. Despite conceptual promise, the MitraClip procedure, which has been effective in the mitral position, has not yet been translated successfully to use in the tricuspid position. Challenges to a tricuspid edge-to-edge repair include the trileaflet nature of the tricuspid valve, wide malcoaptation gaps, and increased chordal density. The Mitralign procedure involves partial annuloplasty of the mitral valve with two sets of paired anchors percutaneously placed through the posterior valve annulus behind P1 and P3. These anchors are then plicated together resulting in a reduction in the annular circumference and a reduction in the anteroposterior diameter. The Mitralign procedure has been adapted for use on the tricuspid annulus for the treatment of functional TR. The procedure is based on the bicuspidalization procedure with plication of the annulus along the posterior and septal leaflets. Finally, efforts are underway to create a percutaneously delivered tricuspid annuloplasty ring. Technologies for developing both flexible and rigid transcatheter rings are currently under development (see also Chaps. 54 and 55).

56.6 Concluding Remarks

Severe functional tricuspid regurgitation is a challenging clinical condition for which medical management has limited efficacy. Concomitant surgical repair of even mild TR at the time of mitral valve surgery should be considered if there is evidence of tricuspid annular dilation or right ventricular enlargement. The application of a rigid or semirigid ring has been shown to improve durability over suture-based or other non-ring approaches that should be avoided. A randomized trial comparing benign neglect of TR versus earlier intervention will be required to solidify the currently available data in this field, which are currently retrospective. For patients with failing tricuspid bioprostheses, tricuspid valve-in-valve therapy is an attractive alternative to reoperation. Finally, emerging transcatheter therapies for FTR may provide a therapeutic option for patients currently at high or prohibitive surgical risk.

Conflicts of Interest Jason H. Rogers is a consultant for St Jude Medical, Edwards, and Medtronic. S.F. Bolling is a consultant for St. Jude Medical, Sorin-Carbomedics, Medtronic, and Edwards Lifesciences.

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Chapter 57
Aortic Valve Stenosis and Aortic Regurgitation: Pathophysiology and Treatment

Wilbert S. Aronow

Abstract Patients with aortic stenosis (AS) have an increased prevalence of coronary risk factors, coronary artery disease (CAD), and other atherosclerotic vascular diseases. Angina pectoris, syncope or near syncope, and congestive heart failure are the three classic manifestations of severe AS. Prolonged duration and late peaking of an aortic systolic ejection murmur best differentiate severe AS from mild AS on physical examination. The severity of aortic regurgitation (AR) correlates with the duration of the diastolic murmur. Doppler echocardiography is used to diagnose the severity of AS and AR. Indications for aortic valve replacement (AVR), use of warfarin after AVR in patients with mechanical prostheses, and use of aspirin or warfarin after AVR in patients with bioprostheses are discussed. Transcatheter aortic valvular implantation (TAVI) should be performed in inoperable patients with symptomatic severe AS; TAVI has been shown to improve survival and quality of life compared with medical therapy.

Keywords Aortic stenosis • Aortic regurgitation • Doppler echocardiography • Heart failure • Angina pectoris • Syncope • Heart murmurs • Mechanical prosthetic valve • Porcine bioprosthesis • Transcatheter aortic valvular implantation • Warfarin • Aspirin

57.1 Aortic Stenosis

57.1.1 Etiology and Prevalence (Also See Chap. 54)

Valvular AS in elderly patients is usually due to stiffening, scarring, and calcification of aortic valve leaflets. The commissures are not fused as in rheumatic AS. Calcific deposits in the aortic valve are common in elderly patients and may lead to valvular AS [1–5]. Aortic cuspal calcium was present in 295 of 752 men

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(36 %), mean age 80 years, and in 672 of 1,663 women (40 %), mean age 82 years [4]. Of 2,358 patients, mean age 81 years, 378 (16 %) had valvular AS, 981 (42 %) had valvular aortic sclerosis (thickening of or calcific deposits on the aortic valve cusps with a peak flow velocity across the aortic valve ≤1.5 m/s), and 999 (42 %) had no valvular AS or aortic sclerosis [5]. Aortic valve and mitral annulus calcium may coexist [1, 6].

In the Helsinki Aging Study, calcification of the aortic valve was diagnosed by Doppler echocardiography in 28 % of 76 patients aged 55–71 years, in 48 % of 197 patients aged 75–76 years, in 55 % of 155 patients aged 80–81 years, and in 75 % of 124 patients aged 85–86 years [3]. Aortic valve calcification, aortic sclerosis, and mitral annular calcification (MAC) are degenerative processes [7, 8], accounting for their high prevalence in an elderly population.

Otto et al. [8] showed that the early lesion of degenerative AS is an active inflammatory process with some similarities to atherosclerosis, including lipid deposition, macrophage and T-cell infiltration, and basement membrane disruption. In a prospective study of 571 patients, mean age 82 years, 292 patients (51 %) had calcified or thickened aortic cusps or root [9]. A serum total cholesterol ≥200 mg/dL, a history of hypertension, diabetes mellitus, and a serum high-density lipoprotein (HDL) cholesterol <35 mg/dL were more prevalent in patients with calcified or thickened aortic cusps or root than in patients with normal aortic cusps and root [9]. In the Helsinki Aging Study, age, hypertension, and a low body mass index were independent predictors of aortic valve calcification [10].

In 1,275 patients, mean age 81 years, AS was present in 52 of 202 patients (26 %) with 40–100 % extracranial carotid arterial disease (ECAD) and in 162 of 1,073 patients (15 %) with 0–39 % ECAD [11]. In 2,987 patients, mean age 81 years, peripheral arterial disease was present in 193 of 462 patients (42 %) with AS and in 639 of 2,525 patients (25 %) without AS [12].

In 290 patients with valvular AS who had follow-up Doppler echocardiograms, patients with MAC had a greater reduction in aortic valve area (AVA)/year than patients without MAC [13]. Significant independent risk factors for progression of AS in 102 patients who had follow-up Doppler echocardiograms were cigarette smoking and hypercholesterolemia [14]. Palta et al. [15] also found that cigarette smoking and hypercholesterolemia accelerate progression of AS. These and other data suggest that aortic valve calcification, MAC, and coronary atherosclerosis in elderly patients have similar predisposing factors [8–16].

A retrospective analysis of 180 patients with mild AS who had follow-up Doppler echocardiograms at ≥2 years showed that significant independent predictors of progression of AS were male gender, cigarette smoking, hypertension, diabetes, a serum low-density lipoprotein cholesterol ≥125 mg/dL at follow-up, a serum HDL cholesterol <35 mg/dL at follow-up, and use of statins (inverse association) [17]. A retrospective analysis of 174 patients with mild-to-moderate AS showed that statin therapy reduced progression of AS [18]. A retrospective study of 156 patients with AS also showed at 3.7-year follow-up that statins reduced progression of AS by 54 % [19]. However, a trial in which 1,873 patients with mild-to-moderate AS were randomized to simvastatin 40 mg plus ezetimibe 10 mg daily versus placebo showed

at 52-month follow-up that the primary outcome of cardiovascular death, aortic valve replacement (AVR), nonfatal myocardial infarction (MI), hospitalization for unstable angina, coronary artery bypass graft surgery (CABGS), percutaneous coronary intervention, or nonhemorrhagic stroke was 35.3 % in the simvastatin-ezetimibe group versus 38.2 % in the placebo group (p not significant) [20].

The frequency of AS increases with age. AS was diagnosed by Doppler echocardiography in 141 of 924 men (15 %), mean age 80 years, and in 322 of 1,881 women (17 %), mean age 81 years [21]. Of these 2,805 elderly patients, severe AS (peak gradient across aortic valve of ≥50 mmHg or AVA <0.75 cm^2) was diagnosed in 62 patients (2 %), moderate AS (peak gradient across aortic valve of 26–49 mmHg or AVA of 0.75–1.49 cm^2) in 149 (5 %), and mild AS (peak gradient across aortic valve of 10–25 mmHg or AVA ≥.50 cm^2) in 25 patients (9 %) [21]. In 924 men, mean age 80 years, AS was present in 36 of 236 African-Americans (15 %), 19 of 135 Hispanics (14 %), and 86 of 553 whites (16 %) [21]. In 1,881 women, mean age 81 years, AS was present in 84 of 494 African-Americans (17 %), 33 of 188 Hispanics (18 %), and 205 of 1,199 white women (17 %) [21]. In 501 patients aged 75–86 years in the Helsinki Aging Study, critical AS was present in 3 % and moderate-to-severe AS in 5 % of patients [3].

57.1.2 Pathophysiology

In valvular AS, there is resistance to ejection of blood from the left ventricle (LV) into the aorta, with a pressure gradient across the aortic valve during systole and an increase in LV systolic pressure. The pressure overload on the LV leads to concentric LV hypertrophy, with an increase in LV wall thickness and mass, normalizing systolic wall stress, and maintenance of normal LV ejection fraction and cardiac output [22]. A compensated hyperdynamic response is common in elderly women [23]. Elderly patients with a comparable degree of AS have more impairment of LV diastolic function than do younger patients [24]. Coronary vasodilator reserve is more severely impaired in the subendocardium in patients with LV hypertrophy caused by severe AS [25].

The compensatory concentric LV hypertrophy leads to abnormal LV compliance, LV diastolic dysfunction with reduced LV diastolic filling, and increased LV end-diastolic pressure, further increased by left atrial systole. Left atrial enlargement develops. Atrial systole plays an important role in diastolic filling of the LV in patients with AS [26]. Loss of effective atrial contraction may cause immediate clinical deterioration in patients with severe AS.

Sustained LV hypertrophy eventually leads to LV chamber dilatation with decreased LV ejection fraction and, ultimately, congestive heart failure (CHF). The stroke volume and cardiac output decrease, the mean left atrial and pulmonary capillary pressures increase, and pulmonary hypertension occurs. Patients with both obstructive and nonobstructive coronary artery disease (CAD) have an increased incidence of LV enlargement and LV systolic dysfunction [27]. In a percentage of elderly patients with AS, the LV ejection fraction will remain normal and LV diastolic dysfunction will be the main problem.

In 48 elderly patients with CHF associated with unoperated severe valvular AS, the LV ejection fraction was normal in 30 patients (63 %) [28]. The prognosis of patients with AS and LV diastolic dysfunction is usually better than that of patients with AS and LV systolic dysfunction, but is worse than that of patients without LV diastolic dysfunction [28, 29].

57.1.3 Symptoms

Angina, syncope or near syncope, and CHF are the three classic manifestations of severe AS. Angina is the most common symptom associated with AS in elderly patients. Coexistent CAD is frequently present. However, angina may occur without CAD as a result of increased myocardial oxygen demand with a reduction in myocardial oxygen supply at the subendocardial level. Myocardial ischemia in patients with severe AS and normal coronary arteries is due to inadequate LV hypertrophy with increased LV systolic and diastolic wall stresses causing decreased coronary flow reserve [30].

Syncope in patients with AS may be caused by reduced cerebral perfusion following exertion when arterial pressure drops because of systemic vasodilatation in the presence of a fixed cardiac output. LV failure with a decrease in cardiac output may also cause syncope. Syncope at rest may be caused by a marked reduction in cardiac output secondary to transient ventricular fibrillation or transient atrial fibrillation (AF) or transient atrioventricular block related to extension of the valve calcification into the conduction system. Coexistent cerebrovascular disease with transient cerebral ischemia may contribute to syncope in patients with AS.

Exertional dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema may be caused by pulmonary venous hypertension associated with AS. Coexistent CAD and hypertension may contribute to CHF in patients with AS. AF may also precipitate CHF.

CHF, syncope, or angina occurred in 36 of 40 patients (90 %) with severe AS, in 66 of 96 patients (69 %) with moderate AS, and in 45 of 165 patients (27 %) with mild AS [31]. Sudden death occurs mainly in symptomatic AS patients [28, 31, 32]. It may also occur in 3–5 % of asymptomatic patients with AS [32]. Marked fatigue and peripheral cyanosis in patients with AS may be caused by low cardiac output. Cerebral emboli causing stroke or transient cerebral ischemic attack, bacterial endocarditis, and gastrointestinal bleeding may also occur in AS patients.

57.1.4 Signs

A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward the apex, or at the apex is an aortic systolic ejection murmur (ASEM) [1, 2, 33]. An ASEM was heard in 265 of 565 elderly patients (47 %) [1]. Of 220 elderly patients with an ASEM and echocardiograms of the aortic valve, 207

(94 %) had aortic cuspal or root calcification or thickening [1]. Of 75 elderly patients with an ASEM, AS was diagnosed by Doppler echocardiography in 42 patients (56 %) [33].

Table 57.1 shows that an ASEM was heard in 100 % of 19 patients with severe AS, in 100 % of 49 patients with moderate AS, and in 95 % of 74 patients with mild AS [2]. However, the ASEM may become softer or absent in patients with CHF associated with severe AS because of low cardiac output. The intensity and maximal location of the ASEM and transmission of the ASEM to the right carotid artery do not differentiate among mild, moderate, and severe AS [1, 2, 33]. The ASEM may be heard only at the apex in some elderly patients with AS. The apical systolic ejection murmur may also be louder and more musical than the basal systolic ejection murmur in some elderly patients with AS. The intensity of the ASEM in AS increases with squatting and by inhalation of amyl nitrite and decreases during the Valsalva maneuver.

Prolonged duration of the ASEM and late peaking of the ASEM best differentiate severe AS from mild AS [1, 2, 33]. However, the physical signs do not distinguish between severe and moderate AS (Table 57.1) [2, 33].

A prolonged carotid upstroke time does not differentiate between severe and moderate AS in elderly patients [2]. A prolonged carotid upstroke time was palpable in 3 % of elderly patients with mild AS, in 33 % of elderly patients with moderate AS, and in 53 % of elderly patients with severe AS (Table 57.1) [2]. Stiff noncompliant arteries may mask a prolonged carotid upstroke time in elderly patients with severe AS. The pulse pressure may also be normal or wide rather than narrow in elderly patients with severe AS because of loss of vascular elasticity. An aortic ejection click is rare in elderly patients with AS or severe AS because the valve cusps are immobile from loss of valvular elasticity [2, 33].

An absent or decreased A_2 (aortic component of second heart sound) occurs more frequently in patients with severe or moderate AS than in patients with mild AS (Table 57.1) [2, 33]. However, an absent or decreased A_2 does not differentiate between severe and moderate AS [2, 33]. The presence of AF, reversed splitting of S_2, or an audible fourth heart sound at the apex also does not differentiate between severe and moderate AS in patients [33]. The presence of a third heart sound in patients with AS usually indicates presence of LV systolic dysfunction and elevated LV filling pressure [34].

Table 57.1 Association of physical signs of aortic stenosis with severity of aortic stenosis

	Severity of aortic stenosis		
Physical sign	Mild ($n=74$)	Moderate ($n=49$)	Severe ($n=19$)
ASEM	95 %	100 %	100 %
Prolonged duration ASEM	3 %	63 %	84 %
Late-peaking ASEM	3 %	63 %	84 %
Prolonged carotid upstroke time	3 %	33 %	53 %
A_2 absent	0 %	10 %	16 %
A_2 decreased or absent	5 %	49 %	74 %

Source: Adapted from Ref. [2]

ASEM aortic systolic ejection murmur, *A2* aortic component of second heart sound

57.1.5 Electrocardiography and Chest Roentgenography

Table 57.2 shows that echocardiography is more sensitive than electrocardiography in detecting LV hypertrophy in patients with AS [2]. Rounding of the LV border and apex may result from concentric LV hypertrophy. Post-stenotic dilatation of the ascending aorta is commonly seen. Calcification of the aortic valve is best seen by echocardiography or fluoroscopy.

In a study of 1,533 patients with asymptomatic AS, electrocardiographic LVH was associated at 4.3-year follow-up with a 5.8 times increase in heart failure, a 2.0 times increase in aortic valve replacement (AVR), and a 2.5 times increase in myocardial infarction, CHF, or cardiovascular death [35]. LV strain was associated with a 3.1 times increase in myocardial infarction [35].

Involvement of the conduction system by calcific deposits may occur in patients with AS. In 51 patients with AS who underwent AVR, conduction defects occurred in 58 % of 31 patients with MAC and in 25 % of 20 patients without MAC [6]. In 77 elderly patients with AS, first-degree atrioventricular block occurred in 18 %, left bundle branch block in 10 %, intraventricular conduction defect in 6 %, right bundle branch block in 4 %, and left axis deviation in 17 % of patients [36].

Complex ventricular arrhythmias may be detected by 24-h ambulatory electrocardiograms in patients with AS. Patients with complex ventricular arrhythmias associated with AS have a higher incidence of new coronary events than patients with AS and no complex ventricular arrhythmias [37].

57.1.6 Echocardiography and Doppler Echocardiography

Two-dimensional and Doppler echocardiography are very useful in diagnosing AS. Of 83 patients with CHF or angina and a systolic precordial murmur in whom severe AS was diagnosed by Doppler echocardiography, AS was not clinically diagnosed in 28 patients (34 %) [38]. Echocardiography can detect thickening, calcification, and reduced excursion of aortic valve leaflets [1]. LV hypertrophy is best diagnosed by echocardiography [2]. Chamber dimensions and measurements of LV end-systolic and end-diastolic volumes, LV ejection fraction, and assessment of global and regional LV wall motion give important information on LV systolic function.

Table 57.2 Prevalence of electrocardiographic and echocardiographic left ventricular hypertrophy (LVH) in mild, moderate, and severe aortic stenosis

	Severity of aortic stenosis		
	Mild ($n=74$)	Moderate ($n=49$)	Severe ($n=19$)
Electrocardiographic LVH	11 %	31 %	58 %
Echocardiographic LVH	74 %	96 %	100 %

Source: Adapted from Ref. [2]

Doppler echocardiography measures peak and mean transvalvular gradients across the aortic valve and identifies associated valve lesions. Aortic valve area (AVA) can be calculated by the continuity equation using pulsed Doppler echocardiography to measure LV outflow tract velocity, continuous-wave Doppler echocardiography to measure transvalvular flow velocity, and two-dimensional long-axis view to measure LV outflow tract area [38, 39]. The agreement in quantitation of severity of AS between Doppler echocardiography and cardiac catheterization is greater than 95 % [40]. Patients with a peak jet velocity ≥4.5 m/s had critical AS, and those with a peak jet velocity <3.0 m/s had noncritical AS. Slater et al. [41] found a concordance between Doppler echocardiography and cardiac catheterization in the decision to operate or not to operate in 61 of 73 patients (84 %) with AS. In 75 patients with AS, the Bland-Altman plot showed that 4 of 75 patients (5 %) had disagreement between cardiac catheterization and Doppler echocardiography outside the 95 % confidence limits [42].

Although most patients do not require cardiac catheterization before AVR, they require selective coronary arteriography before AVR. Patients in whom Doppler echocardiography shows a peak jet velocity between 3.6 and 4.4 m/s and an AVA >0.8 cm^2 should undergo cardiac catheterization if they have cardiac symptoms attributable to AS. Patients with a peak jet velocity between 3.0 and 3.5 m/s and a LV ejection fraction >50 % probably do not need AVR but should undergo cardiac catheterization if they have symptoms of severe AS [40]. Patients with a peak jet velocity between 3.0 and 3.5 m/s and a LV ejection fraction <50 % may have severe AS, requiring AVR, and should undergo cardiac catheterization [40].

57.1.7 Natural History

In patients with severe AS, the average survival rate was 3 years after onset of angina, 3 years after onset of syncope, and 1.5–2 years after the onset of CHF [32]. At the National Institutes of Health, 52 % of patients with symptomatic severe AS not operated on were dead at 5 years [32]. At 10-year follow-up, 90 % of these patients were dead. At 4-year follow-up of patients aged 75–86 years in the Helsinki Aging Study, cardiovascular mortality was 62 % in patients with severe AS and 35 % in patients with moderate AS [53]. At 4-year follow-up, total mortality was 76 % in patients with severe AS and 50 % with moderate AS [43].

In a prospective study, at 19-month follow-up (range 2–36 months), 90 % of 30 patients with CHF associated with unoperated severe AS and a normal LV ejection fraction were dead [34]. At 13-month follow-up (range 2–24 months), 100 % of 18 patients with CHF associated with unoperated severe AS and an abnormal LV ejection fraction were dead [34].

Table 57.3 shows the incidence of new coronary events in patients with no, mild, moderate, and severe AS. Independent risk factors for new coronary events in this study were prior MI, AS, male gender, and increasing age [31]. At 20-month follow-up of 40 patients with severe AS, CHF, syncope, or angina occurred in 36 of 37

patients (97 %) with new coronary events and in none of 3 patients (0 %) without new coronary events [31]. At 32-month follow-up of 96 patients with moderate AS, the symptoms of CHF, syncope, or angina occurred in 65 of 77 patients (84 %) with new coronary events and in 1 of 19 patients (5 %) without new coronary events [31]. At 52-month follow-up of 165 patients with mild AS, the symptoms of CHF, syncope, or angina occurred in 40 of 103 patients (39 %) with new coronary events and in 5 of 62 patients (8 %) without new coronary events [31].

In 981 patients with aortic sclerosis and 999 patients without aortic sclerosis, patients with aortic sclerosis had at 46-month follow-up a 1.8 times higher incidence of new coronary events than those without valvular aortic sclerosis [5]. In 5,621 men and women, AS and aortic sclerosis increased cardiovascular morbidity and mortality [44].

In 38 patients with symptomatic moderate AS and 28 patients with minimally symptomatic moderate AS, the probabilities of avoiding death from AS were 0.86 for patients and 1.0 for patients with minimally symptomatic moderate AS at 1-year follow-up, 0.77 for patients with symptomatic AS and 1.0 for patients with minimally symptomatic AS at 2 years, 0.77 for patients with symptomatic AS and 0.96 for patients with minimally symptomatic AS at 3 years, and 0.70 for patients with symptomatic AS and 0.90 for patients with minimally symptomatic AS at 4 years [45]. During 35-month follow-up, 21 patients had AVR.

At 5-year follow-up of 106 patients with unoperated AS, 60 (57 %) died [46]. Multivariate analysis showed that severity of AS, CAD, and CHF were important predictors of survival in unoperated patients. Some studies have shown that patients with asymptomatic severe AS are at low risk for death and can be followed until symptoms develop [47, 48].

Rosenheck et al. [49] followed 126 patients with asymptomatic severe AS for 22 months. Eight patients died and 59 patients developed symptoms necessitating AVR. Event-free survival was 67 % at 1 year, 56 % at 2 years, and 33 % at 4 years. Five of six deaths from cardiac disease were preceded by symptoms. Of patients with moderately or severely calcified aortic valves whose aortic jet velocity increased by 0.3 m/s or more within 1 year, 79 % underwent AVR or died within 2 years of the observed increase.

When patients with low-gradient AS due to abnormal LV ejection fraction are considered for AVR, failure to respond to dobutamine and large preoperative LV end-systolic and end-diastolic volumes are poor prognostic signs [50, 51]. The

Table 57.3 New coronary events in patients with no, mild, moderate, and severe aortic stenosis (AS)

	No AS (n = 1,496)	Mild AS (n = 165)	Moderate AS (n = 96)	Severe AS (n = 40)
Age (years)	81	84	85	85
Follow-up (months)	49	52	32	20
New coronary events	41 %	62 %	80 %	93 %

Source: Adapted from reference [31]

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines state that dobutamine stress echocardiography is reasonable to evaluate patients with low-flow/low-gradient AS and abnormal LV ejection fraction [52], to determine the transvalvular pressure gradient, and to calculate valve area (following dobutamine infusion and during a baseline state) with the goal of assessing whether stenosis is severe or only moderate in severity.

57.1.8 Medical Management

Prophylactic antibiotics are not recommended to prevent bacterial endocarditis in patients with AS regardless of severity [53]. Patients with CHF, exertional syncope, or angina associated with moderate or severe AS should undergo AVR promptly. Medical therapy does not relieve the mechanical obstruction to LV outflow and does not relieve symptoms or progression of the disorder. Patients with asymptomatic AS should report symptoms possibly related to AS immediately to their physician. If significant AS is present in asymptomatic patients, clinical examination, an electrocardiogram, and Doppler echocardiogram should be performed at 6-month intervals. Nitrates should be used cautiously in patients with angina to prevent orthostatic hypotension and syncope. Diuretics should be used cautiously in patients with CHF to prevent decrease in cardiac output and hypotension. Vasodilators should be avoided. Digitalis should not be used in patients with CHF and normal LV ejection fraction unless needed to control a rapid ventricular rate associated with AF.

57.1.9 Aortic Valve Replacement

Table 57.4 lists four Class I indications and one Class II_a indication for performing AVR in patients with AS [52]. Although the ACC/AHA guidelines do not recommend AVR in patients with asymptomatic severe AS and normal LV ejection fraction, there are data suggesting otherwise [54–58]. Ninety-nine of 338 patients (29 %) with asymptomatic severe AS had AVR during 3.5-year follow-up. Survival at 1, 2, and 5 years was 67, 56, and 38 %, respectively, for unoperated patients and 94, 93, and 90 %, respectively, for those with AVR [54]. In unoperated patients, beta-blocker use reduced mortality by 48 %, and statins use reduced mortality by 48 % [54] (Chap. 54).

Of 622 patients with asymptomatic severe AS, 166 (27 %) developed symptoms and had AVR [55]. Another 97 patients (16 %) had AVR in absence of symptoms. At 3-year follow-up, 52 % of 622 patients had developed symptoms, underwent AVR, or died. The most important risk factor for 10-year mortality was absence of AVR (hazard ratio = 3.53, $p < 0.001$) [55].

Of 197 patients with asymptomatic severe AS, early AVR was performed in 102 patients (52 %) [56]. The estimated actuarial 6-year all-cause mortality rates were

2 % for AVR and 32 % for the conventional treatment group [56]. Despite being asymptomatic, patients with very severe AS have a poor prognosis [57]. Early elective AVR should be considered in these patients [57]. Of 73 patients with severe AS who did not undergo AVR, 15 (14 %) died at 15-month follow-up [58]. Of these 73 patients, symptoms were thought to be unrelated to the AS in 31 patients. Exercise stress tests for symptoms were performed in only 4 % of 42 asymptomatic patients [58].

Asymptomatic patients with low-gradient severe AS and normal LV ejection fraction with reduced stroke volume index had at 46-month follow-up aortic valve events similar to those with normal stroke volume index [59]. Of 248 patients with severe AS and a normal LV ejection fraction, 94 had a low gradient (<30 mmHg mean gradient) (group 1), 87 had a moderate gradient (30–40 mmHg mean gradient) (group 2), and 67 had a severe gradient (>40 mmHg mean gradient) (group 3) [60]. Symptoms were present in 49 % of group 1 patients, in 55 % of group 2 patients, and in 60 % of group 3 patients. At 45–60-month follow-up, the incidence of AVR or death was 71 % for group 1, 77 % for group 2, and 76 % for group 3. Kaplan-Meier survival curves for time to death in all three groups were significantly better for patients with AVR versus no AVR [60]. $E/E^{1}_{lateral}$ was an independent predictor of time to death in patients who did not receive AVR [61].

Echocardiography is recommended in asymptomatic patients with AS every 1 year for severe AS, every 1–2 years for moderate AS, and every 3–5 years for mild AS [52]. Echocardiography should be repeated more frequently if there are changes in symptoms or LV function.

The bioprosthesis has less structural failure in elderly patients than in younger patients and may be preferable to the mechanical prosthetic valve for AS replacement in the elderly due to the anticoagulation issue [62, 63]. Patients with mechanical prostheses need anticoagulant therapy indefinitely. Patients with porcine bioprostheses may be treated with aspirin in a dose of 75–100 mg daily unless the patient has AF, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable condition [52, 63]. Table 57.5 lists four Class I indications and two Class II_a indications for antithrombotic therapy in patients with AVR [52]. Follow-up was performed at 12.6 years in patients aged 65–80 years undergoing AVR with a biological (24,410 patients) or mechanical (14,789 patients) prosthesis [64]. Long-term mortality was similar for both prostheses (hazard ratio (HR) = 1.06).

Table 57.4 American College of Cardiology/American Heart Association Class I indications for aortic valve replacement in severe aortic stenosis (AS)

1. Patients with symptomatic severe AS
2. Patients with severe AS undergoing coronary artery bypass surgery
3. Patients with severe AS undergoing surgery on the aorta or other heart valves
4. Patients with severe AS and a left ventricular ejection fraction <50 %
5. Patients with moderate AS undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves (Class II_a indication)

Source: Modified from reference [52]

Table 57.5 Class I indications for antithrombotic therapy in aortic valve replacement (AVR)

1. After AVR with bileaflet mechanical or Medtronic Hall prostheses, in patients with no risk factors, give warfarin to maintain INR (international normalized ratio) between 2.0 and 3.0; if risk factors are present, the INR should be maintained between 2.5 and 3.5
2. After AVR with Starr-Edwards valves or mechanical disc valves (other than Medtronic Hall prostheses), in patients with no risk factors, warfarin should be given to maintain INR between 2.5 and 3.5
3. After AVR with a bioprosthesis and no risk factors, give aspirin in a dose of 75–100 mg daily
4. After AVR with a bioprosthesis and risk factors, give warfarin to maintain an INR between 2.0 and 3.0
5. During the first 3 months after AVR with a mechanical prosthesis, it is reasonable to give warfarin to maintain an INR between 2.5 and 3.5 (Class II_a indication)
6. During the first 3 months after AVR with a bioprosthesis in patients with no risk factors, it is reasonable to give warfarin to maintain an INR between 2.0 and 3.0 (Class II_a indication)

Source: Modified from Ref. [52]
Risk factors include atrial fibrillation, prior thromboembolism, left ventricular systolic dysfunction, and hypercoagulable condition

Bioprostheses had a higher risk of reoperation (HR = 2.55) and endocarditis (HR = 1.6) but lower risk of stroke (HR = 0.87) and hemorrhage (HR = 0.66) [64].

A United Kingdom heart valve registry of 1,100 patients aged ≥80 years (56 % women) who underwent AVR showed that the 30-day mortality was 6.6 % [65]. The actuarial survival was 89 % at 1 year, 79 % at 3 years, 69 % at 5 years, and 46 % at 8 years. Survival of patients with severe AS, a LV ejection fraction <35 %, and a low transvalvular gradient at 1 year and 4 years was 82 and 78 %, respectively, in 39 patients who underwent AVR versus 41 and 15 %, respectively, in 56 patients in a control group [66]. In 242 patients, mean age 83 years, with AS who had AVR, actuarial survival was 92 % at 1 year and 66 % at 5 years [67]. Concomitant CABGS did not affect late survival [67].

Paroxysmal or chronic AF is a risk factor for mortality in patients with severe AS and a LV ejection fraction ≤35 % undergoing AVR [68]. AVR is associated with a reduction in LV mass and in improvement of LV diastolic filling [69]. At 41-month follow-up of 100 patients with AVR, the yearly cardiac mortality rate was 8 % in patients with electrocardiographic LV hypertrophy and repetitive ventricular premature complexes ≥2 couplets per 24 h during 24-h ambulatory monitoring compared to 0.6 % in patients without either of these findings [70].

If LV systolic dysfunction in patients with severe AS is associated with critical narrowing of the aortic valve rather than myocardial fibrosis, it often improves after successful aortic valve replacement [71]. In 154 patients with AS and a LV ejection fraction ≤35 % who underwent AVR, the 30-day mortality was 9 %. The 5-year survival was 69 % in patients without significant CAD and 39 % in patients with significant CAD. NYHA functional class III or IV was present in 58 % of patients before surgery versus 7 % of patients after surgery. Postoperative LV ejection fraction was measured in 76 % of survivors at a mean of 14 months after surgery. Improvement in LV ejection fraction was found in 76 % of patients [71].

57.1.10 Balloon Aortic Valvuloplasty

AVR is the procedure of choice for symptomatic elderly patients with severe AS. The actuarial survival of 50 elderly patients with symptomatic severe AS in whom AVR was refused (45 patients) or deferred (5 patients) was 57 % at 1 year, 37 % at 2 years, and 25 % at 3 years [72]. On the basis of the available data, balloon aortic valvuloplasty should be considered for elderly patients with symptomatic severe AS who are not candidates for AVR or transcatheter aortic valve implantation (TAVI) and possibly for patients with severe LV dysfunction as a bridge to subsequent valve surgery [73, 74].

57.1.11 Percutaneous Transcatheter Implantation of Aortic Valve Prostheses

The United Kingdom Transcatheter Aortic Valve Implantation (TAVI) Registry followed prospectively 870 high-risk patients, mean age 82 years, with severe AS undergoing 877 TAVI procedures [75]. Survival was 92.9 % at 30 days, 78.6 % at 1 year, and 73.7 % at 2 years [75].

Of 442 patients with severe AS at increased surgical risk, mean age 82 years, 78 were treated with medical management, 107 with AVR, and 257 with TAVI [76]. At 30-month follow-up, mortality was 49 % lower for AVR compared with medical treatment and 62 % lower for TAVI compared with medical treatment. At 1 year, 92.3 % of AVR patients, 93.2 % of TAVI patients, and 70.8 % of medically treated patients were NYHA functional class I or II [76].

In the Placement of Aortic Transcatheter Valve (PARTNER) trial, 699 high-risk patients with severe AS, mean age 84 years, were randomized to AVR or TAVI [77]. All-cause mortality was 3.4 % for the TAVI group versus 6.5 % for the AVR group at 30 days and 24.2 % for the TAVI group versus 26.8 % for the AVR group at 1 year. Major stroke was 3.8 % for the TAVI group versus 2.1 % for the AVR group at 30 days and 5.1 % for the TAVI group versus 2.4 % for the AVR group at 1 year. Major vascular complications at 30 days were 11.0 % for the TAVI group versus 3.2 % for the AVR group. At 1 year, there were similar improvements in cardiac symptoms for both groups [77]. In the PARTNER trial, among inoperable patients with severe AS, compared with standard care, TAVI caused improvements in health-related quality of life maintained for at least 1 year [78]. At 2-year follow-up of 699 patients in the PARTNER trial, all-cause mortality was 33.9 % for TAVI and 35.0 % for AVR [79]. Stroke was 7.7 % for TAVI and 4.9 % for AVR. Moderate or severe paravalvular aortic regurgitation (AR) was 6.9 % for TAVI and 0.9 % for AVR and was associated with increased late mortality [79].

At 2-year follow-up of 180 patients, mean age 84 years, with low-flow inoperable severe AS in the PARTNER trial, mortality was 76 % in the standard therapy group versus 46 % for TAVI [80]. At 2-year follow-up of 350 patients, mean age

84 years, with low-flow inoperable severe AS in the PARTNER trial, mortality was 40 % for AVR versus 38 % for TAVI [80]. At 2-year follow-up of the inoperable group in the PARTNER trial, mortality in patients with a normal stroke volume index was 38 % for TAVI versus 53 % for medical management [80].

One-third of 270 patients undergoing a CoreValve TAVI needed a permanent pacemaker implanted within 30 days [81]. In 138 patients undergoing TAVI, mean age 79 years, with no prior history of AF, new-onset AF developed in 44 patients (32 %) at a median time of 48 h after TAVI [82]. A modified procedure of transapical TAVI with a balloon-expandable prosthesis was associated with a low incidence of relevant prosthetic regurgitation [83].

At 42-month follow-up of 339 patients, mean age 81 years, who had TAVI because they were considered to be inoperable or at very high surgical risk, 188 (56 %) had died [84]. The causes of late death in 152 patients were noncardiac comorbidities in 59 %, cardiac death in 23 %, and unknown in 18 % [84]. TAVI results in similar hemodynamic and long-term clinical outcomes for high-risk surgical patients with low-gradient severe AS and for those with typical severe AS [85].

In the United States, the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy Registry showed that 7,710 patients underwent TAVR (20 % who were inoperable and 80 % who were high-risk but operable) [86]. The median age was 84 years, 49 % were women, and the median STS predicted risk of mortality was 7 %. A transfemoral approach was performed in 64 % of patients, a transapical approach in 29 % of patients, and other alternative approaches in 7 % of patients. Inhospital mortality was 5.5 % and major vascular injury was 6.4 %. At 30-days follow-up, the incidence of mortality was 7.6 % (52 % due to a noncardiovascular cause), stroke was 2.8 %, dialysis-dependent renal failure was 2.8 %, and re-intervention was 0.5 % [86].

The 2012 ACCF/American Association for Thoracic Surgery/Society for Cardiovascular Angiography and Interventions/STS expert consensus document on transcatheter aortic valve replacement recommended TAVI in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival greater than 1 year and who have a prohibitive surgical risk as defined by an estimated 50 % or greater risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease [87]. These guidelines also state that TAVR is a reasonable alternative to AVR in patients at high surgical risk (PARTNER Trial Criteria: STS $\geq$8 %), with the major complications from TAVR being mortality (3–5 %), stroke (6–7 %), access complications (17 %), pacemaker insertion (2–9 % for Sapien and 19–43 % for CoreValve), bleeding, prosthetic dysfunction, paravalvular aortic regurgitation, acute kidney injury, coronary occlusion, valve embolization, and aortic rupture [87].

On the basis of the available data, AVR should be performed in operable patients with severe AS. TAVI should be performed in nonoperable patients with symptomatic severe AS to improve survival and quality of life compared with medical management.

After TAVI, treatment with clopidogrel for 3 months in addition to aspirin is widely practiced. However, a study of 161 patients randomized to clopidogrel for

3 months (a loading dose of 300 mg on the day before TAVI followed by 75 mg daily) plus aspirin 100 mg daily or aspirin 100 mg daily alone showed no difference in major adverse cardiac and cerebrovascular events at 30 days and at 6 months [88]. These data need confirmation by a larger study.

57.2 Aortic Regurgitation (See Chap. 54)

57.2.1 Etiology and Prevalence

Acute AR may be due to infective endocarditis, rheumatic fever, aortic dissection, trauma following prosthetic valve surgery, or rupture of the sinus of Valsalva and causes sudden severe LV failure. Chronic AR may be caused by valve leaflet disease (secondary to any cause of AS, infective endocarditis, rheumatic fever, congenital heart disease, rheumatoid arthritis, ankylosing spondylitis, following prosthetic valve surgery, or myxomatous degeneration of the valve) or by aortic root disease. Examples of aortic root disease causing chronic AR include association with systolic hypertension, syphilitic aortitis, cystic medial necrosis of the aorta, ankylosing spondylitis, rheumatoid arthritis, Reiter's disease, systemic lupus erythematosus, Ehlers-Danlos syndrome, and pseudoxanthoma elasticum. Mild or moderate AR was diagnosed by Doppler echocardiography in 9 of 29 patients (31 %) with hypertrophic cardiomyopathy [89]. The prevalence of AR increases with age [90].

Of 450 patients, mean age 82 years, AR was diagnosed by pulsed Doppler echocardiography in 39 of 114 men (34 %) and in 92 of 336 women (27 %) [90]. Severe or moderate AR was diagnosed in 74 of 450 patients (16 %). Mild AR was diagnosed in 57 of 450 patients (13 %). In 924 men, mean age 80 years, and 1,881 women, mean age 82 years, valvular AR was diagnosed by pulsed Doppler echocardiography in 282 of 924 men (31 %) and 542 of 1,881 women (29 %) [21].

57.2.2 Pathophysiology

The primary determinants of AR volume are the regurgitant orifice area, the transvalvular pressure gradient, and the duration of diastole [91]. Chronic AR increases LV end-diastolic volume. The largest LV end-diastolic volumes are seen in chronic severe AR. LV stroke volume increases to maintain forward stroke volume. The increased preload causes increase in LV diastolic stress and addition of sarcomeres in series. This increases the ratio of LV chamber size to wall thickness. This pattern of LV hypertrophy is called eccentric LV hypertrophy.

Primary myocardial abnormalities or ischemia due to coexistent CAD depresses the contractile state. LV diastolic compliance decreases, LV end-systolic volume increases, LV end-diastolic pressure rises, left atrial pressure increases, and pulmonary venous hypertension results. When the LV end-diastolic radius-to-wall

thickness ratio rises, LV systolic wall stress increases abnormally because of the preload and afterload mismatch [92]. Additional stress decreases the LV ejection fraction response to exercise [93]. Eventually, the LV ejection fraction, forward stroke volume, and effective cardiac output are decreased at rest. An abnormal resting LV ejection fraction occurred in 8 of 25 elderly patients (32 %) with CHF associated with chronic severe AR [94].

In patients with acute severe AR, the LV cannot adapt to the increased volume overload. Forward stroke volume falls, LV end-diastolic pressure increases rapidly to high levels [95], and pulmonary hypertension and pulmonary edema result. The rapid rise of LV end-diastolic pressure to exceed left atrial pressure in early diastole causes premature closure of the mitral valve [96]. This prevents backward transmission of elevated LV end-diastolic pressure to the pulmonary venous bed.

57.2.3 Symptoms

Patients with acute AR develop symptoms due to sudden onset of CHF, with marked dyspnea and weakness. Patients with chronic AR may remain asymptomatic for many years. Mild dyspnea on exertion and palpitations, especially on lying down, may occur. Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and edema are common clinical symptoms when LV failure occurs. Syncope is rare. Angina occurs less often in patients with AR than in patients with AS and may be due to coexistent CAD. However, nocturnal angina pectoris, often accompanied by flushing, diaphoresis, and palpitations, may develop when the heart rate slows and the arterial diastolic pressure falls to very low levels. Most patients with severe AR and those who do not undergo surgery die within 2 years after CHF develops [97].

57.2.4 Signs

The AR murmur is a high-pitched blowing diastolic murmur that begins immediately after A_2. The diastolic murmur is best heard along the left sternal border in the third and fourth intercostal spaces when AR is due to valvular disease. The murmur is best heard along the right sternal border when AR is due to dilatation of the ascending aorta. The diastolic murmur is best heard with the diaphragm of the stethoscope with the person sitting up, leaning forward, and holding the breath in deep expiration. The severity of AR correlates with duration of the diastolic murmur, not with intensity of the murmur. Table 57.6 shows that an AR murmur was heard in 95 % of 74 elderly patients with severe or moderate AR diagnosed by pulsed Doppler echocardiography, in 61 % of 57 elderly patients with mild AR, and in 3 % of 319 elderly patients with no AR [90].

In patients with chronic severe AR, the LV apical impulse is diffuse, hyperdynamic, and displaced laterally and inferiorly. A rumbling diastolic murmur (Austin

Table 57.6 Correlation of aortic regurgitation murmur with severity of aortic regurgitation (AR) in chronic aortic regurgitation

	AR murmur (%)
Severe or moderate AR ($n=74$)	95
Mild AR ($n=57$)	61
No AR ($n=319$)	3

Source: Adapted from Ref. [90]

Flint) may be heard at the apex, with its intensity decreased by inhalation of amyl nitrite. A short basal systolic ejection murmur is sometimes heard. A palpable LV rapid filling wave and an audible S_3 at the apex are usually found. Physical findings due to a large LV stroke volume and a rapid diastolic runoff in patients with severe AR include a wide pulse pressure with an increased systolic arterial pressure and an abnormally low diastolic arterial pressure, an arterial pulse that abruptly rises and collapses, a bisferiens pulse, bobbing of the head with each heartbeat, booming systolic and diastolic sounds heard over the femoral artery, capillary pulsations, and systolic and diastolic murmurs heard over the femoral artery when compressing it proximally and distally.

57.2.5 Electrocardiography and Chest Roentgenography

The electrocardiogram may initially be normal in patients with acute severe AR. Using various electrocardiographic criteria in 30 necropsy patients with chronic severe AR, the prevalence of LV hypertrophy varied from 30 % ($RV_6 > RV_5$) to 90 % (total 12-lead QRS voltage >175 mm) [98]. The PR interval was prolonged in 28 % of patients, and the QRS duration was ≥0.12 s in 20 % of patients.

The chest x-ray in patients with acute severe AR may show a normal heart size and pulmonary edema. The chest x-ray in patients with chronic severe AR usually shows a dilated LV, with elongation of the apex inferiorly and posteriorly and a dilated aorta. Aneurysmal dilatation of the aorta suggests aortic root disease is causing AR. Linear calcifications in the wall of the ascending aorta are seen in syphilitic AR and in degenerative disease.

57.2.6 Echocardiography and Doppler Echocardiography

Two-dimensional and Doppler echocardiography are useful in diagnosing AR. Two-dimensional echocardiography can provide information showing the etiology of the AR and measurements of LV function. Eccentric LV hypertrophy is diagnosed by echocardiography if the LV mass index is increased with a relative wall thickness <0.45 [99, 100]. Echocardiographic measurements predicting an unfavorable response to AVR in patients with chronic AR include a LV end-systolic dimension >55 mm [94], a LV shortening fraction <25 % [101], a LV diastolic radius-to-wall

thickness ratio >3.8 [95], a LV end-diastolic dimension index >38 mm/m^2 [102], and a LV ventricular end-systolic dimension index >26 mm/m^2 [102].

Continuous-wave Doppler echocardiography is very useful in diagnosing and quantitating AR [103]. AR is best assessed by color flow Doppler imaging [104].

57.2.7 Natural History

Patients with acute AR should have immediate AVR because death may occur within hours to days. In one study of patients with hemodynamically significant chronic AR treated medically, 75 % were alive at 5 years after diagnosis [105]. Of patients with moderate-to-severe chronic AR, 50 % were alive at 10 years after diagnosis [105, 106]. The 10-year survival rate for patients with mild-to-moderate chronic AR was 85–95 % [105, 106]. In 14 patients with chronic severe AR who did not have surgery, 13 (93 %) died within 2 years of developing CHF [97]. The mean survival time after the onset of angina is 5 years [107].

During 8-year follow-up of 104 asymptomatic patients with chronic severe AR and normal LV ejection fraction, 2 patients (2 %) died suddenly, and 23 patients (22 %) had AVR [108]. Of 104 patients, 19 (18 %) had AVR because of cardiac symptoms, and 4 patients (4 %) had AVR because of development of LV systolic dysfunction in the absence of cardiac symptoms. Multivariate analysis showed that age, initial end-systolic dimension, and rate of change in end-systolic dimension and resting LV ejection fraction during serial studies predicted outcome.

At 24-month follow-up (range 7–55 months) of 17 patients, mean age 83 years, with CHF associated with unoperated severe chronic AR and a normal LV ejection fraction, 15 patients (88 %) were dead [94]. At 15-month follow-up (range 8–21 months) of 8 patients, mean age 85 years, with CHF associated with unoperated severe chronic AR and an abnormal LV ejection fraction, all 8 patients (100 %) were dead [94]. The 15-year mortality for AR in 1,156 patients was 74 %, and it is increased 1.94 times in patients with moderate or greater pulmonary arterial systolic hypertension [109].

57.2.8 Medical and Surgical Management

Asymptomatic patients with mild or moderate AR do not need therapy. Prophylactic antibiotics are not recommended to prevent bacterial endocarditis in patients with AR [53]. Echocardiographic evaluation of LV end-systolic dimension should be performed yearly if the measurement is less than 50 mm but every 3–6 months if the LV end-systolic dimension is 50–54 mm. AVR should also be considered when the LV ejection fraction approaches 50 % before the decompensated state [91].

Patients with asymptomatic, chronic severe AR have been treated with hydralazine [110], nifedipine [111], or angiotensin-converting enzyme inhibitors [112] to

decrease LV volume overload. Vasodilator therapy is indicated for chronic therapy in patients with severe AR who have symptoms or abnormal LV ejection fraction when AVR is not recommended because of additional cardiac or noncardiac factors (Class I indication) and for short-term therapy to improve the hemodynamic profile of patients with severe CHF symptoms and severe LV systolic dysfunction before proceeding with AVR (Class II_a indication) [52]. Long-term vasodilator therapy with enalapril or nifedipine did not reduce or delay the need for AVR in patients with asymptomatic severe AR and normal LV ejection fraction [113].

Infections should be treated promptly. Hypertension increases regurgitant flow and should be treated. Drugs that depress LV function should not be used. Arrhythmias should be treated. Patients with AR due to syphilitic aortitis should receive a course of penicillin therapy. Prophylactic resection should be considered in patients with Marfan's syndrome when the aortic root diameter exceeds 55 mm [114]. Bacterial endocarditis should be treated with intravenous antibiotics. Indications for AVR in patients with AR due to bacterial endocarditis are CHF, uncontrolled infection, myocardial or valvular ring abscess, prosthetic valve dysfunction or dehiscence, and multiple embolic episodes [115]. CHF should be treated with sodium restriction, diuretics, digoxin if the LV ejection fraction is abnormal, vasodilator therapy, and AVR. Angina should be treated with nitrates.

Patients with acute severe AR should undergo AVR immediately. Patients with chronic severe AR should have AVR if they develop symptoms of CHF, angina, or syncope [52, 108]. AVR should also be performed in asymptomatic patients with chronic severe AR if their resting LV ejection fraction is ≤50 % [52, 108]. Table 57.7 shows three Class I and one Class II_a ACC/AHA indications for AVR in patients with chronic severe AR [56]. Class I indications for AVR include symptoms with abnormal or normal LV ejection fraction, no symptoms but a resting LV ejection fraction ≤50 %, and asymptomatic patients undergoing CABGS or surgery on the aorta or other heart valves [52]. The Class II_a indication for AVR is asymptomatic patients with severe AR with a LV ejection fraction >50 % but a LV end-diastolic dimension >75 mm or a LV end-systolic dimension >55 mm [52].

Elderly patients undergoing AVR for severe AR have an excellent postoperative survival if the preoperative LV ejection fraction is normal [116, 117]. If LV systolic dysfunction was present for less than a year, patients also did well postoperatively.

Table 57.7 American College of Cardiology/American Heart Association Class I indications for aortic valve replacement in persons with chronic severe aortic regurgitation (AR)

1. Symptomatic patients with severe AR and normal or abnormal left ventricular (LV) ejection fraction
2. Asymptomatic patients with severe AR and LV ejection fraction ≤50 % at rest
3. Patients with severe AR undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves
4. Asymptomatic patients with severe AR with LV ejection fraction >50 % but a LV end-diastolic dimension >75 mm or a LV end-systolic dimension >55 mm (Class II_a indication)

Source: Modified from Ref. [52]

If the patient with severe AR has an abnormal LV ejection fraction and impaired exercise tolerance and/or the presence of LV systolic dysfunction for longer than a year, postoperative survival is poor [116, 117]. However, for the patient with AR and severe LV dysfunction, AVR is the preferred treatment and can be performed with acceptable risk and late survival [118]. After AVR, women exhibit an excess of late mortality, suggesting that surgical correction of severe chronic AR should be considered at an earlier stage in women [119].

Operative mortality for AVR in patients with severe AR is similar to that in patients with AVR for AS. Mortality rate is slightly increased in patients with infective endocarditis and in patients needing replacement of the ascending aorta plus AVR.

Of 450 patients with severe AR, 273 (61 %) had a LV ejection fraction ≥50 %, 134 (30 %) had a LV ejection fraction of 35–50 %, and 43 patients (10 %) had a LV ejection fraction <35 % [120]. Operative mortality was 3.7 % for patients with normal LV ejection fraction, 6.7 % for patients with LV ejection fraction of 35–50 %, and 14 % for patients with LV ejection fraction <35 % [120]. At 10-year follow-up, survival rates were 70 % for patients with normal LV ejection fraction, 56 % for patients with LV ejection fraction of 35–50 %, and 41 % for patients with LV ejection fraction <35 % [120].

As in elderly patients with AS, the bioprosthesis is preferable to the mechanical prosthetic valve for AVR in elderly patients with severe AR [62, 63]. Patients with porcine bioprostheses may be treated with antiplatelet therapy alone unless they have AF, abnormal LV ejection fraction, previous thromboembolism, or a hypercoagulable state [52].

AVR was performed in 38 patients with severe AR and normalized LV chamber size and mass in two-thirds of patients undergoing surgery [121]. At 9-month follow-up after AVR, 58 % of patients had normal LV end-diastolic dimension, and 50 % of patients had normal LV mass. At 18–56 months postoperatively, 66 % of patients had normal LV end-diastolic dimension and 68 % of patients had normal LV mass. The LV end-diastolic dimension normalized in 86 % of patients with a preoperative LV end-systolic dimension ≤55 mm. The preoperative LV end-systolic dimension was >55 mm in 81 % of patients with postoperative persistent LV dilatation [121].

In 56 patients undergoing AVR for chronic severe AR, the best predictor of LV remodeling and of outcomes at 3 years was a preoperative stroke volume of ≥97 ml [122]. In 171 patients undergoing AVR for severe chronic AR, preoperative indexed LV end-systolic and end-diastolic dimensions were independent predictors of restored LV systolic function [123]. Of 690 patients, mean age 81 years, with severe AS treated with TAVI, 119 patients (17.2 %) developed ≥2+ AR [124]. In this study, ≥2+ AR was an independent predictor of inhospital death with an adjusted odds ratio of 2.4 [124].

Moderate or severe AR was present in 11.7 % after TAVI in 12,926 patients (16.0 % with the CoreValve and 9.1 % with the Edwards valve) [125]. Moderate or severe AR after TAVI increased mortality 2.95 times at 30 days and 2.27 times at 1-year follow-up [125]. Aortic valve repair is currently considered an option to treat the regurgitant AR after TAVR [126]. Data and experience with TAVI in the treatment of severe native AR are limited [127].

57.3 Concluding Remarks

In conclusion, patients with AS have an increased prevalence of coronary risk factors, CAD, and other atherosclerotic vascular diseases. Angina, syncope or near syncope, and CHF are the three classic manifestations of severe AS. Doppler echocardiography is used to diagnose the severity of AS and AR. Indications for AVR, use of warfarin after AVR in patients with mechanical prostheses, and use of aspirin or warfarin after AVR in patients with bioprostheses are discussed. TAVI should be performed in inoperable patients with symptomatic severe AS. TAVI has been shown to improve survival and quality of life compared with medical therapy.

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Chapter 58
Induction of Valvular Heart Disease by Pharmacological Interventions

Steven Droogmans and Bernard Cosyns

Abstract Drug-induced valvular heart disease (DIVHD) is a very distinct valvulopathy whereby drug-related stimulation of 5-HT_{2B} fibroblast receptors leads to a disturbed valvular architecture with thickening, restrictive motion and finally important valvular dysfunction. This chapter describes its history; diagnostic, histopathological and echocardiographical features; causal drugs and the role of drug dose; treatment duration; and risk factors. Although several drugs have been associated with clinical relevant DIVHD, preclinical testing remains challenging. Hereby, we discuss that 5-HT_{2B} receptor screening and in vivo testing are of the upmost importance.

Keywords Amphetamines • Anorexigens • Drug-induced valvulopathy • Ergot-derived dopamine agonists • Echocardiography • Serotonin

Abbreviations

5-HIAA	5-Hydroxyindole acetic acid
5-HT	5-Hydroxytryptamine serotonin
AR	Aortic regurgitation
FDA	Food and Drug Administration
FDA criteria	MR of moderate or greater severity (≥2/4) or AR mild or greater severity (≥1/4)
Fen-Phen	Fenfluramine/phentermine
GAG	Glycosaminoglycans
MAO(A)	Monoamine oxidase (A)
mCCP	*m*-Chlorophenylpiperazine

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MDMA	3,4-Methylenedioxymethamphetamine (Ecstasy)
MR	Mitral regurgitation
RR	Relative risk
SERT	Serotonin transporter
SSRi	Serotonin-selective reuptake inhibitor
VHD	Valvular heart disease

58.1 Introduction

The possibility that the intake of drugs might be responsible for the onset of valvular heart disease (VHD) was first suggested in the mid-1960s for ergot alkaloids used for migraine prophylaxis – initially methysergide and then ergotamine. In 1997–1998, drug-related VHD was reported for two appetite suppressants – fenfluramine and dexfenfluramine – that had previously been recognized as being associated with the occurrence of pulmonary arterial hypertension. These findings led to the withdrawal from the market of these two drugs. More recently, similar findings of drug-related VHD with ergot-derived dopamine agonists were reported in patients treated with pergolide for Parkinson's disease and cabergoline for hyperprolactinaemic disorders.

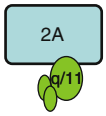
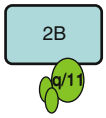
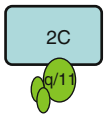
Subsequently, similar drug-related VHD was reported with prolonged use of the recreational drug Ecstasy (3,4-methylenedioxymethamphetamine; MDMA) and with a drug indicated for diabetes in overweight patients, benfluorex. The issue has received increasing attention as more new associations of VHD with several drugs have been reported. Although some of these drugs have subsequently been withdrawn from the market, several cases of patients requiring valve surgery late after the cessation of therapy have been reported, emphasizing the long-term implications of drug-induced VHD [1, 2].

58.2 Pathophysiology of Drug-Induced Valvular Heart Disease

Tryptophan, an essential amino acid, is the precursor for the synthesis of 5-HT. Serotonin synthesis depends on the enzyme tryptophan hydroxylase, a rate-limiting step in the cascade, which transfers a hydroxyl group to the benzyl ring of tryptophan. Subsequent decarboxylation results in the formation of 5-HT. Breakdown of 5-HT occurs through the actions of monoamine oxidase A (MAOA) to form the metabolite 5-hydroxyindole acetic acid (5-HIAA). Over 95 % of 5-HT in the body is synthesized in the enterochromaffin cells of the intestine, stored via serotonin transporter (SERT) into the platelets and transported to the periphery [3].

Drugs that target 5-HT receptor-related mechanisms have been explored extensively for pharmaceutical development, especially with regard to antidepressants and appetite suppressants [4]. However, some pharmacological agents acting

Table 58.1 Types and distribution/function of 5-HT receptors

5-HT2 subtype	Distribution/function	
	CNS	Periphery
	*Drug-induced hallucinogenic responses*	Liver, renal mesangium mitogenesis vasoactive (pulmonary/coronary vessels)
	Anxiety, behaviour, locomotion	Adipocyte differentiation, platelet aggregation, enteric neurotransmitter
	Motor behaviour, anxiety, cerebrovascular tone	*Drug-induced valvulopathy*
		Pulmonary vascular remodelling/ hypertension
		Hepatocellular mitogen
	*Appetite suppression*	Limited expression
	Locomotion, anxiety DA output, stress response	

through 5-HT receptor-related pathways have been associated with a number of significant adverse effects, including pulmonary hypertension, cardiac arrhythmias and cardiac valve abnormalities [4]. Table 58.1 summarizes selected 5-HT receptors, their respective role and related size effects.

In 2000, two research groups independently suggested that the 5-HT_{2B} receptor is the key pathway through which agonistic drugs can cause valvulopathy by inducing mitogenesis in cultured interstitial cells from human cardiac valves [5, 6]. This receptor is plentiful in human cardiac valves and is essential for normal cardiac development [7–9]. The valvulopathic effect is not only dependent on the 5-HT_{2B} activity of the parent drug but also on the pharmacodynamic effects of their metabolites. This makes it more difficult to predict the toxic valvular effect of new drugs that are developed. The valvular lesions are due to stimulation of myofibroblast mitogenesis via activation of 5-HT_{2B} receptors, but the interaction of norfenfluramine and ergots with other 5-HT receptor subtypes may also contribute to these changes (Table 58.2).

Activation of the 5-HT_{2B} receptor is a G-protein-mediated process. Once the receptor is activated, it leads to dissociation of the G-protein, whose subunits (Gq/11 and βγ) can then activate phospholipase Cβ, protein kinase C and extracellular signal-regulated protein kinases 1 and 2, a process that engages mitogenic pathways. G-protein activation may also enhance the activity of transforming growth factor-β (TGFβ), augmenting 5-HT_{2B}-stimulated mitogenesis [10]. The upregulation of TGFβ has been shown to lead to increased extracellular matrix, including collagen and glycosaminoglycans in human aortic valve interstitial cells, potentially playing a significant role in increasing fibrosis and subsequent valvulopathy [11]. The final common pathway for mitogenesis via 5-HT_{2B} receptor stimulation probably involves the phosphorylation of the retinoblastoma protein. Excessive cell division and proliferation leads to an overgrowth valvulopathy and subsequent dysfunction as normally quiescent cells become activated.

Table 58.2 Overview of serotoninergic drugs associated with valvular heart disease (with the exception of lorcaserin)

Drug	Chemical class	Clinical use	Interaction with 5-HT_{2B} receptor	Affected valves	Remarks
Ergotamine	Ergot alkaloid	Migraine prophylaxis	Partial agonist, high affinity	AV, MV and TV	No data on dose dependency or reversibility
Methysergide	Synthetic ergot alkaloid	Migraine prophylaxis	Partial agonist, high affinity	AV and MV	No data on dose dependency or reversibility
Fenfluramine	Fenfluramine	Anorectic drug	Metabolite norfenfluramine, potent agonist and high affinity	AV, MV and TV	Dose-dependent relation, no reversibility present
Pergolide	Ergoline-derived dopamine agonist	Parkinson's disease	Non-selective agonist, high affinity	AV, MV and TV	Dose-dependent relation, reversibility in 50 %
Cabergoline	Ergoline-derived dopamine agonist	Parkinson's disease, hyperprolactinaemia	Non-selective agonist, high affinity	AV, MV and TV Light TV (low dose – hyperprolactinaemia)	Dose-dependent relation
Bromocriptine	Ergoline-derived dopamine agonist	Parkinson's disease, pituitary tumour, hyperprolactinaemia	Weak partial agonist	Subclinical mild TR and MR	Weak evidence
MDMA ('Ecstasy')	Amphetamine	Recreational drug, post-traumatic stress	Agonist with high affinity	AV and MV (one study)	Strong in vivo, but weaker clinical evidence
Benfluorex	Amphetamine	Anorectic and hypolipidaemic agent	Metabolite norfenfluramine, potent agonist and high affinity	AV, MV and TV	Dose-dependent relation
Lorcaserin	Novel class	Anorectic	Full agonist, low affinity	Not reported	New drug, no evidence of DIVHD

AV aortic valve, *MV* mitral valve, *TV* tricuspid valve

58.3 Morphological and Echocardiographic Characteristics

58.3.1 Histopathological Features

Drug-induced VHD shows clinical, histopathological and pathophysiological similarities with the carcinoid syndrome [5, 7]. The latter occurs in only 10 % of patients with carcinoid tumours when hormonally vasoactive tumour products exceeding the hepatic capacity for degradation (in case of hepatic metastasis) reach the systemic venous circulation. Serotonin is a key element that induces right-sided VHD in 40 % of these patients [12–14]. The presence of left heart disease is less frequent as serotonin is normally degraded by monoamine oxidase in the lungs (except in pulmonary metastasis or patent foramen ovale) [7, 15]. In contrast, drug-induced VHD affects even more importantly the aortic and mitral valves [16].

Superficial plaque-like thickening of the valvular leaflets and subvalvular apparatus composed of fibromyxoid tissue can be observed. Usually, no signs of calcification are present. Macroscopically, valves and tendinous cords are thickened, shortened and may have a pearly white appearance [17, 18].

58.3.2 Echocardiographical Characteristics

Echocardiography is the key examination for screening and grading iatrogenic valve disease. The echocardiographic features are common for all drug-induced VHDs. Variable degrees of valve regurgitation are observed. Drug-induced valve disease is generally not responsible for severe valve stenosis. It can be difficult to attribute a causal relationship between a specific drug and valve damage because pretreatment echocardiographic data are not available in the majority of cases. Moreover, mere detection of regurgitation does not provide information on the aetiology.

Actually, diagnosis using two-dimensional echocardiography is based, above all, on studying the texture and motion of the valves and analysing the subvalvular apparatus for mitral and tricuspid VHD. Typically, one can generally see mild or moderate valve thickening in the absence of calcification or marked commissural fusion (in contrast with rheumatic valve disease). Restricted valve motion, which is responsible for the regurgitation, is the most characteristic feature of drug-induced valve disease.

In mitral valve regurgitation, the restriction generally affects both mitral leaflets but often predominates at the posterior leaflet. Leaflet thickening is often minimal but is generally associated with unequivocal thickening and shortening of the chordae tendineae (Chap. 55).

In aortic regurgitation, valve thickening is often mild (and may not be present). Variable degrees of leaflet retraction are observed, responsible for malcoaptation and regurgitation during diastole. Using two-dimensional echocardiography, a small central triangular valve hiatus during diastole is observed in the short-axis view,

sometimes associated with a subtle 'domelike' aspect of the aortic valve during systole. Aortic regurgitation visualized with colour Doppler is generally central (Chap. 57).

Tricuspid and pulmonary drug-induced VHD is less common; echocardiographic findings seem similar to those observed in mitral and aortic damage.

In younger patients (<50 years), the background prevalence of aortic regurgitation (AR) and mitral regurgitation (MR) in normal subjects is low or even absent [19]. Therefore, the FDA applied criteria for the diagnosis of drug-induced VHD. These were at least light to moderate AR and/or moderate to severe MR [20].

However, in older patients, e.g. with Parkinson's disease, underlying valvular sclerosis and calcification might be present with AR or MR. For this reason, the FDA criteria cannot be used in this subgroup of patients. A scoring system had been used [18] in which restrictive tricuspid valve leaflet involvement was considered more important in defining ergot-like abnormalities compared to restrictive mitral and aortic valve motion (score 1–4: from very likely to unlikely):

1. Proven restrictive VHD (confirmed with histopathology and/or regression after interruption of ergot treatment)
2. Important restrictive valve disease (regurgitation >2/4) or restrictive tricuspid disease even if regurgitation less than 2/4
3. Mild to moderate (regurgitation <2/4) restrictive valve disease
4. No restrictive valve dysfunction

Another potential approach to quantify the restrictive tricuspid and/or mitral valve motion is to determine the tenting area and tethering distance as described in ischaemic heart disease [21].

Before the diagnosis of drug-induced VHD can be made, other causes of restrictive VHD need to be excluded: remodelling of the left ventricle (i.e. ischaemic MR), rheumatic heart and other interstitial diseases, carcinoid syndrome, cardiac mass (e.g. atrial myxoma), infectious endocarditis (i.e. intravenous drug use) and congenital abnormalities. In rheumatic heart disease, valvular damage and thickening are usually more pronounced and, to a certain extent, commissural fusion of valvular leaflets occurs leading to valvular stenosis, which is not a typical feature of drug-induced VHD. As usual, blood pressure should be a part of the echocardiographic examination since it might influence the severity of MR and AR (Chap. 54).

58.4 Drugs Associated with Valvular Heart Disease

58.4.1 Ergotamine and Methysergide

Ergotamine and methysergide were the first drugs described to be associated with VHD since 1966 [22]. Until the early nineties, only sporadic cases were reported [23–25]. With the routine use of two-dimensional echocardiography and later on second harmonic imaging, valvular morphology and function were easier to

evaluate. This led to a better echocardiographic and pathological correlation and an increased awareness and reports of toxic valvulopathy [26]. Ergotamine and methysergide are still used in some countries for the prophylactic treatment of vascular headache. Before 1990, toxic valvulopathy remained mostly undiscovered until symptoms such as fatigue, dyspnoea, chest pain, palpitations and a new heart murmur become apparent [27]. At that point, valvular damage was already pronounced so that valvular replacement seemed the only therapeutic option. There are no reports of case–control series of ergotamine or methysergide-induced VHD, and no dose-dependent relation has been described.

58.4.2 Fenfluramine/Phentermine and Dexfenfluramine

In 1997, Connolly reported a series of case reports of young women that developed VHD several months after treatment with the anorectic agents *(dex)fenfluramine* and the combination *Fen-Phen* [17]. Echocardiographically and histopathologically, these valves showed a striking resemblance to carcinoid valvular heart disease, which occurs in about 10 % of carcinoid syndrome. Based on this study and other case reports, the FDA reported that toxic valvulopathy was identified in 113 young women (mean age 44 years) that took slimming drugs and that valve replacement was needed in 24 % of patients. These findings led to the rapid withdrawal of fenfluramine from the market in 1997 [28]. Later on, several retrospective case–control and follow-up studies were published confirming the association between (dex)fenfluramine use and VHD [29–34].

A subsequent meta-analysis conducted by Sachdev et al. in 2002 showed that (dex)fenfluramine-induced VHD was less common than initially reported but still present in one out of eight patients treated for more than 90 days [35]. In another meta-analysis by Hopkins and colleagues, a much higher relative risk for aortic (RR 19,6) and mitral (RR 5,9) valvulopathy after (dex)fenfluramine exposure was found compared to previous reports when they corrected for several bias factors [36]. The same group recently published the largest single centre observational study in 5,743 patients that had taken fenfluramine before. In this study, the prevalence of FDA criteria-positive AR or MR was 19.6 % in women and 11.8 % in men [1]. Valve surgery was performed on 38 patients (0.66 %), 25 (0.44 %) with clear evidence of fenfluramine-related aetiology.

58.4.3 Pergolide and Cabergoline

In 2002, Pritchett reported the association between *pergolide* and VHD [37] for the first time. This relation was confirmed in 2004 by Van Camp and colleagues in a cross-sectional case–control study of 78 patients with Parkinson's disease treated with high-dose pergolide [18]. Restrictive VHD with MR, AR and tricuspid

regurgitation was found in 33 % of patients treated with pergolide. Besides increased prevalence of valvular regurgitation, an increase in mitral tenting areas and distances was also found in the pergolide group compared to controls. Pergolide and also *cabergoline* are ergot-derived dopamine agonists with an ergolinic structure and 5-HT_{2B} agonist activity.

Recent population-based studies have more clearly defined the relative risk associated with the use of different agonists in patients with Parkinson's disease. From these studies, a clearly increased risk for the development of toxic valvulopathy with pergolide and cabergoline use [18, 38–43] was found. In a recent review, Antonini calculated from these studies a prevalence of 22 and 34 % of moderate to severe regurgitation in at least one heart valve in patients with Parkinson's disease treated with pergolide and cabergoline, respectively [44]. All these studies were conducted in patients from Europe or North America.

Similar to these studies, a Japanese study of Yamamoto et al. reported an increased risk of valvular regurgitation in patients taking cabergoline [40]. However, this Japanese and a Korean study were excluded from this analysis because the average daily pergolide dose was 1.40 and 1.13 mg, respectively, compared to 3.0 mg in the other studies [40, 45]. The low dose of pergolide used in Asian patients could explain why no increased rates of regurgitation were found. A recent meta-analysis and observational study by Corvol et al. found a similar prevalence of 22 % of moderate to severe valvulopathy in pergolide-treated patients compared to 7.1 % in the control group [46]. In another meta-analysis by Simonis et al. including seven cross-sectional studies with 477 patients treated with ergot-derived dopamine agonists pergolide or cabergoline, a prevalence of 26 % of moderate to severe VHD was found compared to 10 % in non-ergot-derived dopamine agonists and 10 % in controls [47].

Cabergoline is also used for the treatment of prolactinoma. In contrast to Parkinson's disease, this population is younger with a more female predominance, and most importantly, the cumulative dose is about ten times less. Until now, seven cross-sectional studies have been published of which six did not find an association with clinically relevant regurgitation, as reported by Kars et al. [48]. However, one study shows a significant increase in moderate tricuspid regurgitation, and two studies show a mild increase in tricuspid regurgitation [49–51]. The clinical relevance of these findings is therefore still uncertain.

58.4.4 Bromocriptine

One recent cross-sectional case–control study from Singapore found an increased risk of valvular regurgitation in Parkinson's patients treated with *bromocriptine* compared to controls [52]. However, another study in Korea did not find increased frequencies of valvular regurgitation in patients treated with bromocriptine [45]. This might be due to a lower cumulative dose in the latter study. Bromocriptine is a weak partial 5-HT_{2B} receptor agonist and was not thought to be associated with toxic valvulopathy. More studies are needed to confirm this possible relation between bromocriptine and toxic valvulopathy.

58.4.5 3,4-Methylenedioxymethamphetamine (MDMA, 'Ecstasy')

Besides the above-mentioned drugs, *MDMA* also is a potent 5-HT_{2B} receptor agonist and induces fenfluramine-like proliferations of human valvular interstitial cells in vitro [53]. Until now, only one cross-sectional case–control study has been published, suggesting an association between MDMA abuse and toxic valvulopathy [54]. An increased incidence of mild AR and MR was found in patients younger than 30 years old taking MDMA on a regular and recreational basis compared to age- and sex-matched controls. MDMA is not only used for recreational purposes but is currently under investigation for the treatment of post-traumatic stress syndrome. By consequence, these findings may have important health implications but need to be confirmed by larger trials.

58.4.6 Benfluorex

Benfluorex is the most recent drug found to be involved in inducing VHD. This drug is structurally related to amphetamines and is partially metabolized to norfenfluramine. It was initially indicated in patients with hypertriglyceridaemia or for diabetes mellitus in overweight patients in combination with dietetic recommendations. In France, following reassessment of the benefit–risk balance in patients with hypertriglyceridaemia, the Medicines Drug Agency decided in April 2007 to limit benfluorex use to its other indication, diabetes mellitus in overweight patients (BMI $\geq$25 kg/m^2) in association with an appropriate diet. Benfluorex had also been widely prescribed in France as an appetite suppressant.

Two studies have compared patients selected as having 'unexplained' mitral regurgitation with age- and sex-matched patients who had mitral regurgitation with aetiological or functional explanations [55]; the latter patients were used as the control group. In the first study, performed by Frachon et al. [55], 27 patients with unexplained mitral regurgitation were compared with 54 controls. The use of benfluorex was documented in 19 patients in the first group and in three in the second group, with an odds ratio of 17.1 (3.5–83) after adjustment for BMI, diabetes and dexfenfluramine intake.

In a second study confirming these results, 22 patients with unexplained mitral regurgitation were compared with 22 of 156 patients who underwent surgery for dystrophic MR, matched for age, body weight and diabetes [56]. Eight of the 22 patients (36.4 %) in the first group but only one (4.5 %) in the group with dystrophic valvulopathy had a history of benfluorex use. The total duration of benfluorex treatment associated with unexplained MR was 63 (12–175) months; the duration of benfluorex treatment was 56 months at the time of valvular disease diagnosis.

More recently, 40 cases identified retrospectively in the cardiology departments in eight hospitals in France have been reported and analysed [57]. Owing to hospital

recruitment of symptomatic patients, the observations collected represent the most severe presentation of these VHDs. The cases analysed in this multicentre registry had quite a homogeneous presentation: patients were middle aged and mainly women, with obesity and/or diabetes mellitus and exposure to benfluorex for a mean duration of 72 ± 53 months. Most patients had symptomatic heart failure. Multiple fibrotic valve diseases were present in more than 75 % of patients, displaying predominantly an association of aortic and mitral regurgitations (72.5 %) and leading to combined valve surgery in 11 cases (27.5 %). These morphological and histological features (valvular tissue thickening and an abundant extracellular matrix of glycosaminoglycans and collagen with proliferation of myofibroblasts and smooth muscle cells) were similar to those previously reported after exposure to other appetite suppressants and ergot alkaloids.

A cohort study using two large French national databases, with patients aged 40–69 years with reimbursements for antidiabetic drugs in 2006, was recently analysed [58]. The risk of hospitalization for valvular regurgitation in the following 2 years was found to be 2.5 times higher when taking benfluorex for MR, 4.4 times higher for AR and 3.9 times higher for valvular replacement surgery. The estimated number of hospitalizations for a diagnosis of VHD was found to be 5 per 10,000 patient-years. The re-evaluation of the benefit–risk balance of benfluorex in the light of these data led to the suspension of the marketing authorization of the drug in France and then in Europe, in November and December 2009, respectively [58].

More recently, the randomized prospective REGULATE trial [59], whose results were published in 2012, included 847 patients with type II diabetes (mean age, 59 years) randomized to 1 year of treatment with a combination of either benfluorex–sulphonylurea ($n = 423$) or pioglitazone–sulphonylurea ($n = 424$). Emergence (appearance or deterioration) of valvular regurgitation was observed more frequently (27 % vs 11 %; $P < 0.0001$) in the group treated with benfluorex (OR 2.97 [1.91–4.63]).

Last, an echocardiography-based multicentre study [60] compared the frequency of left heart valve regurgitation in diabetic patients exposed to benfluorex for at least 3 months and in diabetic controls never exposed to the drug: 293 patients and 293 controls were matched for age, gender, body mass index, smoking, dyslipidaemia, hypertension and coronary artery disease. The frequency and relative risk (OR) of mild or more severe left heart valve regurgitation were significantly increased in benfluorex-exposed patients compared with controls: 31.0 % vs 12.9 % (OR 3.55 [2.03–6.21]) for aortic and/or mitral regurgitation, 19.8 % vs 4.7 % (OR 5.29 [2.46–11.4]) for aortic regurgitation, and 19.4 % vs 9.6 % (OR 2.38 [1.27–4.45]) for mitral regurgitation. This study, therefore, confirmed that the use of benfluorex is associated with a significant increase in the frequency of left heart valve regurgitation in diabetic patients. Estimates of the number of benfluorex-associated deaths in France have been proposed as probably being higher than 500 [61] and were more recently calculated to be around 1,300 due to VHD in these patients; this number is regarded as possibly underestimated [62].

58.4.7 Lorcaserin

New drugs such as lorcaserin have been released to treat obesity and even approved by the FDA. Recent publications have provided reassuring data regarding the absence of VHD in the group of patients treated by this drug [63]. Interestingly, the methodology used was the FDA valvulopathy criteria that may be inappropriate as mentioned above. On the other hand, a recent paper is dealing with the unacceptable risk represented by lorcaserin in treated obese patients [64]. Knowing that lorcaserin has an effect on 5-HT_{2B} receptors, even with a low affinity for 5-HT_{2B} receptors compared to 5-HT_{2C} receptor, a close follow-up of the patients receiving this drug is mandatory.

58.5 Influence of Drug Dose, Treatment Duration and Risk Factors

Besides the aetiological association, some studies also addressed the issue of dose dependency and other risk factors that could influence the progression towards toxic valvulopathy. This has mostly been studied for the anorectic agents, pergolide and cabergoline. Based on the data of these studies, such dose-dependent relation is very likely to exist.

In 1999, Li et al. examined 74 case reports received by the FDA, meeting the FDA case definition for valvulopathy [65]. They found that patients with severe aortic or mitral VHD were more likely to have taken more than 60 mg fenfluramine a day. In another study, Jollis and colleagues performed an echocardiogram study in 1,163 patients who had taken fen-phen compared to 672 controls [66]. An increased risk of aortic valvulopathy was observed in proportion to the duration of fen-phen treatment. The relative risk for aortic valvulopathy increased from 2.4 at 6 months of fen-phen treatment to 6.2 at 2 years. This was not found for the mitral valve. A smaller uncontrolled observational study (85 patients) of Lepor et al. also suggested an increased risk of combined aortic and mitral valvulopathy with fen-phen daily treatment dose (>60 mg) and duration [67]. In Hopkins' meta-analysis, appearance of new AR was strongly related to the duration of (dex)fenfluramine exposure, while this was not found for the mitral valve. In their observational study (Dahl et al.) of 5,743 patients, duration of fenfluramine use was strongly predictive for AR, MR and TR [1].

For pergolide and cabergoline, too, convincing data about such dose-dependent relationship also exist. As already mentioned above, studies that investigated relatively high dosages of pergolide (>3–5 mg/day) found an increased risk of toxic aortic, mitral and tricuspid valvulopathy, while this was not the case for studies reporting lower dosages [18, 45, 68–70]. This was also found in two recent studies, in which high daily dosages or higher cumulative dose of pergolide and cabergoline

increased the risk of valvulopathy [41, 43]. In a recent meta-analysis by Corvol et al., the risk of developing valvulopathy was significantly correlated with pergolide cumulative dose [46]. For cabergoline-induced valvulopathy also an association was found with daily dose, cumulative dose and treatment duration [40, 70]. In contrast to the anorexigens, no separate data of the aortic or mitral valve with regard to dose relationship have been reported for the dopamine agonists pergolide and cabergoline.

Finally, other factors may influence the evolution towards toxic valvulopathy. Some case reports describe the development of severe valvulopathy even at low dosages of pergolide [71–73]. Moreover, two thirds of patients do not develop valvulopathy, despite several years' exposure, suggesting that susceptibility is a key factor. Subgroups of patients may be at a higher risk of VHD. One cross-sectional study in 412 patients exposed to dexfenfluramine found that factors independently related to FDA-defined aortic valvulopathy were older age, higher diastolic blood pressure at the time of echocardiography and shorter time from drug discontinuation to echocardiogram [74]. In the study of Dahl et al., age and fenfluramine use in women were higher risk factors [1]. For the dopamine agonists, age, Parkinson's disease duration and sex seem not related to an increased risk of toxic valvulopathy [40, 46]. However, these factors were secondary end points in these studies. In a recent case–control study by Oeda et al. conducted in 223 patients with Parkinson's disease receiving pergolide or cabergoline, age above 70 years and hypertension manifestly increased the risk of valvular regurgitation (relative risk 94) [75]. These data suggest that special attention should be paid when prescribing pergolide or cabergoline in older hypertensive patients.

58.6 Natural Course of Toxic Valvulopathy

Echocardiographic follow-up studies of patients with toxic valvulopathy show that regression of VHD may occur in some patients. Hensrud et al. described in 1999 regression of VHD after 6 months in 8 of 15 subjects who had discontinued fenphen, while no progression of disease was observed [76]. Similar findings were observed in a larger study of 50 patients with previous exposure to fenfluramines [77]. In serial echocardiograms obtained 12 months apart, MR and AR improved at least by one grade in 45 and 44 % of patients, respectively. No significant progression of AR and MR was noted in 4 %.

In a large double-blind placebo-controlled trial, 914 patients were followed 1 year after dexfenfluramine exposure of 3 months [78]. Compared to the placebo group, a greater proportion of patients previously treated with dexfenfluramine had a decrease in AR of at least one grade (5.8 % of patients). There were no significant changes in MR or leaflet mobility, and no progression of valvular regurgitation was found.

In another large trial by Gardin and colleagues, 1,142 obese patients with longer anorexigen exposure (ranged from 1 to 63 months) were followed for 1 year [79].

Significant echocardiographic regression of AR was noted in 6.4 % of dexfenfluramine patients and 4.5 % of fen-phen patients compared to 1.7 % of controls. In this study, neither significant progression of VHD (0.2 %) nor changes in mitral valve regurgitation or leaflet mobility and thickness were found.

In the study by Dahl et al., follow-up echocardiograms were available in 1,020 fenfluramine users [1]. With a mean follow-up time of 30 months, most regurgitations remained unchanged, while improvement was found in one quarter and worsening in 17 % of patients. Only in this study progression occurred in some patients, while this was not reported in the other follow-up studies. Most importantly, regression might occur in up to one third of patients, even soon after 6 months.

However, in patients with end-stage renal disease due to Chinese herbs, a high incidence of fenfluramine-induced AR (52 %) has been observed even 6 years after stopping appetite suppressants [80]. In this case, the potential role for reversibility could have been altered because of long treatment with high dose of appetite suppressants in these patients taken together with the metabolic disturbances due to renal failure. It is not clear from these studies if more damaged valves are less likely to regress.

For pergolide, only very few follow-up data are available. When combining several case reports, regression of VHD has been described in only 12 out of 24 patients about whom a follow-up was reported [18, 81–83]. Only one recent case–control study describes the echocardiographic follow-up in ten patients in whom pergolide was recently stopped because of restrictive VHD [84]. After 13 months, a significant improvement was found in six patients for MR but not for AR. In two patients who refused to stop pergolide, valvulopathy remained unchanged. However, this was a very small study, and no follow-up data were reported on restrictive mobility.

For benfluorex, a retrospective analysis of a cohort of one million diabetic patients (4 % treated with benfluorex) reported a dose–effect relationship, with a relative risk of hospitalization of 2.9 (95 % CI 2.2–3.7). Patients with lower cumulative doses (40.5 g) were less likely to be hospitalized for valvular insufficiency [58].

58.7 Small Animal Models of Drug-Induced Valvular Heart Disease

Regarding causal relationship, cumulative dose and potential for reversibility of drug-induced VHD, only indirect clinical data exist since prospective randomized trials are difficult to conduct, because of evident ethical considerations. Echocardiography in small animals may overcome these limitations because recent reports show the feasibility of studying drug-induced VHD in rats [12, 85–89].

In this way, we demonstrated that long-term pergolide injections for 20 weeks led to VHD in rats [85]. This was shown by serial in vivo echocardiographic assessment of valvular changes and histopathological evaluation. There was a good correlation between both techniques. Pergolide and serotonin led to an increased biosynthesis of collagen and glycosaminoglycans, which accumulated in the aortic

and mitral valvular sponge layer in a more diffuse pattern. In contrast, the age-related valvular changes in the controls were more subtle, and only nodular or segmental myxoid transformations of the distal free edges of the valvular leaflets were present. In another study, we found a dose-dependent effect of serotonin on heart valve function and morphology in rats after 12 weeks of treatment [9]. At that time, regurgitant aortic and mitral valves were also thicker than the non-regurgitant valves on histopathology. Cessation of serotonin administration subsequently led to the absence of further increase of regurgitations compared to controls and recovery of valvular thickness to the same amount as controls at week 20. These results suggest that the lowest possible dose of potential valvulopathic drugs should be used, as higher dosages are more likely to induce valvulopathy.

Recently, we also found that cyproheptadine had a preventive effect against the development of pergolide-induced valvulopathy in this rat model [88]. Besides the 5-HT_{2B} receptor antagonism, cyproheptadine also antagonizes several other 5-HT receptor subtypes. Hence, the exact mechanism by which cyproheptadine prevented pergolide-induced valvulopathy in this study needs to be further investigated.

Such a model has the potential to screen new candidate drugs for toxic valvular side effects and to evaluate new treatment strategies involving the 5-HT_{2B} receptor.

58.8 Practical Recommendations for the Use of Potential Valvulopathic Drugs

Echocardiography is the method of choice for evaluating valvular morphology and function before, during and after treatment with potential valvulopathic drugs. It allows reliable and reproducible quantification of valvular function and also valvular motion in terms of valve tenting area and distance. However, subtle and early changes in valvular function and motion (regurgitation, thickening) are more difficult to evaluate and subject to the echocardiographers' experience and interpretation.

Future (pre)clinical studies might identify in greater detail which patients are at the risk of developing toxic valvulopathy. Also the exact pathophysiological mechanisms need to be further elucidated in order to predict the valvulopathic risk of certain drugs. This might also give the opportunity to develop specific prophylactic or therapeutic strategies.

58.9 Concluding Remarks

Drug-induced valvular heart disease has been described with ergotamine, methysergide, fenfluramine, pergolide, cabergoline, MDMA and benfluorex. Although most of these drugs were withdrawn from the market, several cases of patients requiring valve surgery even years after the cessation of therapy have been reported. DIVHD

is not infrequent and may be severe. Even after drug cessation, long-term implications of this type of VHD may persist. Therefore, this disease needs to be known, screened for and identified as soon as possible before significant valvular dysfunction occurs in any individual who has taken the above drugs. In order to avoid future catastrophes for patients, drugs and their metabolites need to be screened for 5-HT_{2B} agonistic activity, and in vivo testing in preclinical models might be promising.

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Part VIII
Cardiovascular Conditions of Childhood and Pregnancy

Chapter 59
Pathophysiology and Pharmacotherapy of Adult Congenital Heart Disease

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Abstract Major technical advances in the medical and surgical therapy for congenital heart defects (CHD) over the last 40 years have allowed the majority of infants born with CHD to survive to adulthood. Indeed, roughly two thirds of all CHD patients in the USA are now adults. Despite their improved survival, these patients continue to face the sequelae of their original defects and of their surgical correction. One of the principal predictors of long-term outcomes in patients with both palliated and unpalliated CHD is the state of the pulmonary vasculature and the presence or absence of pulmonary vascular disease. Over the past two decades, there have been dramatic strides in the understanding of the pathophysiology of pulmonary vascular disease, and this improved understanding has permitted the development of targeted drug therapies for pulmonary hypertension. A growing body of clinical research has documented impressive results when patients with idiopathic pulmonary arterial hypertension (iPAH) are treated with these new agents. While the clinical research on subjects with PAH related to congenital heart disease (PAH-CHD) has lagged behind that for iPAH patients, emerging data are establishing a clear role for these advanced therapeutic strategies in patients with PAH-CHD. This chapter will provide a basic overview of the pathophysiology of PAH-CHD and review the current evidence-based pharmacotherapy for this population of patients.

Keywords Congenital heart disease • Pulmonary hypertension • Eisenmenger syndrome • Cardiac shunts • Endothelin-1 • PDE5 inhibitors • Prostanoid and endothelial dysfunction • Phosphodiesterases • Pulmonary circulation • Congenital heart defects

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59.1 Introduction

Congenital heart defects occur in approximately 8 of 1,000 live births in the USA [1]. Advances in pediatric cardiology and cardiac surgery have resulted in dramatically improved survival and have created an interesting shift in the demographics of congenital heart disease (CHD) [2–4]. The prevalence of CHD increased by 11 % in children and 57 % in adults from 2000 to 2010 and that of severe CHD subgroup increased by 19 % in children and 55 % in adults [6]. Thus, by 2010, there were estimated to be 1.3 million adults in the USA with CHD, and adults accounted for 66 % of the entire CHD population [5–7]. Therefore, adults now constitute a significant majority of CHD patients, a fact that compels us to understand the drivers of long-term outcomes and accordingly reshape the delivery of healthcare services for patients with CHD. Although our understanding of adult CHD (ACHD) has grown in recent years, the spectrum of disease and late complications are constantly changing due to ongoing development of improved surgical techniques [7]. Most repairs of congenital defects are palliative rather than curative, and patients are therefore left with residual disease or sequelae of their operations and frequently have to face multiple further surgical and interventional procedures, arrhythmias, and other complications. Meticulous and regular follow-up and management of these patients are crucial to reduce the risks of heart failure and premature death. The guidelines for management of patients with CHD are primarily based on expert consensus rather than randomized controlled trials, and a lot of research is still required to define the optimal treatment algorithms for these patients [2, 8–11]. In this chapter, we will summarize the current understanding of the pathogenesis of PAH-CHD. We will then provide a succinct review of the current state of clinical research in PAH-CHD and of the modern, evidence-based advanced therapy for PAH-CHD.

59.2 Classification of Congenital Heart Disease

Congenital heart defects are often classified anatomically using a segmental approach with sequential chamber localization [12–14]. This type of classification involving a systematic description of the segmental anatomy of the heart provides a valuable tool for planning the surgical approach aimed at reconstructing the blood circulation and thus avoiding mixing of blood. Furthermore, such an approach allows for construction of a conceptual framework for understanding the relationships between defects, the complexity and variety of which can be overwhelming when considered as a simple list of diagnoses.

- Abnormalities in development of the sinus venosus, which gives rise to the posterior portion of the atria and their venous connections, give rise to a number of related defects that frequently coexist. These include atrial septal defects (ASD), partial anomalous pulmonary venous return and total anomalous

pulmonary venous return (PAPVR and TAPVR). These defects result in left-to-right shunting at the atrial level and pulmonary overcirculation.

- Abnormalities in cardiac looping and in endocardial cushion patterning may cause a diverse group of anatomical disorders. These include congenitally corrected transposition of the great vessels (cc-TGA, also referred to as l-TGA), tricuspid atresia, partial and complete AV canal defects (also referred to as AV septal defects or endocardial cushion defects), and double-inlet left ventricle, along with other "single-ventricle" defects. In cc-TGA, the position of the ventricles is inverted, and the aorta is located anterior and to the left of the pulmonary artery. This allows vena caval blood from the right atrium to pass through the mitral valve into the malpositioned left ventricle and then through the pulmonic valve to the lungs. Blood returning from the lungs enters the left atrium from the pulmonary veins but then passes through a tricuspid valve into a morphologic right ventricle, which pumps this oxygenated blood to the aorta. In the absence of common associated lesions (such as ventricular septal defect and pulmonic stenosis), the pulmonary and systemic blood flows are equal, and the arterial blood is fully saturated. In tricuspid atresia, double-inlet ventricle, the other "single-ventricle" lesions, and the most severe forms of AV canal defects, there is partial or complete admixture of systemic and pulmonary venous blood within the heart. The amount of pulmonary blood flow is variable, and the degree of cyanosis is inversely proportional to the amount of pulmonary blood flow (Chap. 54).
- Abnormalities in patterning of the outflow tract of the looping heart tube can lead to a variety of defects. In this complex region, cells of multiple embryonic origins come together and interact in critical ways. Disruption of the orchestrated molecular signaling, transcriptional activity, and tissue growth that occur in this lead to malpositions of the great vessels, manifesting as tetralogy of Fallot (TOF), complete transposition of the great vessels (d-TGA), double-outlet right ventricle (DORV), valvular pulmonic stenosis, membranous ventricular septal defect (VSD), pulmonary atresia (with intact ventricular septum or VSD), and persistent truncus arteriosus communis. Many of these defects, often referred to as "conotruncal anomalies," can be seen as members of a related group of abnormalities, characterized by altered rotation of the outflow tract (Fig. 59.1). In TOF, the conal septum dividing the aorta and pulmonary artery is displaced anteriorly and superiorly relative to the crest of the ventricular septum, resulting in a narrow outflow tract and membranous VSD which is straddled by an overriding aorta. Pulmonary blood flow is reduced, and deoxygenated blood in the right ventricle is shunted through the aortic valve into the systemic circulation, producing cyanosis. Pulmonary atresia and DORV with subaortic VSD can be conceptualized as extreme variants of TOF. In d-TGA, the aorta is malpositioned anteriorly and to the right of the pulmonary artery such that it communicates with the right ventricle. As a result, systemic venous blood in the right atrium passes through the tricuspid valve into the right ventricle, which pumps it through the aortic valve back to the systemic circulation, while oxygenated blood in the pulmonary veins enters the left atrium, passes through the mitral valve into the morphologic left ventricle, and is then pumped through the pulmonic valve back

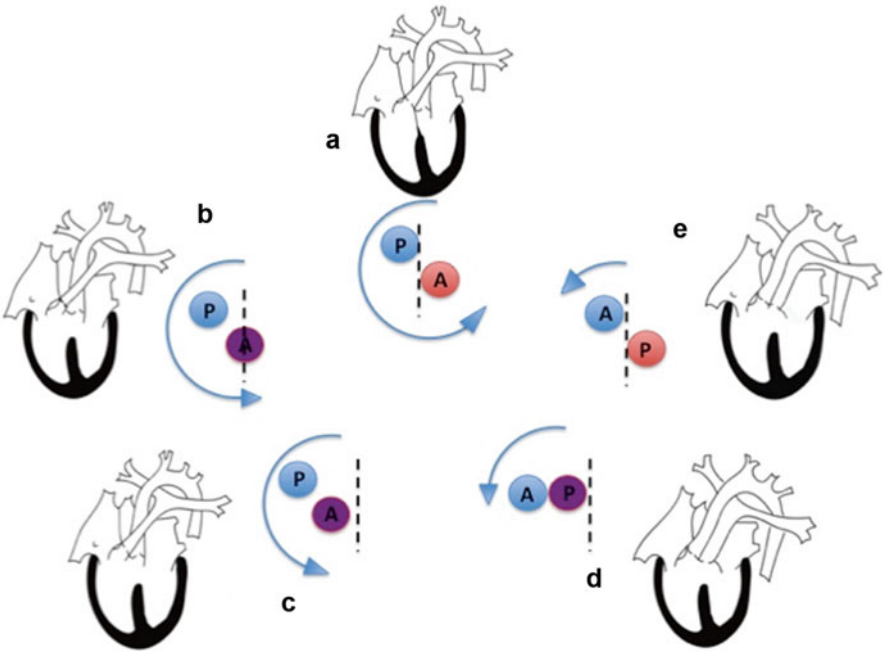

Fig. 59.1 The conotruncal anomalies can be seen as a related group of disorders characterized by an altered rotational relationship between the aorta and the pulmonary artery. (**a**) Normal heart, (**b**) TOF, (**c**) DORV, (**d**) DORV with malposition/subpulmonic VSD (Taussig-Bing anomaly), and (**e**) d-TGA

to the lungs. Survival is dependent on an atrial-level communication or patent ductus arteriosus to allow for mixing of these otherwise parallel circulations. In truncus arteriosus communis, the pulmonary artery and aorta are incompletely septated by invading neural crest-derived mesenchyme, and there is invariably a VSD. As a result, there is obligate mixing of systemic and pulmonary venous blood in the ventricles. Pulmonary blood flow is variable, depending on the presence of pulmonic obstruction, and the degree of cyanosis is inversely proportional to the pulmonary blood flow.

- A number of related developmental abnormalities may produce obstructive lesions on the left side of the heart. These include bicuspid aortic valve (BAV), congenital mitral stenosis, and coarctation of the aorta (CoA). Defects in blood flow through the left side of the heart are thought to produce abnormalities in growth of the left ventricle. In its most severe form, this phenomenon is referred to as hypoplastic left heart syndrome (HLHS). Typically, obstruction of blood flow causes the proximal aorta and arch to be small, and deoxygenated blood in the pulmonary artery enters the systemic circulation through a patent ductus arteriosus (PDA).

There are several other ways to classify CHD: alphabetical order, cyanotic and acyanotic, site of the defect (veins, atria, ventricles, septa, and great arteries),

Table 59.1 Pathophysiological classification of congenital heart defects

I. Acyanotic CHD with increased pulmonary blood flow (septal defects without pulmonary obstruction and left-to-right shunt)	II. Cyanotic CHD due to right-to-left shunt
Partial anomalous pulmonary venous drainage	Pulmonary valve stenosis/atresia with ASD
Atrial septal defects (ASD)	Pulmonary valve stenosis/atresia with VSD (tetralogy of Fallot)
Complete atrioventricular septal defect	Ebstein anomaly of the tricuspid valve with interatrial communication
Ventricular septal defects (VSD)	Double-outlet right ventricle
Persistent truncus arteriosus, aortopulmonary window, patent ductus arteriosus	Persistent truncus arteriosus communis
	Eisenmenger syndrome
III. Cyanotic CHD due to admixture of pulmonary and systemic venous blood	IV. CHD incompatible with postnatal blood circulation
Tricuspid atresia	Parallel systemic and pulmonary circulations (complete transposition of great arteries) without interatrial communication
Total anomalous pulmonary venous connection with interatrial communication	Total anomalous pulmonary venous drainage without interatrial communication
Univentricular atrioventricular connections (double-inlet left ventricle)	Ductus-dependent CHD (pulmonary atresia, aortic and mitral atresia, and interrupted or atretic aortic arch)
V. Acyanotic CHD without shunt	
Bicuspid aortic valve	
Pulmonic stenosis	
Coarctation of the aorta	
Congenital anomalies of the coronary arteries	
Congenitally corrected transposition of the great arteries	

embryologic origin of the defects, etc. [15–17]. However, a pathophysiological classification, namely, a classification based upon the clinical consequences of structural defects impairing the physiology of blood circulation [18], may be more helpful for understanding the clinical presentation and anticipating the long-term consequences of these lesions and thus for planning of appropriate pharmacotherapy. Pathophysiologically, these defects can be categorized into five types as listed in Table 59.1.

Patients in group I are acyanotic at birth, but the increased pulmonary blood flow may result in damage of the small pulmonary arteries and arterioles, leading to pulmonary vascular disease and increased pulmonary resistance. This ultimately reverses the direction of the shunt, converting it from a left-to-right shunt into a right-to-left shunt. When the shunt reverses, cyanosis occurs, resulting in the Eisenmenger syndrome. On the other hand, patients in groups II and III are cyanotic

at birth due to right-to-left shunt or to mixing of systemic and pulmonary venous blood and have variable pulmonary blood flow. This is a heterogeneous group, but their clinical presentation and their long-term outcomes are influenced markedly by the presence and/or development of pulmonary vascular disease later in life.

59.3 Pathophysiology of Congenital Heart Disease

59.3.1 Developmental Genetics of CHD

Although epidemiological data point to environmental influences like drugs, toxins, etc., as risk factors for developing CHD [17], the observation of frequent familial recurrence of defects suggests that genetic factors are at play in the development of cardiac defects. Genetic animal models have identified a core group of regulatory genes involved in cardiac development. Chief among these are several key transcription factors (e.g., *nkx2-5*, *gata4*, *mef2c*, *tbx5*), along with their transcriptional targets, and signaling molecules (particularly fibroblast growth factors, bone morphogenetic proteins, hedgehog, notch, and retinoic acid). These studies have suggested the possibility that disruptions in these genes may result in congenital heart defects, and indeed, several clinical reports have identified mutations in these loci in patients with structural CHD [19]. The earliest cardiac progenitors arise from lateral plate mesoderm, controlled by a cascade of interacting transcription factors. Additional inputs come from secreted molecules, such as fibroblast growth factors, bone morphogenetic proteins, Wnt proteins, and others [19]. The discovery of a "second" heart field (SHF) has led to new understanding of the origin and patterning of the embryonic heart [20]. The SHF is medial and dorsal to the early differentiating cardiomyocytes that comprise the "cardiac crescent" and give rise to a large portion of the heart, including the outflow tract, right ventricle, and parts of the atria. The SHF is further subdivided into a number of lineage pools, which contribute either to anterior structures (such as the outflow tract) or posterior components (such as the atria) [20]. These findings help explain how mutations affecting specific cell lineages within the SHF result in a spectrum of complex defects in heart structures. Altered hemodynamics, signaling defects leading to valve disease, and misregulated expression and function of microRNAs have also recently been implicated as mechanisms for the development of CHD in humans [21]. See also Chap. 62 on miRNAs in cardiovascular development.

Remarkable strides have been made in recent years in the field of cardiac development, particularly in dissecting the transcriptional network (e.g., involving the transcription factors TBX5, NKX2-5, GATA4, TBX1, SALL4, TBX20, TFAP2B, and THRAP2) [21–34], and recognizing that these proteins participate in a complex set of interactions has been important for understanding the regulation of cardiac gene expression and cardiac development. These discoveries have also provided some insight into the etiology of human congenital heart diseases and their patterns of inheritance. However, our understanding of the genetics of CHD is currently

incomplete, and the mechanisms of how molecular defects in these transcriptional pathways translate to a structural defect need to be explored further.

59.3.2 Physiological Consequences of CHD

Although the structural variations seen in congenital heart disease constitute an encyclopedic list of complex malformations, these defects can be understood in a more limited physiologic spectrum as described in Table 59.1. Defects in each category impose three basic pathophysiologic burdens on the cardiovascular system: pulmonary overcirculation with ventricular volume overload, ventricular pressure overload, and hypoxemia. Ultimately, these pathophysiologic conditions can result in myocardial failure or pulmonary vascular disease. Medical and surgical management strategies are thus generally focused on minimizing the pathophysiologic consequences of these lesions. However, since CHD is a developing field, future studies are needed to develop specific strategies for management of these pathophysiological consequences. Pulmonary vascular disease, which is a major driver of long-term outcomes in most of the complex congenital heart lesions, is one of the only areas in ACHD where randomized controlled data regarding pharmacotherapy are available, and thus this topic will be the focus of the remainder of this chapter.

59.4 Pulmonary Vasculature

The normal pulmonary circulation differs dramatically from the systemic circulation in its biophysical and hemodynamic properties, structural organization, and physiology. While the systemic circulation is designed to deliver nutrients and oxygen to the tissues, the pulmonary circulation is designed to maximize oxygen uptake in the blood that will ultimately nourish the rest of the body. In order to maximize gas exchange, the pulmonary circulation has an extremely high capacitance, receiving 100 % of cardiac output during each cardiac cycle. Despite the expansive volume of blood present, the pulmonary circulation maintains a low pressure and a low resistance, allowing the right heart to effectively and efficiently pump this large volume of blood through the pulmonary vascular circuit.

59.4.1 Development of the Pulmonary Vascular Bed

The human intrapulmonary arterial branching system develops by the continuous expansion of the mesenchymal primary capillary plexus [35]. The preacinar intrapulmonary arteries are formed primarily by vasculogenesis, a coalescence of cells derived from the mesenchyme into endothelial tubes. During

development, endothelial tubes are continuously added at the lung periphery. These arteries increase in size with age and become invested with smooth muscle cells that also mature with age judged by their cytoskeletal protein expression. Thus, the older, more proximal arteries have a more mature cytoskeleton than do the peripheral arteries during development, but by birth, all show a similar expression of proteins. The pulmonary arterial smooth muscle cells seem to originate from more than one source (bronchial smooth muscle cells surrounding the airway, lung mesenchyme, and endothelial cells), but all appear to follow the same pattern of maturation, expressing the same cytoskeletal proteins sequentially in utero [35].

59.4.2 Pathophysiology of Pulmonary Vascular Disease

Pulmonary arterial hypertension (PAH) is a dynamic and multifactorial process related to vasoconstriction and remodeling of the pulmonary vascular bed that is aggravated and accelerated by thrombosis [36]. Several histopathological abnormalities associated with PAH due to congenital shunt lesions (PAH-CHD), such as extension of smooth muscle cells into peripheral pulmonary arteries, medial hypertrophy, formation of plexiform lesions, and rarefaction of the pulmonary arterial tree, have been described [36–38]. Reflecting these histological changes, classifications of pulmonary vascular changes have been developed, including those introduced by Heath and Edwards in 1958 [38] and Rabinovitch in 1978 [39]. It has been suggested that these histological changes may correlate with clinical severity of PAH [40]. In addition to histological studies in patients with PAH, several animal models of congenital heart disease have been established [41, 42] and have provided additional insights into the pathophysiology of the disease (Chap. 45).

The classical model of the pathophysiology of pulmonary vascular disease related to congenital shunt lesions has focused on the notion that high flow and pressure induce pulmonary vascular endothelial damage, leading to a loss of endothelial barrier function [43, 44]. This may be associated with degradation of extracellular matrix (activation of endogenous vascular elastase and matrix metalloproteinases) as well as release of growth factors (fibroblast growth factor and transforming growth factor-β) [45]. In turn, these factors induce smooth muscle cell hypertrophy and proliferation, resulting in extension of smooth muscle cells into peripheral pulmonary vasculature and smooth muscle cell migration with neointima formation [46, 47]. Furthermore, endothelial damage may result in adhesion and activation of platelets and leukocytes, resulting in an inflammatory response, as well as thrombosis and activation of coagulation pathways [36]. Activation of platelets and the coagulation cascade is thought to reinforce the inflammatory reaction in the pulmonary endothelium and proliferative reactions in the smooth muscle [48]. The extent to which inflammation plays a role in the pathogenesis of PAH-CHD is not yet known. However, several studies have shown that markers of inflammation correlate with disease activity and prognosis [49].

In the classical model, high pulmonary blood flow, particularly as a consequence of high-pressure, post-tricuspid shunts, results in endothelial dysfunction, characterized by dysregulation of several signaling pathways involved in control of pulmonary vascular tone and proliferation of pulmonary vascular smooth muscle. Chief among these are nitric oxide (NO) signaling pathway, the prostacyclin signaling pathway (including prostaglandin I_2 and thromboxane), and the endothelin signaling pathway [50]. These factors normally maintain a dynamic equilibrium between vasoconstriction and vasodilation that regulates pulmonary vascular resistance to meet metabolic demands. The changes in these signaling processes shift the balance in favor of factors inducing vasoconstriction and ultimately pulmonary vascular remodeling [50]. This complex process of endothelial dysfunction forms the basis of our current approach to treatment, and these altered signaling pathways are the targets of "advanced therapy."

Different mediators influencing pulmonary vascular tone have been identified, some of which are currently amenable to pharmacological therapy. Extensive activation of the endothelin system is one of the hallmarks of PAH and is likely to contribute to pulmonary vasoconstriction and vascular remodeling [43, 44]. In addition, circulating endothelin levels have been found to correlate with disease severity and outcome in PAH patients [45]. Decreased production of prostacyclin is an additional feature of PAH. Prostacyclin, a metabolite of arachidonic acid, is a potent pulmonary and systemic vasodilator [51]. In patients with PAH, prostacyclin production is impaired, and levels of prostacyclin metabolites are reduced [52, 53]. Nitric oxide, a potent endothelium-derived factor inducing vasodilation and suppressing proliferation, is involved in the pathophysiology of PAH [52, 53]. Nitric oxide activates cyclic guanylyl cyclase in vascular smooth muscle cells, leading to increased intracellular levels of cGMP; cGMP in turn is degraded by phosphodiesterases. Pharmacological inhibition of phosphodiesterases provides a way to induce cGMP-dependent vasodilation (see Chap. 31).

The classical view of endothelial dysfunction is clearly incomplete as a framework for advanced therapy, and further studies are needed in order to develop a more complete understanding of the pathogenesis of PAH-CHD. Indeed, preliminary data suggest additional mechanisms at play in the development of PAH-CHD. First, there are differences in the risk of developing pulmonary vascular disease when one compares different lesions with the same pulmonary blood flow and initial pulmonary pressures. This suggests the possibility that these defects may differ in terms of underlying genetic susceptibility. Much focus of genetic studies has been on mutations that affect transforming growth factor-β (TGF-β) superfamily signaling. Indeed, mutations in *bmpr2*, which encodes the bone morphogenetic protein (BMP) type II receptor, and *alk1*, which encodes activin-like kinase type 1, have been implicated in both familial PAH and in up to 6 % of patients with PAH-CHD [54–57].

Additional abnormalities have been described in PAH associated with congenital heart disease that might provide new insights into pathophysiology and also may have future therapeutic implications. These include increased turnover of serotonin, a pulmonary vasoconstrictor, compared with healthy individuals [58] and emerging evidence of altered intrapulmonary expression of TGF-β_1 and its receptors in an

animal model of shunt-induced pulmonary vascular disease [54]. Furthermore, altered expression of pulmonary potassium channels associated with an accentuated response to hypoxia has been shown in an ovine model [55].

These preliminary data reflect the complex interplay between genetic susceptibility and environmental factors such as pulmonary blood flow or pressure in the etiology of PAH associated with congenital heart disease.

59.5 Pharmacotherapy for Pulmonary Vascular Disease Associated with Congenital Heart Disease

In the European guidelines, PAH-CHD patients have been classified into four main clinical groups (Table 59.2) [59]. Current guidelines recommend that CHD patients requiring PAH-specific therapy be managed in specialized centers. Although some data on the use of PAH-specific therapies are available, particularly for Eisenmenger syndrome patients, guidelines are generally based on the clinical experience of experts rather than formal evidence from clinical trials [59].

59.5.1 General Management and Background Therapy

General measures for the treatment of patients with PAH-CHD and, in particular, those with Eisenmenger syndrome include recommendations for physical activity, prevention of dehydration, infections, air travel, exposure to high altitudes and

Table 59.2 Clinical classification of congenital, systemic-to-pulmonary shunts associated with pulmonary arterial hypertension (PAH)

Group A. Eisenmenger syndrome
Eisenmenger syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple-organ involvement are present
Group B. PAH associated with systemic-to-pulmonary shunts
In these patients with moderate-to-large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest
Group C. PAH with small defects
In cases with small defects (usually VSD <1 cm and ASD <2 cm of effective diameter assessed by echocardiography), the clinical picture is very similar to idiopathic PAH
Group D. PAH after corrective cardiac surgery
In these cases, CHD has been corrected, but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant postoperative residual congenital lesions or defects that originate as a sequelae to previous surgery

PVR pulmonary vascular resistance, *VSD* ventricular septal defect, *ASD* atrial septal defect, *CHD* congenital heart disease

elective surgery, and that psychological assistance be provided as necessary [60]. Patients with Eisenmenger syndrome are at particular risk during anesthesia and surgery, and special care is required. Pregnancy is contraindicated in patients with Eisenmenger syndrome, as there is a high risk of maternal and fetal mortality; adequate contraception is therefore mandatory. Patients with Eisenmenger syndrome are at an increased risk of coagulation disorders. The high incidence of pulmonary artery thrombosis (up to 20 %) is associated with increasing age, biventricular dysfunction, and dilatation of the pulmonary arteries. However, the use of anticoagulants in this population is controversial as there is also an increased risk of hemoptysis and hemorrhage [10]. Routine laboratory-guided phlebotomy should not be performed as secondary erythrocytosis is beneficial for oxygen transport and delivery [61]. If moderate-to-severe symptoms of hyperviscosity are present, and iron deficiency and dehydration have been excluded, phlebotomy with isovolumic replacement should be performed carefully when the hematocrit is >65 % [10]. Iron deficiency has been shown to be associated with a higher risk of adverse outcomes (all-cause mortality, transplantation, and hospitalization due to cardiopulmonary causes) in Eisenmenger syndrome patients, and iron replacement therapy improves exercise tolerance and quality of life [61, 62]. However, care should be taken to avoid an excessive rise in hemoglobin concentration and decompensated polycythemia [61].

One of the first classes of drugs to be studied for the treatment of patients with PAH are the calcium channel blockers (CCBs). In one early study, 64 patients with iPAH were treated with nifedipine or diltiazem, and those who had a hemodynamic response were treated for 5 years. This subgroup was found to have improved survival compared with those who did not respond. While this finding may suggest a role for CCBs in patients with PAH-CHD, the systemic vasodilatory effect of these agents may result in worsening of the right-to-left shunt, thereby posing a risk to the patient. There are no data from clinical trial to support the use of CCBs in patients with PAH-CHD, and the current guidelines suggest that their use be avoided [59]. In fact, their use is contraindicated in Eisenmenger syndrome patients as their vasodilatory effect can result in an acute decrease in systemic vascular resistance and therefore an increase in right-to-left shunting, which may lead to syncope and sudden death [63]. Embolization therapy of collateral vessels may be helpful in the management of selected patients with acute significant hemoptysis but must be weighed against the risk associated with the consequent reduction in the cross-sectional area of the pulmonary vascular bed [59]. The use of supplemental oxygen therapy is controversial, and it should be used only in whom it produces a consistent increase in arterial oxygen saturation [59].

59.5.2 Management of PAH-CHD with PAH-Specific Therapies

In the past two decades, multiple randomized controlled studies [64–91] have demonstrated the efficacy of three classes of drugs or their combination for the treatment of PAH (see Table 59.3), namely, (i) prostanoids, (ii) endothelin receptor

Table 59.3 Pharmacotherapy of pulmonary arterial hypertension

Agents	Route of administration	Dose	Half-life	Adverse effects
Prostanoids				
Epoprostenol	Continuous intravenous	1–2 ng/kg/min initially Increased by 1–2 ng/kg/min every 1–2 weeks until therapeutic response or dose-limiting toxicity occurs No maximal dose established	3–5 min (single dose) 15 min (continuous infusion)	Jaw pain, diarrhea, flushing, and arthralgias. Excess dose may cause high-output cardiac states Adverse effects related to the intravenous pump
Treprostinil	Intravenous, subcutaneous (used less often)	0.625–1.25 ng/kg/min initially Dose titrated up every 1–2 weeks until therapeutic response or dose-limiting toxicity occurs	4 h	Same as above
	Inhaled	One to three inhalations (i.e., 6–18 μg), four times daily initially Maintenance dose may be gradually titrated up to nine inhalations (i.e., 54 μg), four times daily	4 h	
Iloprost	Inhaled	2.5–5 μg, six to nine times daily	20–30 min	Main disadvantage is the need for frequent administration
Endothelin receptor antagonists				
Bosentan	Oral	62.5–125 mg, two times daily Dose is adjusted for low body weight or drug interactions	5 h	Hepatotoxicity, peripheral edema, teratogenic
Ambrisentan	Oral	5–10 mg daily	9 h	Peripheral edema, worsening of idiopathic pulmonary fibrosis, teratogenic, least hepatotoxic among ERAs

Table 59.3 (continued)

Agents	Route of administration	Dose	Half-life	Adverse effects
Macitentan	Oral	3–10 mg per day	14–18 h	Nasopharyngitis, anemia, teratogenic, edema less common
Phosphodiesterase type 5 inhibitors				
Sildenafil	Oral Intravenous	20 mg, three times daily 10 mg, three times daily Dose is adjusted for drug interactions	4 h 4 h	Flushing, diarrhea, headache, myalgia, and visual disturbances
Tadalafil	Oral	40 mg daily Dose is adjusted for drug interactions	35 h	
Soluble guanylyl cyclase stimulant				
Riociguat	Oral	0.5–1 mg three times daily initially Titrated up by 0.5 mg three times per day every 2 weeks until therapeutic response or dose-limiting toxicity occurs (maximum dose 2.5 mg three times daily)	12 h	Syncope

antagonists. and (iii) phosphodiesterase (PDE)-5 inhibitors (see also Chap. 45). The rationale supporting the use of these drugs is based on targeting the mediators of endothelial dysfunction [92, 94]. Most randomized trials of pulmonary vasodilators have included mostly patients with idiopathic PAH, with only a small percentage of PAH-CHD patients. The clinical database is therefore limited.

Prostanoids – Prostanoid formulations used to treat PH include intravenous epoprostenol (prostacyclin), intravenous treprostinil, subcutaneous treprostinil, inhaled treprostinil, and inhaled iloprost [51, 93]. The clinical utility of all of these agents is limited by the fact that they must be administered parenterally.

Epoprostenol – Intravenous epoprostenol is the advanced therapy that has been best studied. It improves hemodynamic parameters, functional capacity, and survival in patients with iPAH [94, 95]. However, survival has not been adequately evaluated due to limited sample sizes [96]. Data supporting the use of epoprostenol in patients with PAH-CHD come primarily from uncontrolled case series. In one

retrospective study of 20 PAH-CHD patients who had failed conventional therapy with diuretics, digitalis, and warfarin, chronic treatment with intravenous epoprostenol was associated with a long-term improvement in pulmonary hemodynamics, functional class, and exercise tolerance. A later retrospective study confirmed these clinical and hemodynamic improvements in patients treated with intravenous epoprostenol [98].

Treprostinil – Treprostinil can be given intravenously or subcutaneously, although subcutaneous administration is used less often due to severe pain at the injection site. Inhaled treprostinil has more recently been approved for patients who are WHO functional class III. Intravenous and subcutaneous treprostinil improves hemodynamic parameters, symptoms, exercise capacity, and possibly survival [70, 93, 97, 99]. Advantages of parenteral treprostinil, compared to epoprostenol, include the option of continuous subcutaneous delivery, a longer half-life that may make interruption of the infusion less immediately life threatening, and no need for refrigeration. Based on the results of two clinical trials, an oral formulation of treprostinil was approved by the US Food and Drug Administration (FDA) [81, 82]. The benefits of oral treprostinil in these studies were small although statistically significant. As with epoprostenol, there are no prospective, randomized controlled trials of treprostinil in PAH-CHD patients. However, a retrospective study suggested benefit in these patients.

Iloprost – Inhaled iloprost has advantages in targeting the lung vasculature and does not require intravenous administration. The main disadvantage is the need for frequent administration (6–9 times per day). It has shown to produce improvement in the six-minute walk test compared to placebo (17 versus 5 %) [72] in patients with iPAH. There are no randomized controlled trials studying its use in PAH-CHD.

Endothelin receptor antagonists – Endothelin-1 (ET-1) is a potent vasoconstrictor and smooth muscle mitogen. High concentrations of ET-1 have been recorded in the lungs of patients with congenital cardiac shunt lesions [100]. Endothelin receptor antagonism emerged as an initial therapy for patients with CHD in the late 1990s. There are two receptors (endothelin receptors A and B) that are targeted by endothelin receptor antagonists (ERAs). ERAs that have been tested in clinical trials include the nonselective dual receptor antagonists, bosentan and macitentan, and the selective antagonists of endothelin receptor A, ambrisentan and sitaxsentan. Among these agents, only bosentan and macitentan (nonselective) and ambrisentan (selective) are available. Sitaxsentan was withdrawn in 2010 following several fatal cases of hepatotoxicity [79, 101]. A meta-analysis of 12 randomized trials (1,471 patients) [102] showed improved exercise capacity, dyspnea, and hemodynamic measures (pulmonary artery pressure, pulmonary vascular resistance, and cardiac index) with ERAs.

Bosentan – The BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) and its long-term open-label extension study demonstrated the benefit of bosentan in patients with Eisenmenger syndrome in terms of significant improvements in exercise capacity, hemodynamics, and functional class compared with placebo, independently of the location of the septal defect [64, 103, 104].

Bosentan has been shown to delay clinical worsening and improve pulmonary vascular hemodynamics and exercise capacity [68, 70]. The mortality of bosentan-treated iPAH patients appears favorable compared to historical controls [100, 105]. It appears to be effective in patients with severe PAH [70] (WHO functional class III or IV) and may also be effective in patients with moderate PAH [90] (WHO functional class II). Importantly, treatment with bosentan has been shown not to reduce systemic arterial blood oxygen saturation over short-term [64] and long-term treatment [106], demonstrating that it had no negative effect on the overall shunt. Treatment with bosentan has also been shown in retrospective studies and uncontrolled cohort studies to have a positive long-term effect on quality of life, a particularly important consideration for Eisenmenger syndrome patients [107–110].

Macitentan – In patients with moderate-to-severe PAH (WHO functional classes II–IV) treated over a 2-year period [91], fewer patients on macitentan progressed or died on therapy (38 and 31 % versus 46 %). This benefit was observed independent of whether patients were receiving additional advanced oral therapy for PAH. Exercise capacity and WHO functional class also improved with macitentan treatment. This was a landmark study in that it studied a composite end point that included death. However, the applicability to patients with PAH-CHD may be limited, since only 8 % of the study participants fell into this group [91].

Ambrisentan – In a study of patients with iPAH treated for up to 2 years, ambrisentan delayed disease progression and clinical worsening [83, 111]. In addition, ambrisentan has been associated with improved exercise tolerance, WHO functional class, pulmonary vascular hemodynamics, and quality of life. As with some of the agents above, the data supporting the use of ambrisentan in patients with PAH-CHD are limited. A retrospective cohort of its use in this population suggests that it improved functional status and exercise tolerance in the short term (3–9 months) and was associated with a delay in decline in oxygen saturations and exercise tolerance in the longer term (>1 year) [112].

PDE5 inhibitors – Sildenafil, tadalafil, and vardenafil are orally administered cyclic GMP phosphodiesterase type 5 (PDE5) inhibitors that prolong the vasodilatory effect of nitric oxide and are also used to treat erectile dysfunction.

Sildenafil – Sildenafil improves pulmonary hemodynamics and the 6-min walk distance, and these effects persist during 1-year [74] and 3-year follow-up [84]. The estimated 3-year survival rate in patients on sildenafil is reported to be 79 % [84]. Treatment with the PDE5 inhibitor sildenafil has been shown to improve exercise capacity, Borg dyspnea score, functional class, quality of life, and hemodynamics in patients with PAH-CHD/Eisenmenger syndrome and appears to be well tolerated [62, 113–117]. Again, the data supporting this therapy are limited by the fact that they come primarily from retrospective and open-label studies.

Others (tadalafil and vardenafil) – Tadalafil (40 mg) significantly increased the six-minute walk distance and the time to clinical worsening in patients with iPAH while decreasing the incidence of clinical worsening and improving health-related quality of life [85]. This improvement of the six-minute walk distance was sustained for an additional 52 weeks [118]. Similarly, vardenafil has been shown to increase the mean six-minute walking distance and cardiac index, while decreasing the mean

pulmonary arterial pressure, pulmonary vascular resistance, and number of clinical worsening events [88]. There are no prospective trials of these agents in patients with PAH-CHD.

Guanylyl cyclase stimulant – Stimulators of the nitric oxide receptor, soluble guanylyl cyclase (sGC), have a dual mode of action. They increase the sensitivity of sGC to endogenous nitric oxide (NO), a pulmonary vasodilator, and they also directly stimulate the receptor to mimic the action of NO. They may therefore be promising agents in the management of PAH. Riociguat is an oral sGC stimulant that has reported modest increase in the six-minute walking distance (increase by 30 m versus decrease by 6 m) in patients with PAH due to chronic pulmonary thromboembolic disease [89]. This benefit was observed regardless of whether patients were receiving concurrent advanced therapy during the study (prostanoids, endothelin receptor antagonists). Riociguat had a favorable safety profile and was well tolerated, with syncope as the most frequent reported side effect (4 versus 1 %). There are no data yet supporting its use in PAH-CHD patients.

Long-term PAH-specific therapy in patients with PAH-CHD has been shown to improve both objective exercise capacity and subjective symptoms, although escalation of therapy over time may be required if symptoms deteriorate during treatment [119]. There are also data to show that PAH-specific therapies increase quality of life scores in patients with PAH-CHD [106]. The Current European Society of Cardiology guidelines therefore recommend the initiation of treatment with bosentan in PAH-CHD patients with functional class III symptoms (class I, level of evidence B) [10]. This recommendation is made in consideration of the strength of the evidence supporting bosentan. In patients who have an inadequate clinical response or side effects related to monotherapy with bosentan, it has been proposed that combining pharmacologic agents with different mechanisms of action may produce an additive effect or may induce the same effect at lower doses of each agent. Consideration may therefore be given to the use of other endothelin receptor antagonists in patients with side effects on bosentan or to the escalation to combination therapy with phosphodiesterase type-5 inhibitors or prostanoids (class IIa, level of evidence C) [10]. Clinical studies have begun to evaluate combination therapy. Various combinations that have been studied include: (A) either epoprostenol or treprostinil added to bosentan [75, 98], (B) treprostinil added to either bosentan or sildenafil [120], (C) oral treprostinil added to an endothelin receptor antagonist and/or a phosphodiesterase-5 inhibitor, [81, 87] (D) sildenafil added to epoprostenol [121]; and (E) sildenafil added to bosentan [121].

Based on these promising preliminary results in patients with PAH-CHD, the accepted indications for pulmonary vasodilator therapy are expanding. For instance, ACHD practitioners are now applying pulmonary vasodilator therapy to patients who have had palliation of single-ventricle lesions with variants of the Fontan operation. In these patients, the pulmonary blood flow is passive, and the single ventricle is therefore required to pump blood through two resistance beds in series [122]. The resultant increase in total afterload may therefore impose an undue hemodynamic burden on the single ventricle, and the passive pulmonary blood flow may be limited, even when the pulmonary vascular resistance is relatively normal. As a result,

there has been recent interest in defining the utility of pulmonary vasodilator therapy in these patients. Sildenafil was evaluated in 28 children and young adults with Fontan physiology in a phase II randomized, placebo-controlled crossover trial. The patients receiving sildenafil in this cohort demonstrated improved ventilatory efficiency during exercise [123]. Similarly, bosentan was shown in a prospective open-label study of ten patients to result in an improvement in the six-minute walk distance and MRI indices of cardiac output [124].

59.6 Concluding Remarks

Adults with congenital heart disease constitute a rapidly growing population, and there are currently very limited data informing pharmacotherapy in this field. Pulmonary vascular resistance plays an important role in the clinical behavior of congenital lesions involving shunts, and several signaling pathways in the pulmonary vascular bed have been identified as drug targets. These are among very few specific drug targets that have been evaluated clinically in patients with congenital heart disease, and data from small clinical studies offer hope for effective disease modification through advanced pulmonary vasodilator therapy. However, the current state of knowledge is still lacking, and there is a critical ongoing need for clinical trials to help guide therapy in this population. The use of pulmonary vasodilators is expanding in clinical practice as well, to include not only patients with traditionally defined pulmonary vascular disease but also those with passive pulmonary blood flow and congenital heart lesions characterized by venous admixture. Finally, a more complete understanding of the pathophysiology of pulmonary vascular disease in patients with congenital heart disease, particularly with regard to the genetic susceptibility factor and to the role of inflammation and platelet activation, will be critical in developing future directed pharmacotherapy.

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Chapter 60
Cardiac Disease in Pregnancy

Henry Boardman and Lucy Mackillop

Abstract An increasing number of women with complex cardiac disease are becoming pregnant which brings challenges for cardiologists, obstetricians and anaesthetists. Assessing risk and counselling patients prior to pregnancy is important; however, often women have unplanned pregnancies, or their cardiac condition is not diagnosed until during pregnancy. Normal pregnancy requires the mother to mount profound cardiovascular physiological changes, which can increase the risk of cardiac decompensation in women with underlying cardiac disease. Close monitoring by specialist multidisciplinary teams and detailed planning are essential to reduce both maternal and foetal risk. Changing patient demographics mean that there is an increase in women with complex congenital heart disease who require careful preconceptual evaluation and planning for their pregnancies. Another emerging problem is that of an increasing prevalence of atherosclerotic ischaemic heart disease in women of child-bearing years. Various risk stratification classifications are available to aid the clinician and patient alike. Management for most conditions remains close to that of the non-pregnant population, but risks associated with cardiovascular and obstetric drugs need to be borne in mind.

Keywords Pregnancy • Cardiac disease • Contraception • Maternal risk • Delivery • Labour • Risk prediction

60.1 Introduction

Pregnancy is a common condition that 74 % of women in the USA and 80 % in the UK will experience. It leads to significant physiological changes and stresses on the human body particularly with the cardiovascular system. Over the past few decades,

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the characteristics of women becoming pregnant have gradually changed; the age of women becoming pregnant is rising, with the number of women becoming pregnant aged 40–44 in the USA rising by 10 % from 2007 to 2011 making up 10.3 % of all pregnancies. The mean age of first birth in 2013 in the USA was 26.0 years [1], 4.6 years older than in 1970. Cardiac disease in pregnancy is common; the incidence of congenital heart is 0.8 % and acquired heart disease 0.1 % in the UK [2]. The incidence and complexity of cardiac disease seen in pregnancy is likely to increase further due to:

- Increasing prevalence of traditional cardiovascular (CV) risk factors (increasing age, obesity, hypertension and diabetes) in populations becoming pregnant
- Increasing population with congenital heart disease becoming pregnant when previously they would either have not survived to fertile age or been advised to avoid pregnancy
- Diagnostic improvements

Importantly, many pregnancies are unintended, and therefore, the potential associated health risks and implications are not anticipated (49 % of pregnancies in the USA are not planned [3]). This can result in those who would benefit from counselling or management prior to conception not receiving it.

Globally, maternal mortality rates are falling both in the developing world (317.6 maternal deaths per 100,000 live births in 1990 (95 % confidence interval 289.9–344.5) to 232.8 (207.3–260.6) in 2013) and developed world (24.5 (23.0–26.1) to 12.1 (10.4–13.7) in the same period) [4]. However, this worldwide trend is in contrast to the USA where they are rising (12.4 maternal deaths per 100,000 live births in 1990 (95 % confidence interval 11.1–13.9) to 18.5 (14.8–22.9) in 2013) [4]. However, part of this increase is attributed to better coding of deaths during pregnancy, and it is also likely that there is impact from rising levels of chronic health conditions in pregnant women. Cardiovascular disease (which includes cardiomyopathy, hypertensive disorders of pregnancy and stroke) is the largest cause of maternal deaths in the USA (39% in 2011) [5]). A cross-sectional study by Kuklina [6] assessing more than 14 million pregnancies in the USA reported a prevalence of hospitalisation for myocardial disorders of 1.33 per 1,000 deliveries, with approximately a third of these for cardiomyopathies.

The confidential enquiries into maternal deaths in the UK are an unusually detailed report analysing every maternal death in the UK. It was last published in 2011 [7], reporting on deaths in the period 2006–2008. During that time, 261 women died; the overall maternal mortality rate was 11.39 per 100,000 maternities. Cardiac disease was the most common cause of death. Fifty-three women died from cardiac disease in the 3 years covered, a rate of 2.31 per million maternities. The most common causes of death in order of frequency were sudden adult death syndrome, peripartum cardiomyopathy, aortic dissection, myocardial infarction, ischaemic heart disease (without myocardial infarction), other cardiomyopathy and myocarditis.

60.2 Risk in Pregnancy

60.2.1 Reducing Maternal Risk

- Counselling and management of women of child-bearing age should occur before pregnancy occurs.
- Planning pregnancy in women with complex cardiovascular disease prior to conception with management by a multidisciplinary team including an obstetrician, anaesthetists, obstetric physician and cardiologist in a specialist centre is highly recommended.
- A clear plan should be made in the maternity notes with regular follow-up and examination with investigations such as ECG, echocardiogram and cardiopulmonary exercise testing as required.
- In some cases, adjustments in medications are required to minimise teratogenic and fetotoxic effects; again, this is most effectively achieved if planned pre-conceptually.

60.2.2 Risk Stratification

There are several classifications for assessing maternal cardiovascular risk in pregnancy (CARPREG, ZAHARA and WHO). The most well established is CARPREG (cardiac disease in pregnancy) which uses four categories to predict risk: prior cardiovascular event (heart failure, stroke, arrhythmia), dyspnoea (New York Heart Association III or more), obstructive left-sided lesion (mitral stenosis: mitral valve area <2 cm^2, aortic stenosis: aortic valve area <1.5 cm^2, left ventricular outflow obstruction – peak gradient >30 mmHg) and LV systolic impairment (ejection fraction less than 40 %) to calculate risk. Those fulfilling one or more than one of the above criteria are estimated to have a 27 and 75 % risk of maternal cardiovascular complication, respectively [8].

There is also a condition-specific classification, modified WHO [9] (Table 60.1).

Conditions with WHO 1 Pregnancy Risk

- Uncomplicated, small or mild:
  - Pulmonary stenosis
  - Ventricular septal defect
  - Patent ductus arteriosus
  - Mitral valve prolapse with no more than trivial mitral regurgitation
- Successfully repaired simple lesions, e.g.:
  - Ostium secundum atrial septal defect
  - Ventricular septal defect

Table 60.1 Modified WHO classification

WHO 1	Risk no higher than general population
WHO 2	Small increased risk of maternal mortality and morbidity
WHO 3	Significant increased risk of maternal mortality and morbidity. Expert cardiac and obstetric pre-pregnancy, antenatal and postnatal care required
WHO 4	Pregnancy contraindicated: very high risk of maternal mortality or severe morbidity. Termination should be discussed. If pregnancy continues, care as for class 3

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  - Patent ductus arteriosus
  - Total anomalous pulmonary venous drainage

- Isolated ventricular extrasystoles and atrial ectopic beats

Conditions with WHO 2 Pregnancy Risk

- Unoperated atrial septal defect
- Repaired tetralogy of Fallot
- Most arrhythmias

Conditions with WHO 2 or 3 Pregnancy Risk Depending on Individual

- Mild left ventricular impairment
- Hypertrophic cardiomyopathy
- Native or tissue valvular heart disease not considered WHO 4
- Marfan syndrome without aortic dilatation
- Heart transplantation

Conditions with WHO 3 Pregnancy Risk

- Mechanical valve
- Systemic right ventricle (e.g. congenitally corrected transposition, simple transposition post Mustard or Senning repair)
- Post Fontan operation
- Cyanotic heart disease
- Other complex congenital heart diseases

Conditions with WHO 4 Pregnancy Risk

- Pulmonary arterial hypertension of any cause
- Severe systemic ventricular dysfunction
  - NYHA III–IV or LVEF, <30 %
- Previous peripartum cardiomyopathy with any residual impairment of left ventricular function
- Severe left heart obstruction
- Marfan syndrome with aorta dilated >40 mm

60.3 Contraception

Helping patients prevent unplanned pregnancies and the cardiovascular complications that they might cause is an important consideration in patients of child-bearing age with complex cardiac disease. Some contraceptives carry cardiovascular risks for which patients should be counselled. Medroxyprogesterone should be avoided in those with reduced LV function as it is associated with fluid retention. Contraceptive pills containing estrogen or estradiol are associated with increased risk of thromboembolism and should be avoided in those at pre-existing increased risk. Implanting of intrauterine devices has a 5 % risk of vasovagal episode and should only be performed in a hospital environment in those with complex cardiac disease [10] (Table 60.2).

60.4 Physiological Changes of Pregnancy

60.4.1 Cardiac Physiological Changes

Pregnancy causes a progressive and increasing cardiovascular challenge, typically ending with the peak stress during labour. Stroke volume increases from week 8 and peaks at week 20. The heart rate increases from week 5 and peaks at week 32 with an increase of 17 % [12]. These factors combine to cause cardiac output to increase by week 5 gestation and peaks at 24–32 weeks with 48 % rise compared to preconception levels [12] with further rises of up to 80 % during and after labour (Fig. 60.1). The additional cardiac output is mainly directed towards the kidneys, uterus and skin. By term, the uterus receives 15–20 % of cardiac output. Cardiac output is increased additionally by 15 % in twin pregnancies compared to singleton

Table 60.2 Effectiveness of different methods of contraception

	% of women experiencing an unintended pregnancy within the first year of use	
Method	Typical use	Perfect use
No method	85	85
Diaphragm	16	6
Condom (female)	21	5
Condom (male)	15	2
Combined pill and minipill	8	0.3
Depo-Provera	3	0.3
Mirena – intrauterine device	0.1	0.1
Female sterilisation	0.5	0.5
Male sterilisation	0.15	0.10

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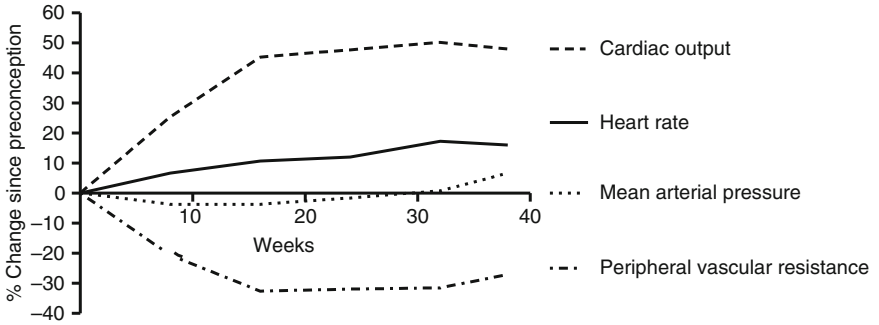

Fig. 60.1 Physiological changes from pre-conception through term (Figure constructed based on the data from Robson et al. [12])

pregnancies [13]. Cardiac output approximates pre-pregnancy values within 2 weeks of delivery with subtle further resolution completing by 6 months [13]. An increase in LV wall thickness and a 50 % increase in left ventricular mass suggest myocardial hypertrophy; these structural changes resolve more gradually than the functional cardiac changes of pregnancy but are typically resolved by 6 months. The left atrial dimensions increase by 16 %, peaking at 28 weeks [12]. Valve annuli dilate, peaking at 14 % increase in area in weeks 32–38 [12], and hence physiological valve regurgitation increases throughout pregnancy, due to reduced leaflet coaptation, with the majority resolved by 6 weeks postpartum [14]. Pulmonary capillary wedge pressure and pulmonary pressures are unchanged. Myocardial contractility also increases in the first two trimesters [12] (Chap. 54).

The gravid uterus progressively exerts pressure on the inferior vena cava which can reduce filling pressure. Cardiovascular adaptations can be significantly altered by posture in the second half of pregnancy, and the effect of the gravid uterus restricting venous return whilst lying supine can cause up to 30 % reduction in cardiac output. This can cause supine hypotensive syndrome which can cause faintness, dyspnoea, dizziness, nausea, visual disturbances and numbness and can lead to syncope [15]. Pregnant women experiencing this naturally shift position to displace the compressive uterus, but in situations where the women is restrained or sedated such as surgery, this is an important consideration. The aorta increases in size from week 24 onwards, returning to baseline in the majority of women by 6 weeks postpartum [16]. Arterial compliance increases, by as much as 30 % in the first trimester, and remains elevated through pregnancy [17].

60.4.2 Vascular Physiological Changes During Pregnancy

The plasma volume increases from week 4, reaching up to 30–50 % from baseline early in the third trimester. Systemic vascular resistance is measurably reduced by week 6 and is reduced by 34 % by week 20 [12]. Systemic vasodilation triggers baroreceptors and triggers the renin, aldosterone and angiotensin II levels to rise to maintain circulating volumes and pressures by retaining water and sodium.

Aldosterone levels increase from the first to third trimester; plasma renin is increased, and atrial natriuretic peptide is reduced suggesting the pregnant circulating system is under-filled compared to the non-pregnant state and that vasodilation precedes and predominates the increase in plasma volume. Blood pressure falls in the first trimester and reaches a nadir in the second trimester and rises to pre-pregnancy levels towards the end of the third trimester [12].

Red blood cell mass increases 20–30 % through pregnancy; this results in a mild reduction in haematocrit as the plasma volume rises more than red cell mass. This is most marked in the first half of the third trimester and results in reduced viscosity which further reduces systemic vascular resistance and afterload. These changes tend to resolve to pre-pregnancy values by 8 weeks postpartum. There is also an increase in concentration of coagulation factors [18] and a 6–22-fold increase in the risk of thromboembolism [19].

Glomerular filtration rate increases within the first month of conception, peaks before 20 weeks and declines at the end of the third trimester. This is due to increased renal blood flow secondary to increased cardiac output and renal vasodilation. This leads to a fall in creatinine by approximately a third.

60.4.3 Relevant Non-cardiovascular Physiological Changes

Oxygen consumption increases by 20 % at term, and minute ventilation increases by 50 % by term. This change in ventilation is predominantly mediated through an increase in tidal volume with little change in respiratory rate. The result of this mismatch in consumption and ventilation is an increase in pO2, a decrease in pCO2 and mild compensated respiratory alkalosis [20].

Total cholesterol and triglyceride levels rise through pregnancy [21], and insulin resistance increases [22]. This allows greater fat utilisation for maternal fuel and carbohydrate for the foetus.

60.5 Evaluating the Pregnant Patient

60.5.1 History Taking

Some women develop symptoms during pregnancy, and it can be difficult to determine whether they are due to normal physiological changes or cardiovascular disease (Table 60.3).

60.5.2 Cardiovascular Examination: Points to Consider

Blood pressure measured after 20 weeks gestation should be assessed in the left lateral position or sitting up to avoid supine hypotensive syndrome where blood pressure falls due to reduced venous return to the heart due to uterine compression of the inferior vena cava. Murmurs develop in nearly all women during pregnancy.

They are usually soft, mid-systolic and heard at the mid to upper left sternal border and are secondary to increased blood flow. A continuous bruit resulting from increased blood flow to the breasts, the 'mammary soufflé', can also be commonly heard.

60.5.3 Cardiac Investigations: Changes in the Pregnant Patient

ECG:

- 15–20° leftward shift in QRS axis, which can lead to small Q wave in III

Chest X-ray (CXR):

- In normal pregnancy, the heart can be enlarged, with increased lung markings.
- Typical radiation dose is 1.5 mGy to the mother and 0.5 mGy to the uterus of which there is no evidence of risk to the foetus.

Echocardiography:

- As pregnancy progresses, the physical changes (elevated and splinted diaphragm) affect the echo windows, and subcostal windows in particular are more challenging in the third trimester.
- Ejection fraction does not change significantly as the increase in CO is predominantly through heart rate and stroke volume changes due to increased chamber size.
- LV end-diastolic volume increases by approximately 20 %, and left ventricular mass increases by approximately 50 %.
- Valve function is unaltered, but the Doppler flow across valves is slightly increased (as a result of the increased stroke volume), but there is unlikely to be a significant gradient if there is no pre-existing stenosis.

Table 60.3 Symptoms and signs during healthy pregnancy and cardiac disease

	Normal	Abnormal
Symptoms	Mild dyspnoea	Severe or progressive dyspnoea
	Fatigability	Paroxysmal nocturnal dyspnoea
	Decreased exercise tolerance	Syncope with exertion
	Palpitations	Palpitations
Signs	Mild pedal oedema	Severe peripheral oedema
	Full, sharp, collapsing pulse	Clubbing and cyanosis
	Prominent LV impulse	Persistent neck vein distension
	3rd heart sound	Cardiomegaly
	Grade 1–2 ejection systolic murmur	4th heart sound
	Premature beats	Diastolic murmurs
		Sustained arrhythmias

MRI:

- Limited data on the safety in pregnancy exists. It is recommended to be used only in the second and third trimester when diagnostic information cannot be gained from echocardiography.
- Gadolinium crosses the placenta and, as the risks to the foetus are not known, should ideally be avoided in pregnancy.

Radiation Exposure

- If a radiological investigation is indicated to exclude a significant pathology, it should be performed at any gestation, and chest X-rays confer a negligible radiation dose to the foetus at any gestation.
- Childhood rates of leukaemia are not altered by doses below 5 mGy; at 10 mGy, there is a small increased risk of incidence of 1 case per 1,700 exposed individuals [23].
- Congenital malformations are not increased at radiation doses below 100–200 mGy [23].
- The radiation dose which a foetus is exposed to during a typical investigation: chest X-ray 0.01 mGy and CT pulmonary angiogram 0.005–0.1 mGy depending on gestation.

60.6 Delivery

60.6.1 Physiological Changes During Delivery

Catecholamine levels rise, blood loss to a variable degree is almost inevitable, and post-labour, a large volume of extravascular fluid is mobilised by the contracting uterus. This acts as an autotransfusion to attenuate the hypovolaemia caused by the blood loss. During uterine contractions, systolic blood pressure increases 15–25 %, and diastolic blood pressure increases 10–15 %. Cardiac output increases during stage 2 (delivery of the baby) and further still after delivery due to autotransfusion from the contracting uterus [24]. The majority of cardiovascular adaptations of pregnancy resolve by 6 weeks.

60.6.2 Potential Cardiovascular Problems During Delivery

There can be an increased tendency to arrhythmia due to increased sympathetic drive leading to tachyarrhythmias and Valsalva manoeuvres (e.g. bearing down and straining) leading to bradyarrhythmias. Blood loss and/or vasodilation due to

regional anaesthesia or analgesia can lead to hypovolaemia and hypotension. Autotransfusion from the contracting uterus (postpartum), delivery drugs causing vasoconstriction (see drugs below) and aggressive fluid resuscitation can precipitate pulmonary oedema and acute heart failure.

60.6.3 Mode and Timing of Delivery

Spontaneous labour is appropriate for most women with cardiac conditions. Complex cardiac conditions or those requiring anticoagulation sometimes need elective delivery.

Vaginal delivery is associated with reduced blood loss and risk of infection compared to caesarean section and is usually recommended. After delivery, slow oxytocin infusion can prevent postpartum haemorrhage.

Caesarean section is usually indicated for obstetric rather than cardiologic reasons; however, it should be considered for those on oral anticoagulants in preterm labour, patients with Marfan syndrome and dilated aortic roots, those with aortic dissections and those with acute heart failure [10].

60.6.4 Epidurals and Regional Anaesthesia

These can be effective analgesia and reduce sympathetic drive. Effective regional anaesthesia also reduces the tendency and therefore the haemodynamic effects of pushing. However, it can reduce systemic vascular resistance and blood pressure which can be dangerous in those with obstructive lesions (such as HCM and aortic stenosis).

60.7 Cardiac Diseases

60.7.1 Coronary Heart Disease (CHD)

Maternal deaths due to CHD are increasing in the developed world. Pregnancy raises the risk of CHD by three- to fourfold. The risk of CHD is 30 times greater for a pregnant woman over 40 than for a pregnant woman under 20. Previously undiagnosed CHD usually presents in the third trimester. All pregnant women assessed with chest pain should have an ECG. Maternal mortality from acute MI can be up to 7 %. All those who died from CHD reported in the most recent CMACE report [4] had identifiable risk factors. Where stenting is required, bare-metal stents are recommended. The majority of literature on stenting during pregnancy reports the use of bare-metal stents, and the risk of drug-eluting stents is unknown; use of

bare-metal stents also allows a potentially shorter duration of dual anti-platelet therapy which if continued is a significant risk factor for haemorrhage during delivery [10] (Chap. 21).

60.7.2 Valvular Heart Disease

Rheumatic heart disease is the leading cause of maternal heart disease in the developing world and is increasingly common in non-native born populations of the developed world (Chap. 54).

Native valvular disease – general points:

- All patients with suspected valve stenosis or regurgitation should be evaluated with transthoracic echocardiography (TTE) before pregnancy [25].
- Patients referred for a valve operation before pregnancy should be counselled on the risks and benefits of all management options and implications for pregnancy [25].
- It is reasonable to exercise test women with asymptomatic severe valvular stenosis or regurgitation pre-pregnancy [25].

60.7.2.1 Mitral Stenosis (MS)

Mild mitral stenosis is usually well tolerated. Moderate to severe mitral stenosis (valve area <1.5 cm^2) often leads to heart failure [10]. Women with mitral stenosis and AF should be anticoagulated unless contraindicated. Vaginal delivery is recommended if it is mild or moderate MS with NYHA I or II and no pulmonary hypertension; otherwise, caesarean section is recommended [10].

60.7.2.2 Aortic Stenosis (AS)

This is usually due to bicuspid valves in pregnant populations. The valvular gradient can increase significantly during pregnancy due to changes in cardiac output and systemic vascular resistance (SVR). Mild to moderate stenosis is usually well tolerated. However, those with severe stenosis have a tendency to develop heart failure and arrhythmias, though mortality is low. Vaginal delivery is recommended in mild or moderate disease and caesarean section for severe stenosis [10].

60.7.2.3 Aortic and Mitral Regurgitation

Most regurgitant lesions are well tolerated as reduced SVR encourages forward flow. However, there is an increased risk of arrhythmias, and if the LV is impaired, an increased risk of heart failure [10].

60.7.2.4 Prosthetic Valves

Patients with prosthetic valves should have evaluation with TTE before pregnancy and have counselling from a cardiologist about the risks involved [25].

60.7.2.5 Bioprosthesis

- Low-dose aspirin (75–100 mg) is recommended for second and third trimesters [25].

60.7.2.6 Mechanical

The decision on the mode of anticoagulation in women with metallic heart valves is a complex one depending on valve type, size, position, comorbidities, dose of warfarin, gestation and patient choice. The European Society of Cardiology guidelines [10] recommend therapeutic anticoagulation with frequent monitoring as below:

- Warfarin use in the first trimester is reasonable if the dose required is ≤5 mg per day.
- Low-molecular-weight heparin (LMWH) (e.g. dalteparin, enoxaparin and tinzaparin) or unfractionated heparin (UFH) is reasonable with frequent monitoring of anti-Xa or activated partial thromboplastin time (APTT), respectively.
- Warfarin and low-dose aspirin are recommended for the second and third trimesters.
- Change to LMWH or i.v. UFH before elective delivery and restart 4–6 h after.

60.7.3 Infective Endocarditis

This is generally rare and occurs in 1 in 100,000 pregnancies; however, it is 100 times more common in those with congenital or valvular heart disease. Prophylaxis is not recommended for delivery (vaginal or caesarean). Diagnosis and treatment remain the same as for the non-pregnant patient – though some antibiotics should be avoided unless vital, due to the potential risk to the foetus.

60.7.4 Cardiomyopathy

60.7.4.1 Peripartum Cardiomyopathy

This is an idiopathic cardiomyopathy typically occurring in the third trimester but can occur up until 6 months postpartum. It is a diagnosis of exclusion and has an incidence from 1:300 to 1:4,000 pregnancies. The aetiology is uncertain. Treatment is the same as for other causes of heart failure. Though bromocriptine has shown some promise as a specific additional therapy in this condition, its benefit is not well established, and it

is not included in either the ESC or AHA guidelines. Prognosis varies, 50 % recover LV function, and 50 % have persistent reduced LV function. Mortality ranges from 0 to 15 % in different populations, and the recurrence in subsequent pregnancies is 30–50 %.

60.7.4.2 Hypertrophic Cardiomyopathy (HCM)

This is an inherited cardiomyopathy characterised by asymmetrical thickening of the septum and also myocardial fibrosis, left ventricular outflow obstruction and increased risk of arrhythmia. The normal physiological changes during pregnancy such as tachycardia, reduced systemic vascular resistance and venous return can increase the risk of cardiac complications in this population. Beta-blockers should be considered for delivery unless HCM is mild. An Italian study [26] assessed the risk associated with pregnancy in a population with HCM; 100 women were included with 199 pregnancies. The vast majority of women included were NYHA I or II, and less than a quarter had a significant LVOT gradient at rest. There were two maternal deaths. This suggested an increase in relative risk associated with HCM during pregnancy of 17.1 (95 % confidence interval 2.0–61.8). However, it should be noted that the deaths occurred in women with a severe phenotype; one woman had a septal thickness of 30 mm, a resting LVOT gradient in excess of 100 mmHg and progression to NYHA IV in her last pregnancy; the second death was in a woman with a strong family history (five young relatives) of sudden cardiac death.

60.7.4.3 Dilated Cardiomyopathy (DCM)

Pregnancy is a time of increased risk for women with dilated cardiomyopathy, though this may in part be due to undermedication. An American cohort study [27] compared those with idiopathic or doxorubicin-related dilated cardiomyopathy during pregnancy with non-pregnant DCM controls. The pregnant cohort was slightly younger than the non-pregnant cohort (32 vs 35 years), with a lower prevalence of NYHA class III or IV symptoms (28 vs 39 %) and all had moderate or severe LV systolic impairment. Fewer participants in the pregnant cohort were prescribed heart failure medications compared to the non-pregnant cohort, ACE inhibitors 11 % vs 94 % and beta-blockers 33 % vs 89 %. Both cohorts were followed for 16 months. Those in the pregnant group were less likely to have event-free survival of 28 % vs 83 % (cardiac events included cardiac arrest, death, heart failure, arrhythmia, stroke, TIA, angina or MI). Features most predictive of potential events were NYHA functional class and severity of LV systolic function. Almost a third of the events in the pregnant cohort occurred within 6 months of delivery.

60.7.4.4 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is an inherited cardiomyopathy characterised by fatty infiltration of the RV and increased risk of arrhythmia. Limited data exists on the risk of pregnancy in this population, though a small Italian study [28] which followed six women with

ARVC through pregnancy with a mean follow-up after delivery of 2.6 years demonstrated only one episode of sustained ventricular tachycardia in the postpartum follow-up.

60.7.4.5 Heart Failure: General Points

In general treat as you would for a the non-pregnant patient but management will depend on gestation, with early delivery being an option for women failing medical therapy. Some drugs will be contraindicated (see below).

60.7.5 Aortic Diseases

Pregnancy accounts for 50 % of all aortic dissections in women under 40 years of age [29], with the main risk factor being hypertension. Dissection typically occurs in the third trimester or early postpartum, and the risk remains elevated until 6 months postpartum. There are several inherited conditions which increase the risk of aortic dilatation and dissection, the most common one being Marfan syndrome (prevalence 7–17 per 100,000 [30]). A Canadian retrospective cohort study [31] reported an increased risk of significant complication during pregnancy compared to a pregnant woman without Marfan syndrome, odds ratio 10.64 (5.49–20.61), and an even greater risk of pneumothorax, odds ratio 51.95 (6.18–437.10). It is also reported that pregnant women with Marfan syndrome were more than twice as likely to deliver preterm. Women with Marfan syndrome and aorta less than 40 mm have a 1 % risk of aortic dissection during pregnancy [10]. If the aortic diameter is more than 40 mm, the risk increases markedly, and therefore, pregnancy should be counselled against. Those who have dilated aortas and aim to complete a pregnancy should consider beta-blockers which may reduce the rate of aortic dilatation. Elective delivery is recommended with vaginal delivery possible for aortas with a diameter <40 mm and caesarean delivery recommended for those >40 mm [32].

60.7.6 Congenital Heart Disease (Also See Chap. 59)

A systematic review [33] including 2,491 pregnancies in women with congenital heart disease reported cardiac complications occurring in 11 % of pregnancies, with the most common being heart failure (4.8 %), followed by arrhythmia (4.5 %) and other cardiovascular events – including MI, stroke and death (1.9 %). There was a significant rate of miscarriage (15 %) and elective abortion (5 %). The risk of thromboembolism was increased at least 20 times compared to a normal pregnant population. Preterm delivery was increased by 50 %.

60.7.6.1 Shunts: Left to Right (Atrial Septal Defect, Ventricular Septal Defect (VSD) and Patent Ductus Arteriosus)

Small shunts do not cause problems. Most shunts will reduce during pregnancy due to reduced systemic vascular resistance. If SVR increases due to drugs or sympathetic activation, then the shunt can increase. If SVR drops significantly (e.g. from regional anaesthesia), then the shunt can potentially reverse and cause hypoxia.

60.7.6.2 Pulmonary Hypertension and Eisenmenger Syndrome (Right to Left Shunts)

Maternal mortality ranges from 17 to 50 % in severe cases. Most deaths occur in the month after delivery [34]. Deaths occur due to pulmonary hypertensive crises, pulmonary thrombosis or RV failure. Patients who are asymptomatic prior to pregnancy can deteriorate significantly during pregnancy. Predictors of poor outcomes are severity of pulmonary hypertension and general anaesthesia [34]. In the event of pregnancy, termination should be offered. If pregnancy continues, circulating volume should be well maintained, and hypotension, hypoxia or acidosis avoided. In patients who are anticoagulated for their pulmonary hypertension pre-pregnancy, this should be continued. In Eisenmenger syndrome, systemic vasodilation during pregnancy increases the right to left shunt and increases cyanosis. There is a high mortality associated with this condition (20–50 %) usually around the peripartum. The risk can sometimes be attenuated by delivering prematurely.

60.7.6.3 Tetralogy of Fallot

Tetralogy of Fallot is the most common complex congenital cardiac malformation; it consists of pulmonary stenosis, VSD, overriding aorta and RV hypertrophy. All should be already repaired, and the risk is dependent on the quality of the repair. The majority of problems occur on the right side of the heart. Common complications include RV failure, RV outflow or pulmonary stenosis; both of these can deteriorate during pregnancy due to reduced preload. Other common complications such as pulmonary or aortic regurgitation tend not to deteriorate during pregnancy.

60.7.6.4 Coarctation of Aorta

Coarctation of the aorta is a congenital narrowing of the aorta, and problems are unlikely if successfully repaired. If unrepaired, the risks are high to both mother and foetus, and the blood pressure should be very carefully monitored and managed.

60.7.7 Arrhythmias

Ectopics	Commonly increased in pregnancy and are the cause of the majority of palpitations reported by pregnant women.
Supraventricular tachyarrhythmias (SVT)	More common in pregnancy. Can be terminated with vagal manoeuvres or i.v. adenosine; chronic management can include cardioselective beta-blockers or digoxin. Atrial fibrillation/flutter is rare unless there is structural heart disease or endocrine pathology [10].
Ventricular tachyarrhythmias	These are rare; if this is the first presentation of ventricular tachyarrhythmia, an inherited condition or structural heart disease should be considered [10]. If haemodynamically unstable, patients should be immediately cardioverted. If haemodynamically stable and not related to prolonged QT interval, i.v. sotalol can be used, or if stable, monomorphic VT procainamide can be used [10]. Amiodarone is best avoided during pregnancy due to its potentially long-lasting effects on the foetal thyroid.
Long QT syndrome	The risk of cardiac arrest is greater postpartum than during pregnancy [10]. Beta-blockers are recommended to reduce risk.

60.7.8 Conduction Problems, Pacemakers and Implantable Cardiac Defibrillators (ICD)

Conduction problems are rare during pregnancy.

Sinus node disease	Can occur transiently whilst lying supine due to supine hypotensive syndrome or during delivery due to Valsalva manoeuvres.
Atrioventricular node disease	This is rare and is usually associated with structural heart disease or medications.

Pacemakers and ICDs	Pacemaker implantation during pregnancy is generally safe. Having an ICD is not a contraindication to becoming pregnant, and in some rare cases, pregnant women may need ICD implantation during pregnancy to reduce their risk of sudden cardiac death, though where possible this is preferable prior to conception.

60.8 Cardiovascular Medications in Pregnancy and Breastfeeding

Profound physiological changes during pregnancy and the puerperium such as increased blood volume, renal perfusion and hepatic metabolism alter how some medications are handled by the body. Sometimes, this leads to the need for increased drug doses. However, some drugs cross the placenta to foetal circulation, and some cross into the breast milk, and this can lead to harm to the foetus or baby. There is a paucity of data regarding the safety of many medications during pregnancy and breastfeeding; often a pragmatic approach balancing maternal and foetal risk and benefit is required. A summary of the data on the most common cardiovascular medications is set out in Table 60.4.

Obstetric drugs with cardiovascular effects:

Oxytocin, carbetocin, ergometrine and prostaglandins – These induce uterine contractions and are used to induce labour and/or treat or prevent postpartum haemorrhage; they cause vasoconstriction and in some susceptible patients pulmonary oedema.

General approaches to managing cardiac disease in the pregnant woman:

- Early planning.
- Multidisciplinary approach.
- Regular assessment and follow-up.
- Clear delivery plan.
- Elective delivery in certain circumstances.
- Close monitoring around delivery and postpartum.
- Limited pushing in the second stage can reduce haemodynamic instability, useful in certain cardiac conditions.
- Some routine delivery drugs need to be avoided in certain cardiac conditions.

60.9 Concluding Remarks

Pregnancy constitutes a huge physiological challenge. Women with pre-existing cardiovascular disease may deteriorate in pregnancy, and women with previously undiagnosed cardiovascular disease may become symptomatic for the first time in

Table 60.4 Guidance on using common cardiovascular medications during pregnancy and breastfeeding [35–37]

Drug	Pregnancy/ breastfeeding	Guidance
Aspirin	Pregnancy	Safe in low doses
	Breastfeeding	Avoid unless essential as possible risk of Reye's syndrome
Clopidogrel	Pregnancy	Manufacturer advises to avoid
	Breastfeeding	Manufacturer advises to avoid
Statins	Pregnancy	Should be avoided as possible increased risk of congenital abnormalities
	Breastfeeding	Most manufacturers advise to avoid
ACE inhibitors	Pregnancy	Contraindicated during pregnancy as they can cause cardiovascular and central nervous system malformations and renal problems. Risk to foetus is increased further after the first trimester and can also cause foetal renal, cardiac and pulmonary problems
	Breastfeeding	Benazepril, captopril or enalapril preferred during breastfeeding but advised to avoid unless essential for first few weeks as increased risk of newborn hypotension
Angiotensin II-AT_1 receptor antagonists	Pregnancy	Warnings similar to that of ACE inhibitors (readers may refer to Chap. 36 for more details)
	Breastfeeding	Avoid unless essential
Beta-blockers	Pregnancy	Generally safe, though they have been associated with small risk of intrauterine growth restriction, foetal bradycardia and hypoglycaemia in high doses particularly with atenolol. Labetalol is commonly used to treat hypertension during pregnancy
	Breastfeeding	Most are present in only small amounts in breast milk and are generally safe
Heparin	Pregnancy	Does not cross placenta, can be eliminated more rapidly in pregnancy and therefore might need different doses relative to non-pregnant patients. Sometimes needs to be monitored by checking anti-Xa or APTT levels in patients with prosthetic heart valves. Should be stopped before onset of labour
	Breastfeeding	Safe: not present in significant quantities in breast milk
Warfarin	Pregnancy	Teratogenic, can cross the placenta and should be avoided unless essential in the first trimester due to risk of congenital abnormalities. Use after the first trimester should be avoided where possible due to increased risk of foetal haemorrhage, central nervous system and eye abnormalities
	Breastfeeding	Safe: insignificant quantities in breast milk
Dabigatran	Pregnancy	Manufacturer advises to avoid unless essential as toxicity has been shown in animal studies
	Breastfeeding	Manufacturer advises to avoid, as no data is available
Apixaban	Pregnancy	Manufacturer advises to avoid, as no information is available
	Breastfeeding	Manufacturer advises to avoid as drug is present in milk in animal studies
Rivaroxaban	Pregnancy	Manufacturer advises to avoid, as no information is available
	Breastfeeding	Manufacturer advises to avoid as drug is present in milk in animal studies

Table 60.4 (continued)

Drug	Pregnancy/ breastfeeding	Guidance
Amiodarone	Pregnancy	Can cause foetal hypothyroidism and should only be used in life-threatening arrhythmias which are refractory to treatment
	Breastfeeding	Present in milk in significant amounts (to be avoided)
Flecainide	Pregnancy	Can be used to treat maternal or foetal arrhythmias in specialist centres, those with experience and expertise
	Breastfeeding	Present in breast milk but no known adverse events
Verapamil	Pregnancy	Manufacturer recommends avoiding in the first trimester as it can affect uterine blood flow, generally safe in pregnancy after the first trimester
	Breastfeeding	Generally safe
Diltiazem	Pregnancy	Avoid
	Breastfeeding	Present in breast milk but not known to be harmful
Digoxin	Pregnancy	Generally safe in pregnancy
	Breastfeeding	Not present in significant quantities in breast milk
Loop diuretics	Pregnancy	No known teratogenic effects but can cause reduced uterine blood flow
	Breastfeeding	Generally safe but may inhibit lactation
Spironolactone	Pregnancy	Avoid if possible as risk of feminisation of male foetus
	Breastfeeding	Generally safe
Adenosine	Pregnancy	Generally safe
	Breastfeeding	Likely safe as drug has very short half-life

pregnancy. In many instances, the acute management of the pregnant patient with cardiovascular disease is often the same as the non-pregnant, but there are important extra considerations to take into account which may differ depending on the gestation of the foetus. Thus, careful pre-conceptual assessment and planning is important for those with known cardiovascular disease, and multidisciplinary team management, including cardiologists, obstetricians, obstetric anaesthetists and midwives, is mandatory to ensure optimal care.

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Chapter 61
Placental Insufficiency: The Impact on Cardiovascular Health in the Mother and Her Offspring Across the Lifespan

John Henry Dasinger, Suttira Intapad, and Barbara T. Alexander

Abstract Hypertension during pregnancy including preeclampsia or preeclampsia superimposed with chronic hypertension is the most common disease in pregnancy. Preeclampsia is a serious health concern associated with increased risk for morbidity and mortality in the mother and intrauterine growth restriction in the fetus. Low birth weight, defined as 5.5 lb (2.5 kg) or less, serves as a crude marker for intrauterine growth restriction and results from preterm delivery or slow growth during fetal life. Although low birth weight is a leading cause of infant morbidity and mortality, the adverse impact of low birth weight on chronic health of the offspring extends beyond the neonatal period to include an increased risk of cardiovascular disease across the lifespan including preeclampsia. Furthermore, preeclampsia increases the risk for cardiovascular disease in the mother in later life. This chapter will focus on the mechanisms that contribute to the etiology of hypertension during pregnancy and the increased risk for cardiovascular disease in later life of the mother following a pregnancy complicated by preeclampsia. In addition, this review will highlight how slow fetal growth as a consequence of placental ischemia programs an increased risk for hypertension in the offspring across the lifespan.

Keywords Preeclampsia • Low birth weight • Intrauterine growth restriction • Preterm • Developmental programming • Blood pressure

61.1 Introduction

The placenta is critical for fetal growth and regulates the exchange of nutrients, fluids, and waste products between the mother and fetus [1]. Although maternal nutrition can impact fetal growth, uteroplacental blood flow and placental transfer

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capacity are critical mediators of proper growth and development of the fetus [1]. Pregnancy is associated with numerous physiological changes that facilitate the nutritional needs of the growing fetus [2]. Significant changes in the cardiovascular (CV) system of the mother occur during pregnancy in order to accommodate the optimal growth of the fetus [3]. These include increases in blood volume, cardiac output, and maternal heart rate in addition to decreases in systemic vascular resistance and blood pressure [3]. Sufficient blood flow to the uteroplacental unit is essential to maintain the growth and development of the fetus [2]. Thus, extensive remodeling of the uterine vasculature occurs during pregnancy to allow the structural and functional adaptations necessary to accommodate low pressure and high blood flow to the fetus [4]. Energy homeostasis is also altered during pregnancy to accommodate the increased levels of food intake and the growing energy demands of the fetus [5]. However, complications occur when improper remodeling of the uterine vasculature results in placental ischemia leading to impairment in the normal processes that control CV and metabolic adaptations during pregnancy. Placental ischemia also impairs fetal growth leading to intrauterine growth restriction (IUGR) and increased risk for preterm birth [6].

Complications during pregnancy can adversely impact the health of the mother and lead to an increased risk of morbidity and mortality in the neonate [7]. Importantly, numerous epidemiological and experimental studies indicate that complications during pregnancy can also impact the chronic health of the offspring resulting in increased risk for CV disease including hypertension in later life [8–12]. This chapter will discuss the mechanistic changes during pregnancy that lead to the development of hypertension in the mother and IUGR in the fetus. In addition, this chapter will provide insight into the mechanisms that contribute to the development of hypertension and increased CV risk in later life in the mother and her offspring following a pregnancy complicated by placental insufficiency and IUGR.

61.2 Placental Insufficiency

61.2.1 Etiology of Hypertension During Pregnancy

Preeclampsia or preeclampsia superimposed with preexisting chronic hypertension is the most common disease in pregnancy and is a serious health concern associated with increased risk for morbidity and mortality in the mother and her child [6]. Preeclampsia is a multifactorial disorder of pregnancy associated with hypertension and endothelial dysfunction in the mother [13]. The initiating event in preeclampsia involves the development of placental ischemia that results from improper remodeling of the spiral arteries [13]. The ischemic placenta is the source for a number of factors implicated in the etiology of hypertension that develops during preeclampsia including an imbalance in pro- and anti-angiogenic factors, inflammatory cytokines, and agnostic autoantibodies.

The etiology of preeclampsia involves activation of numerous factors that, when released into the maternal circulation, contribute to widespread vascular endothelial dysfunction in the mother and the development of hypertension during pregnancy [14, 15]. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are upregulated during pregnancy and serve as angiogenic factors critical for proper placental development [14]. Serum levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an endogenous antagonist of VEGF, are elevated in women with preeclampsia [16, 17]. In addition, VEGF and PlGF are decreased in women with preeclampsia [16]. Numerous experimental models are utilized to investigate the mechanisms that contribute to the development of hypertension during pregnancy. Induction of uteroplacental insufficiency mimics the initiating event of placental ischemia and, when induced in the nonhuman primate [18], rat [19], or mouse [20], results in a marked increase in circulating sFlt-1 associated with a marked increase in blood pressure suggestive of a causal role. Overexpression of sFlt-1 in the rodent induces hypertension and fetal growth restriction [16, 21, 22] implicating sFlt-1 as a contributory factor to the etiology of hypertension. The immune-reactive cytokine tumor necrosis factor (TNF)-alpha is also increased in women with preeclampsia [23], and chronic infusion of TNF-alpha in the pregnant rat to mimic the twofold increase observed in preeclamptic woman induces hypertension in the rat [24]. Thus, a role for these factors is implicated in the etiology of hypertension during pregnancy (Chap. 33).

Circulating levels of activating autoantibodies against the angiotensin II type 1 receptor (AT_1R-AA) are also elevated in women with preeclampsia [25]. An important role for the AT_1R-AA in the etiology of preeclampsia is suggested by several studies. Chronic infusion of purified AT_1R-AA into the pregnant rat induces hypertension [26]. IgG isolated from preeclamptic women stimulates sFlt-1 secretion in pregnant mice, immortalized human trophoblast cells, and human placental villous explants through activation of the angiotensin II AT_1 receptor (AT_1R) [27]. These studies suggest that increased production of the AT_1R-AA in women with preeclampsia may be an important contributor to the initiation of sFlt-1 production in addition to the development of hypertension. Circulating levels of AT_1R-AA are also increased in rodent models induced via placental insufficiency or increased TNF-alpha [28]. Thus, these studies suggest that the production of AT_1R-AA is a consequence of placental ischemia or release of inflammatory cytokines. Yet, clearly an imbalance of pro- and anti-angiogenic factors in addition to an increase in inflammatory cytokines and production of agnostic autoantibodies is indicated in the etiology of hypertension that results from placental ischemia [14].

The mechanisms that contribute directly to the development of hypertension during pregnancy are multifactorial. Experimental and human studies indicate an important role for increased production of endothelin [13, 29, 30] and oxidative stress [31, 32] and a decrease in nitric oxide bioavailability [33–35] (see Chap. 31). Expression of endothelin is elevated in women with preeclampsia [36] and in experimental models of hypertension induced by placental insufficiency [37] and administration of exogenous Sflt-1 [22] or AT_1R-AA [26] in the pregnant rat. Blockade of the endothelin type A receptor (ET_AR) attenuates hypertension in these experimental

models [22, 26, 30] including the rat model of placental insufficiency (Fig. 61.1) [29] implicating the importance of endothelin beyond a causal association in the etiology of hypertension during pregnancy. Markers of oxidative stress are also increased in the placenta of women with preeclampsia [38] and in pregnant rats that develop hypertension in response to placental insufficiency [31] or exogenous increases in sFlt-1 [32]. Attenuation of hypertension by chronic treatment with tempol (a superoxide dismutase (SOD) mimetic and pleiotropic intracellular antioxidant) in rodent models of placental insufficiency [31] or exogenous sFlt-1 [32] also suggests a contributory role for oxidative stress in the etiology of hypertension that develops during pregnancy. Additional studies indicate that increase in oxidative stress may result from reductions in antioxidants [34] or may be due to impaired nitric oxide bioavailability as indicated in experimental [33] or clinical studies [35].

61.2.2 Cardiovascular Risk After a Pregnancy Complicated by Placental Insufficiency

Preeclampsia is a multi-organ syndrome that results from the release of soluble factors from the ischemic placenta into the maternal circulation resulting in extensive maternal endothelial dysfunction and hypertension during pregnancy [39]. The

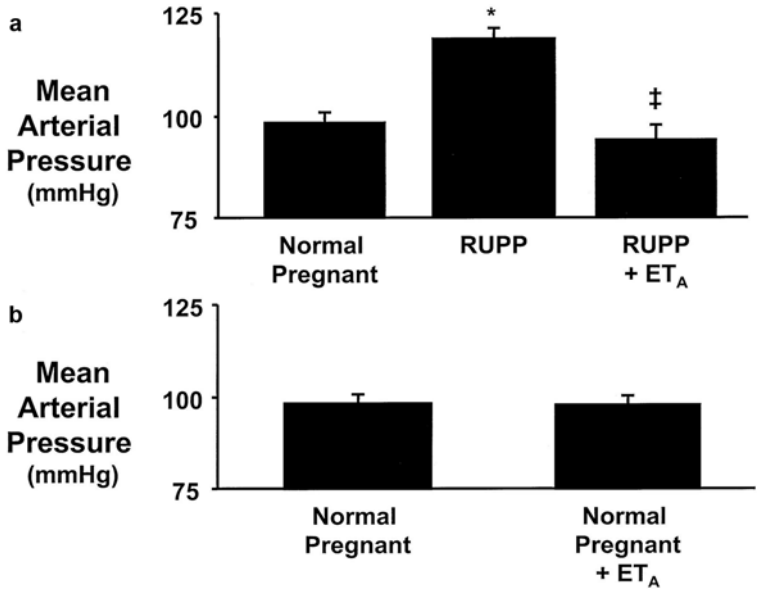

Fig. 61.1 Changes in MAP in response to chronic reduced uterine perfusion (RUPP) in pregnant rats and following pretreatment with an ET_A receptor antagonist (+ET_A) in (**a**) RUPP and (**b**) normal pregnant rats. *$P<0.05$ versus normal pregnant (NP) rats; ‡$P<0.05$ versus RUPP rats and NP rats. All data are expressed as mean ± SEM (Adapted with permission from Ref. [29])

long-term risk to develop chronic hypertension [40] and CV disease across the lifespan [41] is increased following a pregnancy complicated by preeclampsia. One potential contributor to this increased lifetime risk may involve the adverse lingering impact of preeclampsia on CV risk factors in the mother such as altered expression of angiogenesis-related proteins [42] and increased markers of metabolic risk including blood pressure, body mass index (BMI), and insulin resistance [43–47]. Blood pressure and proteinuria remain elevated at 6 weeks after a pregnancy complicated by preeclampsia [43]. Circulating levels of SFlt-1 are reported to remain elevated up to 1 year postpartum [46]. A persistent reduction in endothelial function can persist for several years [44], and increases in BMI, insulin resistance, and blood pressure are observed 2–12 years [45] following a preeclamptic pregnancy. Genetics is also thought to contribute to the risk for preeclampsia (for an extensive review, see reference [48]) and may also impact long-term CV risk following a pregnancy complicated by preeclampsia. Thus, numerous studies indicate that preeclampsia increases a women's CV risk across her lifespan and indicates that her health during pregnancy may provide insight into her future chronic health.

61.3 Low Birth Weight

61.3.1 Etiology of Intrauterine Growth Restriction and Preterm Birth

The etiology of low birth weight includes complications during pregnancy that impact fetal growth including preeclampsia in addition to factors that result in spontaneous preterm delivery. Fetal growth is directly related to nutrient availability, which involves the mother's nutritional intake in addition to the health of the maternal and uteroplacental circulatory system (for an extensive review, see [3]). Although maternal undernutrition can result in improper growth of the fetus, the main cause of fetal growth restriction within the western world involves placental insufficiency [49]. Placental insufficiency can result in the development of hypertension during pregnancy, and it is well established that birth weight decreases with increasing maternal blood pressure [50]. However, blood pressure is also elevated in normotensive pregnancies complicated by IUGR [51–53] suggesting a common etiology of IUGR related to reductions in uteroplacental blood supply. Vessel morphology including decreased lumen circumference is impaired in pregnancies complicated by IUGR [54, 55]. IUGR is also associated with impaired umbilical vein vascular function [55] and increased resistance within the umbilical artery in association with reduced luminal circumference [54]. Additionally, expression of sFlt-1 is significantly increased [56, 57], and circulating levels of PIGF are decreased in the placenta of normotensive pregnancies complicated by IUGR [57]. Maternal smoking is associated with reductions in uteroplacental perfusion [58], and maternal smoking also increases the risk of a pregnancy complicated by IUGR [59]. Thus,

the etiology of IUGR may involve an imbalance in angiogenic and anti-angiogenic factors that leads to impaired uteroplacental perfusion and subsequent IUGR.

Preterm birth is defined as birth before 37 weeks of gestation and is the leading cause of infant morbidity and mortality [60]. The etiology of spontaneous preterm birth involves multiple pathological processes including genetic [61] and environmental factors such as assisted reproductive technology [62], maternal smoking, asthma [59], and maternal stress [63]. Intra-amniotic infections [64] and maternal vascular disease including placental abruption and hemorrhage [65] (for complete review, see reference [60]) are also causative factors for spontaneous preterm delivery. Preterm birth may also be elective due to maternal or fetal complications such as preeclampsia and IUGR [60]. Regardless of these maternal conditions, preterm birth is associated with increased CV risk in the offspring in later life [11].

61.3.2 Developmental Programming of Hypertension

Based on the similar geographical distribution of infant mortality to death from coronary heart disease, David Barker was the first to postulate that factors that slow fetal growth lead to increased CV risk in later life [66]. The inverse association between birth weight and blood pressure supported this original hypothesis [67], and early experimental studies utilizing maternal undernutrition during gestation in the rat to induce hypertension in the offspring provided proof of principle [37, 68]. Currently, it is well established that offspring of pregnancies complicated by preeclampsia [9], preterm birth [11], and IUGR [69] exhibit increased blood pressure in later life. However, despite the etiology of IUGR, slow growth during fetal life is associated with increased blood pressure and CV risk in later life [69]. Extensive investigation into the mechanisms that program increased blood pressure following slow fetal growth indicates that numerous factors contribute to the developmental programming of increased blood pressure and CV risk (for extensive reviews, see [70–72]). The kidney is the primary mediator in the long-term, steady-state control of blood pressure through its ability to regulate chronic fluid and electrolyte balance via the pressure natriuresis mechanism [73]. However, alterations in other regulatory control systems such as the sympathetic nervous system (SNS) [74] and the renin-angiotensin system (RAS) [75] in addition to increased oxidative stress [76] are also indicated in the etiology of essential hypertension (Chaps. 31, 35, and 36). Experimental studies indicate that alterations in these control mechanisms contribute to impaired blood pressure control and the development of hypertension that is programmed in response to slow fetal growth [70–72].

Placental insufficiency in the pregnant rat induces hypertension that is abolished by blockade of the RAS [77] implicating a key role for the RAS in the etiology of hypertension that develops in response to low birth weight. Fetal exposure to a developmental insult leads to significant alterations in expression of the intrarenal RAS in different experimental models of hypertension induced via a development insult (for an extensive review, see reference [10]). In the rat model of IUGR induced

via placental ischemia, temporal changes in expression of the intrarenal RAS are observed [78]. The RAS is critical for proper nephrogenesis [79], and a reduction in nephron number is observed in association with hypertension in rat offspring exposed to placental insufficiency [12]. Intrarenal renin and angiotensinogen expression are reduced during nephrogenesis in the neonatal IUGR rat [78], whereas expression of intrarenal renin and angiotensinogen in addition to renal-angiotensin-converting enzyme (ACE) activity is increased in the male IUGR rat in adulthood [78]. These studies suggest that placental ischemia programs a reduction in the intrarenal RAS during nephrogenesis that may contribute to impaired renal development. However, inappropriate activation of the RAS in later life may contribute to the hypertension that develops in offspring following a developmental insult that induces slow fetal growth and low birth weight.

A reduction in nephron number is observed in individuals with low birth weight [80] and is associated with increased risk for early-onset renal failure in low birth weight individuals [81]. Reduced nephron number is also reported in IUGR rat offspring exposed to placental insufficiency [12]. Low birth weight is also associated with increased susceptibility to renal injury in the rat model of IUGR induced by placental insufficiency [82]. Thus, these studies suggest that slow growth during fetal life impairs renal development in a manner that increases renal vulnerability. However, the importance of reduced nephron number in the development of hypertension following slow fetal growth is not entirely clear. Experimental studies indicate that a reduction in nephron number that occurs during nephrogenesis is associated with increased blood pressure in later life [83]. Congenital defects that result in a solitary functioning kidney also lead to hypertension in later life implicating that a nephron deficiency during development can adversely impact the later long-term control of blood pressure [84]. Yet, glomerular filtration rate and effective renal plasma flow are not altered in hypertensive IUGR rat offspring exposed to placental insufficiency [8] suggesting that a reduction in renal function per se leading to a reduction in pressure natriuresis may not be key mediator of IUGR-induced hypertension. However, as discussed above, inappropriate activation of the RAS may contribute to the development of hypertension programmed in response to low birth weight. In addition, the renal nerves may also play a contributory role in the developmental programming of hypertension following fetal exposure to placental ischemia.

Bilateral renal denervation abolishes hypertension in IUGR rat offspring exposed to placental insufficiency [85–87]. However, the development of hypertension in IUGR rat offspring exposed to placental insufficiency is sex and age dependent with male IUGR rats exhibiting hypertension in young adulthood [8] and females developing hypertension in later life [86]. Therefore, these findings indicate that the stimulus for activation of the renal sympathetic nerves in the hypertension that develops in male IUGR prior to puberty and persists into adulthood may differ from the hypertension that develops in female IUGR in later life.

Hypertension in female IUGR rats is associated with marked increases in total fat mass and circulating leptin [86]. Experimental studies indicate that exposure to a high-fat diet leads to increased adiposity associated with an increase in leptin, renal sympathetic nerve activity, and hypertension [88]. Thus,

the etiology of hypertension that develops in the female IUGR with age may involve increased adiposity resulting in increased leptin. However, hypertension in the male IUGR develops prior to puberty [8] and is not associated with an increase in adiposity or leptin. Thus, programming of high blood pressure in the male IUGR may be inherent and involve a different mechanism relative to the female IUGR.

One potential mechanism may include activation of the renal sympathetic nerves mediated via central activation of the RAS. Angiotensin II generated within the CV control region of the brain is implicated in the renal control of body fluid balance via activation of the renal sympathetic nerves [89]. Blockade of the RAS via intracerebroventricular administration of a losartan, an AT_1 R antagonist, reduces hypertension programmed by maternal protein restriction during fetal life [90] implicating the central RAS in the etiology of hypertension programmed in response to this fetal insult. Although this model of programmed hypertension is induced via maternal undernutrition instead of placental ischemia, systemic blockade of the RAS also abolishes hypertension in low-protein offspring [90, 91], indicating that common mechanistic pathways are involved in the developmental programming of hypertension regardless of fetal insult.

To conclude, these studies indicate that activation of the renal sympathetic nerves contributes to the etiology of hypertension programmed in response to placental ischemia. However, these findings also indicate that the origins of increased renal sympathetic nerve activity may be sex specific implicating that further investigation is needed in order to understand the exact mechanism by which sex impacts the development programming of chronic disease.

Marked increases in renal oxidative stress may also contribute to hypertension induced in response to placental insufficiency. Increases in renal oxidative stress can contribute to renin release and activation of the renal afferent nerves potentiating the development of hypertension [76]. Hypertension in male IUGR rats exposed to placental insufficiency is associated with marked increases in renal markers of oxidative stress [92]. Chronic treatment with tempol abolishes hypertension in male IUGR rats in young adulthood (Fig. 61.2) [92] implicating a role for oxidative stress in the etiology of IUGR-induced hypertension. However, renal markers of oxidative stress are not elevated in normotensive female IUGR rats in young adulthood [92]. Furthermore, renal expression and activity of antioxidant enzymes are increased in female IUGR rats in young adulthood [92] suggesting a compensatory mechanism in the female IUGR.

Clinical studies indicate that the risk for preeclampsia is increased in low birth weight women [93, 94]. The mechanisms that contribute to increased risk for preeclampsia in a woman born with low birth weight are not yet clear. Risk factors for preeclampsia include endothelial dysfunction [95] and a history of chronic conditions such a hypertension, type 2 diabetes, and kidney disease. Low birth weight is associated with endothelial dysfunction [96]. Low birth weight also increases the risk for type 2 diabetes [97], hypertension [67], and renal disease [81] suggesting that low birth weight programs risk factors that enhance susceptibility to preeclampsia. Genetics may also be a contributory factor [98].

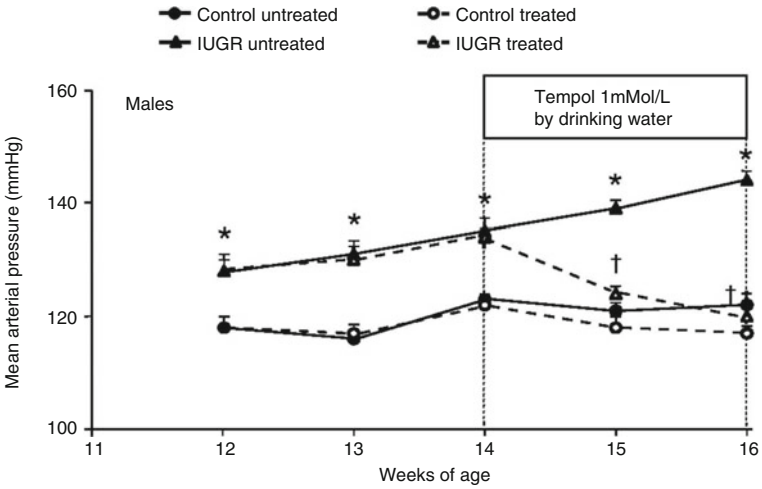

Fig. 61.2 Mean arterial pressure in male control and intrauterine growth-restricted (IUGR) offspring measured by radiotelemetry in conscious, free-moving animals from 12 weeks of age until 16 weeks of age. Animals received the superoxide dismutase (SOD) mimetic tempol (1 mmol/L) or vehicle (tap water ad libitum) for 2 weeks (14–16 weeks of age). $*P<0.05$ versus control-treated and untreated offspring. $\dagger P<0.05$ versus untreated counterpart. Data values represent mean ± SEM (Adapted with permission from Ref. [92])

Therefore, experimental studies are providing insight into the etiology of hypertension that develops in the offspring following a pregnancy complicated by preeclampsia and/or low birth weight. Yet, the translation of the impact of low birth weight and gestational history in consideration of therapeutic interventions and treatments for blood pressure control in later life of an individual born with low birth weight or from a pregnancy complicated by preeclampsia is not yet considered. Additionally, findings from experimental studies indicate that males and females differ in their response to slow fetal growth and highlight the importance of further investigation to discern how sex impacts chronic health following a developmental insult.

61.4 Pharmacological Management of Hypertension During Pregnancy

Clinical trials for the treatment of hypertension in pregnancy are limited, and the use of antihypertensive agents during pregnancy is associated with greater risk for adverse outcomes including IUGR and preterm delivery [99]. However, a task force on hypertension in pregnancy recently provided recommendations for the treatment and management of preeclampsia [6]. The use of antenatal steroids was recommended to improve pulmonary function in preterm babies, whereas magnesium

sulfate was indicated for women with severe preeclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome [6]. The use of antioxidants and vitamins C and E to prevent preeclampsia was contraindicated, and caution was indicated for the use pharmaceutical approaches that inhibited pathways of the RAS including ACE inhibitors and ARBs [6] (Chap. 36). Labetalol, nifedipine, and methyldopa were suggested for the early management of hypertension, and the use of daily low-dose aspirin was recommended to prevent the development of preeclampsia in women at risk [6]. Clearly additional studies are needed to ensure a benefit to maternal outcome versus an adverse impact on fetal development in the pharmaceutical management of a pregnancy complicated by preeclampsia. Investigation into best practices for the management of hypertension in low birth weight individuals is very limited. A survey of antihypertensive medications in Medicaid recipients noted a greater use of calcium channel antagonists in low birth weight black women, whereas ACE inhibitors were more likely prescribed for low birth weight white men [100]. These findings are suggestive of potential insight into physiological differences that may contribute to racial disparities in hypertension management. However, additional studies are warranted to determine the most effective therapy for low birth weight individuals.

61.5 Concluding Remarks

Placental ischemia during pregnancy serves as the initiating event in the etiology of preeclampsia. Placental ischemia impacts fetal growth and development and also exerts a long-term adverse impact on the CV health of the mother and her child. The risk of preeclampsia is increased in women born with low birth weight implicating the transgenerational effect that placental insufficiency in one generation can have on the CV and gestational health of subsequent generations. Clearly the identification of markers for early diagnosis and the development of therapeutic interventions to prevent the development of preeclampsia and low birth weight are warranted to improve chronic health outcomes in women across their lifespan and that of their children.

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Chapter 62
miRNAs in Cardiovascular Development

Katharina K. Wystub and Thomas Boettger

Abstract Understanding the development of the cardiovascular system is essential to comprehend the basis of congenital heart diseases that are among the most common birth defects. Principles and mechanisms in development are also important to understand pathogenic mechanisms in the adult cardiovascular system and for the development of strategies to treat cardiovascular diseases. Cardiovascular development is regulated at many levels, and this always involves the control of gene regulatory networks. The discovery of a novel class of regulatory small noncoding RNAs, miRNAs, allowed new insights into the processes of cardiovascular system development. miRNAs function by binding to the mRNA of protein-coding genes to repress the translation from these mRNAs, thereby regulating protein abundance. The miRNA-target mRNA interaction is independent of transcriptional control of mRNA and independent of the protein encoded by the mRNA; thus, miRNAs offer a new level of regulation that allows increasing complexity of regulatory interactions and is further modified by other factors. Many miRNAs are expressed in the cardiovascular system with different abundance in distinct types of cells. Each miRNA in principle can regulate the expression of hundreds of target genes, and several miRNAs can regulate a target simultaneously. Thus, to understand the impact of miRNA regulation in cardiovascular development, careful and unbiased experimental strategies are essential to pinpoint in vivo functions of miRNAs in the different types of cells of the cardiovascular system in development and disease. In this way, studies on miRNA function are able to reveal general mechanisms of cardiovascular development.

62.1 Introduction

Understanding the development of the cardiovascular system is imperative to comprehend the mechanisms of congenital heart diseases such as atrial/ventricular septal defects (ASD/VSD) or persistent truncus arteriosus (PTA), which account for

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nearly one-third of all major congenital anomalies [1]. Moreover, the understanding of developmental mechanisms might enhance the opportunity to develop new therapeutic approaches that in the future could open possibilities to treat cardiovascular diseases. The heart develops from mesodermal cells of the primary and secondary heart field into a beating linear heart tube that folds to finally form the four chambers of the heart. Chamber specification, cardiac valve formation, increase in cardiomyocyte (CM) number through proliferation, and outflow tract remodeling are subsequent critical steps during heart maturation.

Vascular development involves three major processes: vasculogenesis, angiogenesis, and vascular remodeling. Vasculogenesis is blood vessel formation, and angiogenesis defines the sprouting from preexisting vessels. During early development, mesodermal precursor cells differentiate into blood precursors and vascular precursors (angioblasts), which in turn give rise to blood cells and blood vessels, respectively. In order to ensure the functional circulatory system during development, arteries and veins emerge from the primitive vessel network through extensive remodeling. During this maturation process, mural cells (pericytes and vascular smooth muscle cells, VSMCs) are recruited to provide stability and regulate perfusion.

Development of the cardiovascular system is controlled by a complex regulatory gene network that involves the regulation of genes on epigenetic, transcriptional, and posttranscriptional levels. This regulatory network became increasingly complex during evolution from primitive blood-pumping organs to a four-chambered primate heart [2]. The discovery of small noncoding RNAs, microRNAs (miRNAs, miRs), as regulators of various physiological and pathophysiological processes at the posttranscriptional level identified a new level of regulation to better understand the complex regulatory mechanisms of cardiovascular development.

62.2 microRNAs Are Essential Regulatory Molecules in Cardiovascular Development

Mature functional miRs are single-stranded noncoding RNAs of ~22 nucleotides in length and regulate protein expression of genes at the posttranscriptional level [3, 4]. More than 1,000 different miRNAs have been identified in the vertebrate genome. miRNAs might be encoded in the genome by independent loci or are found in introns of other genes. The intronic miRs can be co-expressed with their host genes or might be expressed from independent promoters. In general, miRNAs are transcribed from the genome by RNA polymerase II resulting in a primary microRNA (pri-miRNA) transcript containing a characteristic hairpin structure. A pri-miRNA transcript may contain more than one microRNA in the case of miRNA clusters.

In the nucleus, the pri-miRNA is processed by a multiprotein complex, containing the RNA-binding protein DGCR8 (DiGeorge syndrome critical region 8) and the RNAse III Drosha to release a ~60–100 nt precursor miRNA (pre-miRNA). The

hairpin-containing pre-miR is exported to the cytoplasm where the RNAse Dicer cuts the pre-miRNA, thereby releasing a microRNA duplex. In most cases one miRNA strand is preferably incorporated into the RNA-induced silencing complex (RISC), whereas the other, also termed miRNA*, is degraded. The mature miRNA guides the RISC to mRNAs containing specific miRNA-binding sites. Binding of the miRNA to its binding site is primarily controlled by a partial complementarity of the miRNA to its miRNA-binding site which is usually located in the 3′untranslated region (3′UTR) of the mRNA. Repression occurs either by destabilization and degradation of the transcript or by blocking the translation. miRNAs thereby modulate gene expression on a posttranscriptional level and enable fine-tuning of miscellaneous processes (Fig. 62.1).

Of special importance for the binding of a miRNA to its target 3′ UTR is the seed sequence that is constituted by the bases 2–7 at the 5′end of the miRNA. Based on such findings, algorithms have been developed and successfully used to predict miRNA-mRNA interactions. Target prediction tools like TargetScan [5] use sequence complementarity of miRNAs to potential target mRNAs to predict the miRNA-mRNA interaction. In addition, conservation of binding sites across species is used to identify functionally important target sites; however, the algorithms predict hundreds to thousands of potential target sites per miRNA. In many cases these potential target sites can be validated in reporter assays; however, whether the expression of a target mRNA is regulated by a miRNA in vivo depends on more factors: for instance, other interacting molecules, expression level, and turnover of miRNA and target RNA. Therefore, under physiological conditions, only a few of the predictable target molecules are indeed regulated by the miRNA, and the functional significance of such regulatory events is not always obvious. Consequently, regulatory events mediated by miRNAs need to be investigated in models that closely resemble in vivo physiological conditions to identify relevant mechanisms.

The RNAse Dicer is essential for the maturation of microRNAs. Deletion of this key enzyme leads to depletion of mature miRNAs. In mice, germ line deletion of Dicer resulted in early embryonic lethality during gastrulation [6]. To circumvent this early lethality and to allow investigation of the requirement of miRNAs for cardiovascular development, other methods such as tissue- and time-specific deletion of Dicer using the loxP-Cre recombinase system were used to obtain conclusive results. Here, the Cre recombinase is expressed in specific tissues at defined developmental stages using appropriate promoters. The Cre recombinase deletes genomic sequences that have been engineered to be flanked by loxP sequences. Fusion of Cre recombinase to domains of the estrogen receptor can be used to induce Cre recombination upon application of tamoxifen to the animals. Cardiac-specific deletion of Dicer in early cardiac progenitors, using NKX2.5-driven Cre recombinase, leads to embryonic lethality due to heart failure 4 days after deletion of Dicer [7]. Deletion of Dicer at an early fetal stage of development using an α-myosin-heavy-chain-driven Cre recombinase resulted in dilation of the heart, and mutant mice died shortly after birth [8]. These Dicer *knockout* hearts displayed aberrant expression of cardiac contractile proteins, as well as sarcomeric disorganization.

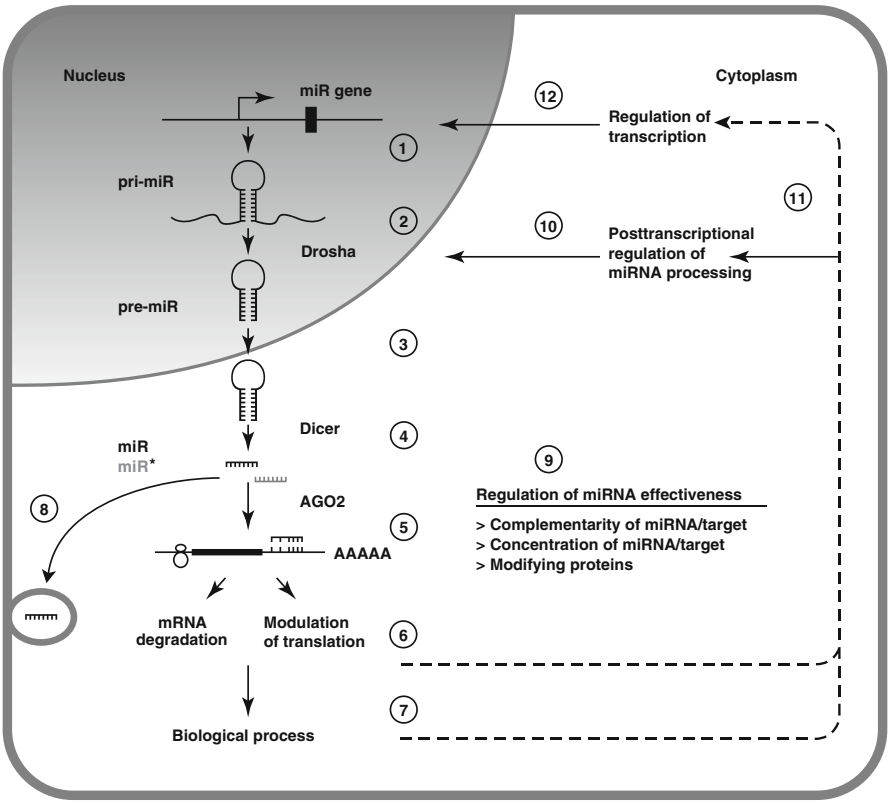

Fig. 62.1 miRNAs are a distinct class of regulatory molecules. MicroRNAs are transcribed from the genome as pri-miRNAs (*1*) that are processed in the nucleus by a protein complex (*2*) containing the DGCR8 and the RNase Drosha as key molecules. The resulting hairpin-structured pre-miRNAs are exported from the nucleus (*3*) and are further processed by the RNase Dicer (*4*). This releases the mature miR molecule and the miR*, the latter is degraded in most cases. Via partial sequence complementarity, the miRNA guides the RNA-induced silencing complex (RISC) to the 3′ untranslated region of protein-coding mRNAs (*5*). The RISC complex containing Argonaute 2 (Ago2) represses translation of mRNAs and may also reduce the abundance of the mRNA molecule. This leads to reduced protein abundance (*6*) and affects biological processes by targeting key molecules or by affecting groups of molecules that may be part of common regulatory processes (*7*). Furthermore miRNA molecules might be released from the cell and are detectable in the extracellular fluids and may exert effects on other types of cells (*8*). The expression of miRNAs is highly regulated not only at the level of transcription (*12*), but also posttranscriptional processing of the miRNA may be regulated (*10*). The effect of the miRNA on a specific target is modulated by many factors including abundance of the miRNA and target molecule in a specific cell, but potentially many other factors like localization of interacting molecules or other RNA-interacting molecules will influence miRNA function (*9*). Interestingly several cases have been identified where miRNAs regulate proteins that themselves may regulate the abundance of the miRNA (*11*), establishing stabilizing regulatory feedback loops

The importance of miRNAs for heart development is further confirmed by the studies using cardiac- and skeletal muscle-specific deletion of DGCR8 in mice. Perinatal deletion of the RNA-binding protein DGCR8, which is part of the miR

processing complex in the heart, resulted in postnatal lethality [9]. The importance of miRNA-mediated regulation for the development of VSMCs has been demonstrated by deletion of Dicer. Smooth muscle-specific deletion of these enzymes leads to extensive hemorrhage at embryonic stages and dilatation of thin-walled blood vessels, caused by a decrease in proliferation of VSMCs [10]. Deletion of Dicer in endothelial cells was compatible with survival of animals; however, angiogenic responses induced in postnatal animals were reduced [11].

In summary, it is clear that miRNAs are essential for cardiovascular development. Every type of cell in the cardiovascular system expresses numerous miRNAs, and many of these miRNAs are more broadly expressed and thus might fulfill more general functions. Thus, we need to focus on the analysis of specific miRNAs to identify specific functions of miRNAs in cardiovascular development (Table 62.1).

62.3 Specific Functions of Individual miRNAs in Heart Development

62.3.1 miR-1/133a Are Essential for Early Embryonic Heart Development

The microRNAs miR-1 and miR-133a are among the most abundant miRNAs found in cardiomyocytes and are specifically expressed in heart and skeletal muscles (Chap. 13). Both miRNAs are evolutionary conserved and are encoded in two

Table 62.1 Summary of important functions of miRNAs in cardiovascular development

microRNA	Type of cell	Function	Ref.
miR-1/133a cluster	Cardiomyocyte	Regulation of smooth muscle gene expression, control of differentiation	[7, 12–14]
miR-208/499 family	Cardiomyocyte	Regulation of structural identity, mediation of cardiomyocyte hypertrophic response	[15, 16]
miR-15 family	Cardiomyocyte	Supports the developmental switch from cardiomyocyte proliferation to hypertrophic growth	[17, 18]
miR-17–92 cluster	Cardiomyocyte	Control of cardiomyocyte proliferation	[19, 20]
miR-16b–25 cluster	Cardiomyocyte	Control of cardiomyocyte proliferation, paralogous to miR-17–92,	[19]
miR-92	Endothelial cell	Limits angiogenesis	[21]
miR-126	Endothelial cell	Affects vascular integrity and angiogenesis, promotes endothelial cell proliferation after injury	[22, 23]
miR-218	Endothelial cells	Essential for endocardial and endothelial cell migration	[24, 25]
miR-143/145 cluster	Vascular smooth muscle cells	Maintenance of contractility and contractile phenotype	[26, 27]

miR-1/133a clusters in the mammalian genome. In humans the miR-1-1/miR-133a-2 cluster is found in an intron of a protein-coding gene on chromosome 20. The miR-1-2/miR-133a-1 cluster is located intergenically on chromosome 18. Both clusters are almost equally expressed in cardiomyocytes and give rise to identical mature miR-1 and miR-133a molecules. The expression of these miRNAs is controlled by factors including SRF (serum response factor), MEF2 (myocyte enhancer factor 2), and MyoD that also induce expression of other muscle-specific genes [28, 29].

Different *loss-of-function* studies demonstrated that the miRNAs miR-1 and miR-133a are essential for proper cardiac development. Deletion of miR-1-2 resulted in a partially penetrant phenotype with ventricular septal defects (VSD), and this was attributed to upregulation of Hand2 transcription factor as a direct target of miR-1 [7]. Deletion of single miR-133a copies did not cause any obvious phenotype, but the complete deletion of both miR-133a genes also resulted in a partial penetrant phenotype with VSD, increased proliferation of neonatal cardiomyocytes, and increased expression of smooth muscle genes in the heart. These observations after complete loss of miR-133a were attributed in part to the upregulation of the direct miR-133a targets cyclinD2 and SRF [12]. In contrast to the previous studies, deletion of both miR-1/133a clusters (dKO) leads to massive defects in early cardiac development [13]. Whereas the initial cardiac specification is not disturbed, deletion of both miR-1/133a clusters leads to massive upregulation of smooth muscle markers in the embryonic heart, reduced proliferation, and thinning of the compact layer of the myocardium.

The miR-1 target myocardin and the miR-133a target Kcnmb1 (calcium-activated potassium channel subunit beta-1) were strongly upregulated after loss of miR-1/133a. Transgenic overexpression of myocardin in the embryonic heart reproduced many aspects of the miR-1/133a phenotype including upregulation of smooth muscle markers, proving that indeed myocardin is an essential miR-1 target that needs to be repressed by miR-1 for proper cardiac development. Myocardin is a cofactor of SRF, and thus increased expression of myocardin also leads to upregulation of miR-1/133a expression. Accordingly, miR-1 and myocardin constitute a regulatory feedback loop that also controls expression of miR-133a and its targets (Fig. 62.2a). Myocardin additionally activates transcription of the smooth muscle-specific potassium channel Kcnmb1 that in turn is a direct target of miR-133a. Taken together these results establish that the miR-1/133a clusters are not needed for initial specification of cardiac cells but act as functional units to repress smooth muscle markers. Moreover, after deletion of miR-1/133a in the embryonic heart, additional previously identified miR-1/133a targets like SRF, Hand2, or Irx5 were not changed in their expression, indicating that regulation of targets might also depend on the developmental stage of the cells or on other modifying factors. These findings were confirmed by the recent miR-1-1 knockout that had a similar phenotype like the miR-1-2 mutants; however, the phenotype also was influenced by the genetic background of mice. Mutation of both miR-1 copies resulted in postnatal lethality due to severe dysfunction and disturbed sarcomeric structures [14]. Although the miR-1 mutant mice survive until 2 weeks after birth, the upregulation of myocardin is the likely cause for the observed ectopic smooth muscle gene expression in the heart.

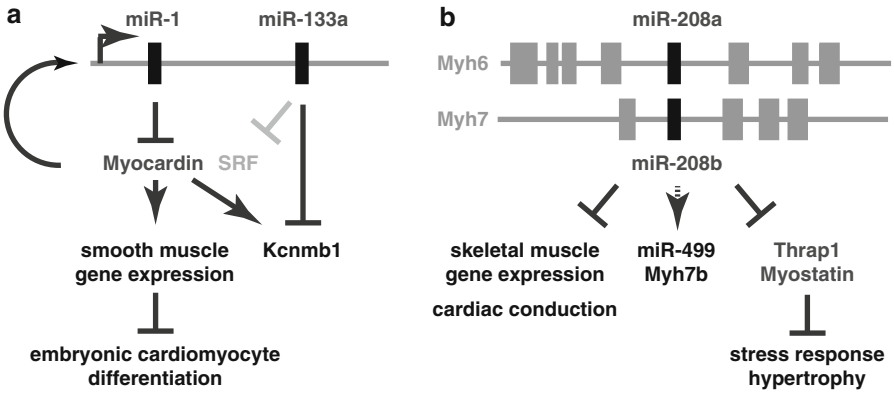

Fig. 62.2 Functions of miRNAs in cardiomyocyte development. miRNAs affect development of the heart at different stages. (**a**) Aside from other functions at later developmental stages, the miRNA cluster miR-1/133a is essential to modulate smooth muscle gene expression in the early heart. In early heart development, well before cardiac chamber formation, cardiomyocytes (CMs) express several smooth muscle marker genes that are repressed during later stages of development. At embryonic stages, miR-1/133a is essential to repress myocardin that together with SRF drives the expression of smooth muscle genes, including Kcnmb1. In a feedback loop, myocardin drives expression of its repressor miR-1/133a, finally leading to repression of smooth muscle gene expression during further cardiomyocyte development. miR-133a directly represses smooth muscle-specific genes like the potassium channel Kcnmb1. In adult stages, miR-133a additionally represses translation of SRF to repress smooth muscle gene expression in adult CMs. (**b**) miRNAs of the miR-208 family have functions in postnatal development of the heart. miR-208a/b are encoded in the myosin-coding genes *Myh6/7* and repress the expression of skeletal muscle-specific genes in the heart. Moreover, the miRNAs drive expression of miR-499 and of its host gene *Myh7b* and are essential to support stress responses of the heart like the hypertrophic growth after specific challenges

62.3.2 miRNAs Affecting Proliferation and Morphogenesis of the Heart

The conserved miR-17–92 cluster comprises six microRNAs (miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, miR-92-1) that are processed from one precursor transcript [19]. Many functions have been assigned to this cluster such as oncogenic potential, functions in skeletal development, and B-cell differentiation. In addition to this cluster two paralogous clusters are found in the genome: the miR-106a–363 (miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92-2, -363) and the miR-106b–25 cluster (miR-106b, miR-93, miR-25). Based on identical seed sequences, the miRNAs in these clusters can be grouped into four miRNA families suggesting at least partial redundancy of the clusters. The miRNA clusters also have a role in cardiovascular development as miR-17–92-deficient mice die after birth due to lung hypoplasia and ventricular septal defects (VSDs), whereas mice deficient of miR-106a–363 or miR-106b–25 cluster are viable. Concomitant deletion of miR-17–92 and miR-106b–25 clusters was embryonically lethal prior to embryonic day

15 with severe disturbance of heart development with thinner ventricular wall and defective ventricular and atrial septation [19]. Heart-specific deletion and overexpression of the miR-17–92 cluster demonstrate that the cluster is required and sufficient for CM proliferation in postnatal and adult hearts [20].

Adult cardiomyocytes cannot proliferate, and this restricts the regenerative potential after injury. However, shortly after birth, mouse CMs still proliferate and then become binucleated and withdraw from cell cycle during early postnatal development [30]. Understanding the developmental mechanisms of cell cycle withdrawal might help to at least partially reverse such processes and to regain CM proliferation after injuries.

Interestingly, the miR-15/195 family of miRNAs is upregulated during the critical postnatal period. Premature overexpression of miR-195 leads to hypoplasia of the heart and limits the regenerative potential of the neonatal heart. Similarly, locked nucleic acid-based inhibition of miR-15 from birth to adulthood increased cardiac function after myocardial infarction in adult mice [17, 18].

62.3.3 miR-208/499 Regulate Adult CM Identity and the Stress Response of the Heart

The miR-208/499 microRNA family (located in the introns of myosin-coding genes) is specifically expressed in the heart and has a function in heart development [15, 16]. The microRNAs 208a and 208b are both encoded within heart-specific myosin genes. miR-208a is found in an intron of *Myh6* (α-MHC), while miR-208b is located in an intron of *Myh7* (β-MHC). The related miR-499 is encoded in an intron of *Myh7b*. In mice, the myosin isoforms are expressed in the heart at different developmental stages with β-MHC in fetal cardiomyocytes and α-MHC in adult cardiomyocytes. However, in larger animals β-MHC expression persists in adults. Deletion of miR-208a in mice does not affect survival of the animals but results in upregulation of skeletal muscle markers and loss of *Myh7b*/miR-499 expression in adult hearts, indicating that the miRNAs co-expressed with their host genes affect the composition of other structural proteins in the heart. Moreover, miR-208 affects cardiac stress response by targeting Thrap1 (thyroid hormone receptor-associated protein 1) and myostatin. Again there are differences in miRNA function at different developmental stages as miR-208a does not affect expression of miR-499 in the embryonic heart but is essential for expression of Myh7/miR-499 in the adult heart (see also Chaps. 13 and 18).

62.4 microRNAs in Endothelial Cell Development

Vessel formation involves the differentiation of angioblasts to endothelial cells, and miRNA profiling of human umbilical cord vein endothelial cells (HUVEC) has demonstrated that miR-126 is highly expressed in endothelial cells (ECs) [31]. The intronic miR-126, also termed angiomiR, has an essential role in angiogenic

signaling and vascular integrity and in hematopoietic stem cells. In mice, targeted deletion of miR-126 caused vessel leakiness, hemorrhage, and partial embryonic lethality. Mutant embryos had defects in EC proliferation, migration, and angiogenesis. A subset of surviving mice suffered from myocardial infarction, due to defective cardiac neovascularization. The study revealed Spred1 to be a primary target of miR-126 regulation. Increased Spred1 after deletion of miR-126 diminished pro-angiogenic signaling by VEGF and FGF that are major regulators of angiogenesis [22].

Interestingly, both mature miRNA strands originating from the pre-miRNA may have distinct functions. The less abundant strand has recently been shown to stimulate EC proliferation to promote endothelial regeneration in adult animals and thus to limit atherosclerotic plague development [23]. Indeed this study suggests a potential miRNA-based therapeutic approach to limit atherosclerosis.

The miRNA miR-218 regulates the Slit/Robo signaling pathway, which is important for the vascular development. In zebrafish, miR-218 controls the expression of Robo1/2, and this interaction is required for heart tube formation by modulating VEGF signaling in endocardial cells [24]. Similarly in mice, the miR-218/Slit/Robo cascade seems to be essential for endothelial cell migration during development [25].

Members of the miR-17–92 cluster, especially miR-92, also have specific roles in angiogenesis. Antagomir-based reduction of miR-92a function in mice enhances reperfusion after injury and limits cardiac damage after myocardial infarction. Moreover, miR-92a forced overexpression in vitro and in vivo blocked new blood vessel formation [21]. Unfortunately, until now genetic dissection of the functions of miR-92 is hindered by the presence of three other miRNAs originating from the paralogous clusters with identical seed sequence and by functions of miR-92 in other organs.

62.5 Function of miR-143/145 in Vascular Smooth Muscle Cells

Vascular smooth muscle cells (VSMCs) in adult animals are specialized cells that are contractile, regulate the blood vessel diameter, and thereby also contribute to regulation of blood pressure. During development, VSMCs are highly proliferative and migratory. They contribute to vessel formation by synthesizing extracellular matrix components and forming gap junctions with endothelial cells [32]. VSMCs in mature vessels proliferate rarely and exhibit a contractile phenotype characterized by specific morphology and gene expression. However, VSMC are capable of changing their phenotype in order to adapt to changes in their environment, i.e., in response to hypertension, vascular injury, or arteriosclerosis. This phenotypic switch facilitates proliferation, migration, and extracellular matrix production.

In principle, miRNAs are essential for smooth muscle development as demonstrated by the late embryonic lethality of the smooth muscle-specific deletion of Dicer. Among other miRNAs, miR-143 and miR-145 are the most prominent for this type of cell, and they are also specific for smooth muscle cells. These miRNAs

are also encoded in a cluster with common regulation of transcription by SRF and myocardin-directing expression in the developing heart and vascular and visceral SMCs [26]. Deletion of the miR-143/145 cluster from mouse genome revealed that these miRNAs are not needed for development of smooth muscle cells; however, they are essential for the contractile phenotype of the VSMCs. This might be mediated by repression of several target genes including KLF4 and angiotensin-converting enzyme (ACE). Loss of ACE repression in the VSMC leads to release of the angiotensin II at the VSMC, thus causing constant activation of signaling pathways inducing contraction of VSMC. Together with other mechanisms, this may lead to desensitization of these pathways and induce the synthetic phenotype of VSMCs. Induction of the synthetic phenotype finally leads to formation of arteriosclerotic lesions in the vessels of miR-143/145 mutant mice [27]. Interestingly, loss of miR-143/145 does not affect specification of smooth muscle cells in vivo, although miR-145 in principle can convert fibroblasts to a smooth muscle cell-like phenotype and miR-145 overexpression can partially rescue Dicer-deficient smooth muscle cells [10].

62.6 Concluding Remarks

In summary, numerous studies have revealed functions of various microRNAs in the development as well as in pathological situations of the cardiovascular system. miRNAs constitute another layer of regulation of physiological processes and thus support the increasing complexity of developmental and physiological regulation in mammals. miRNAs target molecular pathways by influencing specific key molecules or by modulating targets that are common in certain pathways, and this properties might allow the use of miRNAs also in therapeutic applications. Although the recent advances in miRNA research uncover first insights into the importance of miRNAs for cardiovascular development, it is clear that more research is needed to obtain a more comprehensive understanding of miRNA-mediated regulation of cardiovascular system development and function.

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