Ichiro Wakabayashi · Klaus Groschner
*Editors*

# Interdisciplinary Concepts in Cardiovascular Health

## Volume III: Cardiovascular Events

Springer

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# Preface

According to the recent WHO statistics, cardiovascular diseases are the leading cause of death globally with an estimated 17.3 million people dying from cardiovascular disease in 2008, representing 30 % of all global deaths. Of these deaths, an estimated 7.3 and 6.2 million were attributed to coronary heart disease and stroke, respectively. Undisputedly, cardiovascular diseases are predicted to remain as the leading cause of death. Over the past decades, we have gained substantial knowledge about the molecular and cellular mechanisms underlying disease initiation and progression and in parallel have identified a plethora of potential risk factors. Moreover, epidemiology has recently moved closer to molecular pathology, enabling a first glimpse to be captured of essential molecular mechanisms that determine cardiovascular risk within a certain population. This book is an attempt to provide an overview of the recent development in this field.

There is common consent that pathogenesis of cardiovascular disorders is mainly based on atherosclerosis, which progresses with age. Thus, retardation of atherosclerosis progression is considered the most effective strategy to prevent cardiovascular morbidity and mortality. A wide range of risk factors are involved in the pathogenesis of atherosclerosis. Lifestyle-related factors including diet, nutrition, physical activity, habitual smoking and alcohol consumption, socioeconomic factors, and psychological stress as modifiable factors, in addition to age, gender, race/ethnicity, and genetic polymorphisms as destined factors, are recognized to determine the risk for cardiovascular events. These "primary risk factors" typically promote the genesis of disorders that may be understood as "secondary risk factors" such as obesity, hypertension, diabetes, dyslipidemia, hyperuricemia, and metabolic syndrome. Thromboatherosclerotic alterations in arterial wall structure result from a combination of secondary risk factors and lead to terminal cardiovascular events such as ischemic heart disease and stroke. Our book is accordingly structured into sections, published as separate volumes that give detailed information about our current understanding of primary and secondary risk factors, as well as on terminal cardiovascular events. To sustain cardiovascular health, prevention or compensation of primary risk determinants, as well as early diagnosis and treatment of secondary risk factors, are undoubtedly key strategies.

Accumulated groundbreaking insights into cellular mechanisms involved in the pathogenesis of cardiovascular aging and disease include the identification of vasoactive prostanoids, lipoprotein receptors, and nitric oxide. The general scientific

value of these basic findings, as well as their wider impact on our society, is well documented by the Nobel Prizes given for each of these discoveries. This book aims to introduce established principles of both cardiovascular epidemiology and molecular pathophysiology and makes a unique attempt to bridge the gap between epidemiological knowledge and current molecular concepts in cellular pathophysiology. The authors spotlight future avenues for research in basic pathophysiology, as well as in cardiovascular therapy and prevention. The comprehensive overview of cardiovascular pathophysiology provided with this book is expected to help readers to address questions on unresolved pathomechanisms and/or to interpret novel epidemiological findings on cardiovascular disorders.

Finally, the editors would like to express their sincere appreciation to all contributors for their dedicated collaboration in this project. We wish to additionally thank Ms. Karin Osibow for her competent and patient support in editing this book.

We hope our book will enable readers to connect epidemiological knowledge with principles of molecular pathophysiology, thereby promoting the development of new strategies for sustaining cardiovascular health.

Hyogo, Japan — Ichiro Wakabayashi
Graz, Austria — Klaus Groschner

# Contents

# Abbreviations

| | |
|---|---|
| AAA | Abdominal aortic aneurysm |
| ABI | Ankle–brachial systolic pressure index |
| ACE | Angiotensin-converting enzyme |
| ACh | Acetylcholine |
| ACS | Acute coronary syndrome |
| ADP | Adenosine diphosphate |
| AF | Atrial fibrillation |
| AGE | Advanced glycation end products |
| AHA | American Heart Association |
| ALI | Acute limb ischemia |
| AMI | Acute myocardial infarction |
| AMPKα-2 | Adenosine monophosphate-activated protein kinase alpha-2 |
| Ang I/II | Angiotensin I/II |
| ANP | Atrial natriuretic peptide |
| AP-1 | Activator protein-1 |
| ARB | Angiotensin AT1 receptor blocker |
| ARVD | Arrhythmogenic right ventricular dysplasia |
| ASA | Acetylsalicylic acid, aspirin |
| ATBI | Atherothrombotic brain infarction |
| ATP | Adenosine triphosphate |
| AVB | Atrioventricular block |
| AVRT | AV reentry tachycardia |
| BAEC | Bovine aortic endothelial cell |
| $BH_4$ | Tetrahydrobiopterin |
| BMI | Body mass index |
| BNP | Brain/B-type natriuretic peptide |
| BP | Blood pressure |
| CAA | Cerebral amyloid angiopathy |
| CAD | Coronary artery disease |
| CAP | Calponin |
| CAS | Carotid artery stenting |
| CAT1 | Type 1 cationic amino acid transporter |
| CCB | Calcium channel blockers |

| | |
|---|---|
| CCE | Capacitative $Ca^{2+}$ entry |
| CE | Cholesteryl ester |
| CEA | Carotid endarterectomy |
| cGMP | Cyclic guanosine monophosphate |
| CHF | Chronic heart failure |
| CICR | $Ca^{2+}$-induced $Ca^{2+}$ release |
| CKD | Chronic kidney disease |
| CLI | Critical limb ischemia |
| CMB | Cerebral microbleed |
| COPD | Chronic obstructive pulmonary disease |
| COX-1 | Cyclooxygenase-1 |
| CPVT | Catecholaminergic polymorphic ventricular tachycardia |
| CRP | C-reactive protein |
| CSE | Cigarette smoke extract |
| CSVD | Cerebral small vessel disease |
| CT | Computed tomography |
| CTEPH | Chronic thromboembolic pulmonary hypertension |
| Cu,Zn-SOD | Cu,Zn-superoxide dismutase |
| CUS | Compression ultrasound |
| CV | Cardiovascular |
| DAD | Delayed afterdepolarizations |
| DAG | Diacylglycerol |
| DCM | Dilative cardiomyopathy |
| DM | Diabetes mellitus |
| DVT | Deep venous thrombosis |
| EAD | Early afterdepolarizations |
| EC | Endothelial cell |
| ECG | Electrocardiography |
| EDHF | Endothelium-derived hyperpolarizing factor |
| EDRF | Endothelium-derived relaxing factor |
| EF | Ejection fraction |
| EGF | Epidermal growth factor |
| eGFR | Estimated glomerular filtration rate |
| eNOS | Endothelial nitric oxide synthase |
| EPC | Endothelial progenitor cell |
| ESRD | End-stage renal disease |
| ET-1 | Endothelin 1 |
| $ET_{A/B}R$ | Endothelin receptor A, B |
| EVE | Endogenous vascular elastase |
| FAD | Flavin adenine dinucleotide |
| FFA | Free fatty acid |
| FMD | Flow-mediated dilation |
| GFR | Glomerular filtration rate |

| | |
|---|---|
| GPCR | G-protein-coupled receptor |
| GWAS | Genome-wide association study |
| $H_2O_2$ | Hydrogen peroxide |
| HCM | Hypertrophic cardiomyopathy |
| HCN | Hydrogen cyanide |
| HCVD | Hypertensive cardiovascular disease |
| hdAVB | High-degree atrioventricular block |
| HDL | High-density lipoprotein |
| HF | Heart failure |
| HFPEF | Heart failure with preserved ejection fraction |
| HIF | Hypoxia-inducible factor |
| HRV | Heart rate variability |
| hsCRP | High-sensitivity C-reactive protein |
| HUVEC | Human umbilical vein endothelial cell |
| IC | Intermittent claudication |
| ICAM-1 | Intercellular adhesion molecule 1 |
| ICD | Implantable cardioverter–defibrillator |
| IFN-γ | Interferon-gamma |
| IHD | Ischemic heart disease |
| IK | intermediate-conductance $Ca^{2+}$-activated $K^+$ channel |
| IL-1, IL-4, IL-6, IL-8, -18 | Interleukin-1, interleukin-4, interleukin-6, interleukin-8, interleukin-18 |
| IMT | Intima–media thickness |
| iNOS | Inducible nitric oxide synthase |
| $IP_3$ | Inositol 1,4,5-trisphosphate |
| IVC | Inferior vena cava |
| JNK | c-Jun N-terminal kinase |
| LDL | Low-density lipoprotein |
| LI | Lacunar infarction |
| LNA | Locked nucleic acid |
| LOC | Level of consciousness |
| LQT | Long QT |
| LV | Left ventricle (LV) |
| MAPK | Mitogen-activated protein kinase |
| MCP-1 | Monocyte chemoattractant protein 1 |
| MI | Myocardial infarction |
| MIR | Myocardial insulin resistance |
| MLC | Myosin light chain |
| MLCK | Myosin light chain kinase |
| MMP-1, MMP-2, MMP-8, MMP-9 | Matrix metalloproteinase-1, matrix metalloproteinase-2, matrix metalloproteinase-8, matrix metalloproteinase-9 |
| MRA | Magnetic resonance angiography |
| MRI | Magnetic resonance imaging |

| | |
|---|---|
| MRV | Magnetic resonance venography |
| NADP | Nicotin amide adenine dinucleotide phosphate |
| NADPH | Nicotin amide adenine dinucleotide phosphate, reduced form |
| NCX | $Na^+/Ca^{2+}$ exchanger |
| NFkB | Nuclear factor kappa-light-chain enhancer of activated B cells |
| nNOS | Neuronal nitric oxide synthase |
| NO | Nitric oxide |
| NOS | Nitric oxide synthase |
| NVAF | Non-valvular atrial fibrillation |
| ODN | Oligodeoxynucleotide |
| PAC | Single irregular ("premature") atrial contractions |
| PAD | Peripheral arterial disease |
| PAH | Pulmonary arterial hypertension |
| PAI-1 | Plasminogen activator inhibitor 1 |
| PAP | Pulmonary arterial pressure (PAP) |
| PASMC | Pulmonary arterial smooth muscle cell |
| PAWP | Pulmonary arterial wedge pressure (PAWP) |
| PDE3 | Phosphodiesterase 3 |
| PDE-5 | Phosphodiesterase type-5 |
| PDGF | Platelet-derived growth factor |
| PE | Pulmonary embolism |
| $PGH_2$ | Prostaglandin $H_2$ |
| $PGI_2$ | Prostaglandin $I_2$, prostacyclin |
| PH | Pulmonary hypertension |
| PI3-K | Phosphoinositide 3-kinase |
| $PIP_2$ | Phosphatidylinositol 4,5-bisphosphate |
| PKC | Protein kinase C |
| $PLA_2$ | Phospholipase $A_2$ |
| PLC | Phospholipase C |
| PPAR-γ | Peroxisome proliferator-activated receptor gamma |
| pSVT | Paroxysmal supraventricular tachycardias |
| PVC | Single irregular ("premature") ventricular contractions |
| PVR | Pulmonary vascular resistance |
| QOL | Health-related quality of life |
| RAAS | Renin–angiotensin–aldosterone system |
| RAGE | Receptors of AGEs |
| RAS | Renin–angiotensin system |
| RHC | Right heart catheterization |
| ROS | Reactive oxygen species |

| | |
|---|---|
| RV | Right ventricle |
| RyR | Ryanodine receptor |
| SAH | Subarachnoid hemorrhage |
| SCD | Sudden cardiac death |
| SCI | Silent cerebral infarction |
| SERCA2a | Sarcoplasmic reticulum $Ca^{2+}$-ATPase 2a |
| SK | Small-conductance $K_{Ca}$ channel |
| SMC | Smooth muscle cell |
| SOD | Superoxide dismutase |
| SR | Sarcoplasmic reticulum |
| SSS | Sick sinus syndrome |
| STEMI | ST-segment elevation myocardial infarction |
| SVT | Supraventricular tachycardias |
| TCFA | Thin-cap fibroatheroma |
| TGF-β | Transforming growth factor-beta |
| TIA | Transient ischemic attack |
| TIMP-1, TIMP-2 | Tissue inhibitor of MMP-1, tissue inhibitor of MMP-2 |
| TNF-α | Tumor necrosis factor alpha |
| tPA | Tissue plasminogen activator |
| TRPC | Canonical transient receptor potential channel |
| $TXA_2$ | Thromboxane $A_2$ |
| TZD | Thiazolidinedione |
| VCAM-1 | Vascular cell adhesion molecule-1 |
| VEGF | Vascular endothelial growth factor |
| VF | Ventricular fibrillation |
| VSMC | Vascular smooth muscle cell |
| VT | Ventricular tachycardia |
| VTE | Venous thromboembolism |
| WHO | World Health Organization |
| WML | White matter lesion |

# Ischemic Heart Disease

# 1

Yasuhiko Sakata and Hiroaki Shimokawa

**Abstract**

Despite recent advances in the diagnosis and management of ischemic heart disease, it still remains a major cause of morbidity and mortality worldwide and thus warrants continuous challenges in therapeutics and research on its pathogenesis. It is widely accepted that ischemic heart disease is caused not only by plaque rupture and/or anatomical obstruction but also by epicardial and/or microvascular coronary spasm. Thus, further understanding on the pathogenesis of both atherosclerosis and vascular dysfunction and its translation into clinical practice are required for better management of ischemic heart disease. In particular, comprehensive understanding of vascular tone regulation, which plays an important role to develop vascular dysfunction, is necessary because new findings and insights have been accumulated in this field, including nitric oxide as an endothelium-derived relaxing factor (EDRF), $H_2O_2$ as an endothelium-derived hyperpolarizing factor (EDHF), and Rho-kinase pathway as a regulator of vascular smooth muscle contraction. In this chapter, we will briefly review the current concepts of cardiovascular events in ischemic heart diseases, particularly focusing on acute coronary events and vascular dysfunction, with a special reference to endothelial dysfunction, vascular tone, and microvascular angina.

**Keywords**

Ischemic heart disease • Atherosclerosis • Vasospasm • Endothelial function • Rho-kinase • Microvascular angina

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## 1.1 Introduction

Ischemic heart disease is the leading cause of morbidity and mortality worldwide. Cardiovascular events usually occur in association with episodes of myocardial ischemia, caused by an imbalance between myocardial oxygen supply and demand in patients with ischemic heart diseases. This imbalance is often caused by obstruction of coronary blood flow by coronary stenosis, thrombosis, and/or hyperconstriction (vasospasm) of epicardial and microvascular coronary arteries, resulting in cardiac dysfunction, arrhythmias, myocardial infarction, and sudden death. Thus, management and prevention of both atherosclerosis and vasospasm is clinically important to prevent cardiovascular events. In this chapter, we will briefly review the current concepts of cardiovascular events, particularly focusing on acute coronary events and then vascular dysfunction, with a special reference to endothelial dysfunction, the Rho-kinase pathway, and microvascular angina.

## 1.2 Cardiovascular Events

### 1.2.1 Epidemiology

Among the cardiovascular events, acute coronary events including acute myocardial infarction (AMI) are the leading cause of morbidity and mortality worldwide. In the United States, it is reported that more than 1,000,000 per year suffer coronary events and more than 400,000 per year die of coronary artery disease including acute coronary syndrome (ACS) and sudden cardiac death (Roger et al. 2011). Along with the industrialization and/or urbanization of lifestyles worldwide, the population is rapidly aging in association with the epidemics of obesity and metabolic syndrome since the decades ago, particularly in Japan (Yamada et al. 1997).

We have recently revealed that the incidence of AMI has been increasing, using the database of the Miyagi-AMI Registry Study, a multicenter observational study that prospectively registers all of the AMI patients in the Miyagi Prefecture, Japan (Takii et al. 2010). The Miyagi Prefecture, located in northeastern Japan, has a typical balance of urban and rural areas. Between 1979 and 2008, the Miyagi-AMI Registry Study enrolled 22,551 AMI patients and demonstrated that the age-adjusted incidence of AMI (/100,000 persons/year) markedly increased from 7.4 in 1979 to 27.0 in 2008 (Fig. 1.1) (Takii et al. 2010). Another analysis of the Miyagi-AMI Registry Study (Hao et al. 2012) revealed that the incidence of AMI (/100,000 persons/year) increased more rapidly in the rural area (24.2–51.4) than in the urban area (31.3–40.8) ($P<0.001$), with rapid aging in both areas from 1998 to 2009 (Fig. 1.2). Interestingly, in the rural area, the age-adjusted incidence of AMI in young (<44 years) and middle-aged (45–64 years) male patients (both $P<0.05$) significantly increased, along with a markedly increased prevalence of dyslipidemia (Hao et al. 2012). Thus, urbanization and lifestyle changes have been associated with the increased incidence and mortality from AMI in the contemporary era of Japan.

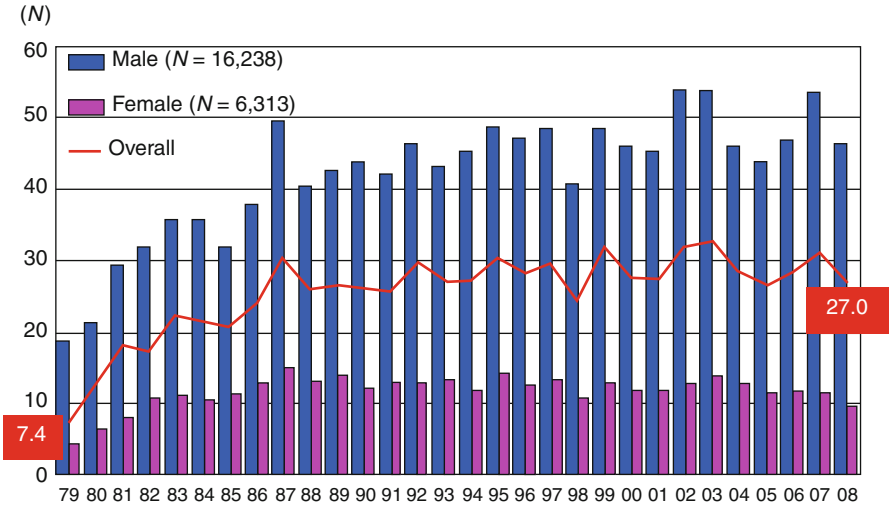


**Fig. 1.1** Trends in incidence of acute myocardial infarction in the Miyagi Prefecture, Japan: age-adjusted incidence (/100,000 persons/year) of acute myocardial infarction has increased from 7.4 in 1979 to 27.0 in 2008 (Reproduced from Takii et al. (2010) with permission)

Contrary to the decrease in mortality after AMI, an increase in incidence of heart failure during the hospital course and long-term follow-up has also been reported in post-AMI patients in the United States (Velagaleti et al. 2008; Ezekowitz et al. 2009). As for in Japan, we also have revealed an increase in the prevalence of coronary artery disease as a background of heart failure, along with changes in clinical characteristics of heart failure patients registered to the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study (Shiba et al. 2011). Thus, appropriate management of coronary artery disease is of great clinical importance to prevent development of heart failure and other cardiovascular events in patients with ischemic heart diseases.

### 1.2.2 Management

During the past two decades, a series of large clinical trials have demonstrated the efficacy and safety of novel treatments for ACS, particularly for AMI. Both mechanical and pharmacological reperfusion strategies and adjunctive antithrombotic or cardioprotective treatments have been proven to decrease mortality of AMI patients. There are also lines of evidence for antiplatelet therapy, β-blockers, statins, and renin-angiotensin-system (RAS) inhibitors to reduce morbidity and mortality of AMI patients.

The optimal treatment of ACS (AMI) has dramatically changed along with the incorporation of evidence from clinical trials. To date, many clinical guidelines have underlined the importance of early reperfusion and the use of evidence-based therapies to reduce morbidity and mortality, and the implementation of evidence-based

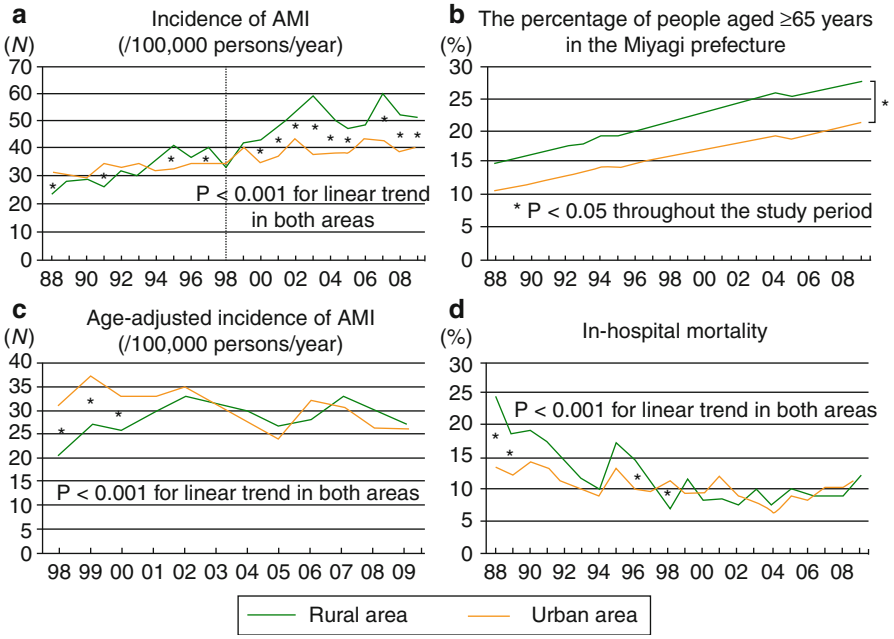


**Fig. 1.2** The 20-year trend of acute myocardial infarction (AMI) in the Miyagi Prefecture: the incidence of AMI has significantly increased in both rural and urban areas with a greater extent in the rural area (**a**), accompanied with rapid aging in both areas (**b**). The age-adjusted incidence of AMI in the rural area increased significantly, whereas that in the urban area decreased between 1998 and 2009 (**c**). In-hospital mortality after AMI (%) decreased and remained at a low level in the past 10 years in both areas (**d**). *$P<0.05$ for the difference between the rural and the urban areas (Reproduced from Hao et al. (2012) with permission)

strategies seemed to have resulted in reduced mortality. For example, our Miyagi-AMI Registry Study revealed that in-hospital mortality rate was decreased in accordance with an increased application of percutaneous coronary intervention as a reperfusion strategy of AMI between 1979 and 2008 (Takii et al. 2010). As a result, in-hospital mortality rate was dramatically decreased in both the urban and rural areas over the last 20 years (Fig. 1.2); however, it remained relatively higher in female than in male patients. This sex difference may be caused by higher age of the onset, longer elapsing time for admission, and lower prevalence of primary coronary intervention in female patients in both the urban and rural areas (Hao et al. 2012). A national Swedish registry of patients with ST-segment elevation myocardial infarction (STEMI) also reported an overall increase in the use of evidence-based treatments between 1996 and 2007, which coincided with a decrease in 30-day and 1-year mortality (Jernberg et al. 2011). Although it is difficult to show a direct causality between increase in evidence-based therapies and decreased mortality, these lines of evidence derived from the observational studies have confirmed the impact of evidence-based medicine and provided valuable insights into STEMI management.

The mechanism of sudden cardiac death in the majority of patients with ischemic heart failure is ventricular fibrillation. Transient or prolonged myocardial ischemia

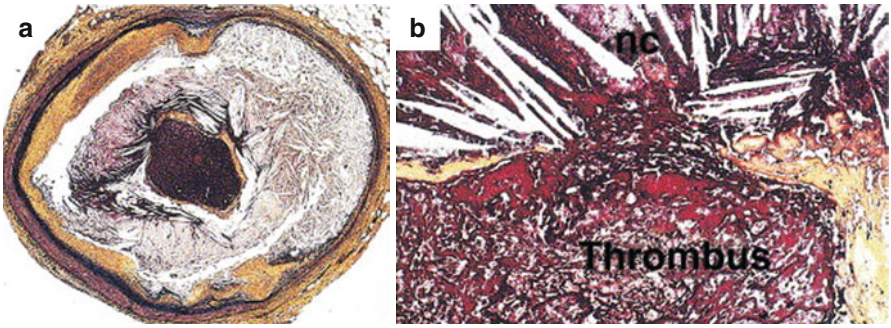


**Fig. 1.3** Coronary plaque rupture. (**a**) Low-power view of a circumferential coronary plaque with fibrous cap rupture. There is a large necrotic core with numerous cholesterol clefts and a focal disruption of a thin fibrous cap with an occlusive luminal thrombus (Movat pentachrome, ×20). (**b**) High-power view of the rupture site showing fibrous cap disruption. There is a communication between the thrombus and the underlying necrotic core (Movat pentachrome, ×400) (Reproduced from Virmani et al. (2006) with permission)

in ischemic heart disease induces arrhythmias, usually ventricular arrhythmias, which sometimes progress to ventricular fibrillation. A number of clinical trials have demonstrated the superiority of implantable cardioverter-defibrillator (ICD) in the prevention of death from malignant arrhythmias for ischemic patients with reduced left ventricular function. However, it has been reported that ICDs are underused in both the United States and Canada.

## 1.2.3 Pathogenesis

### 1.2.3.1 Atherosclerosis

Most of coronary events are associated with underlying coronary atherosclerosis and dysfunction that cause plaque rupture and/or spasm. Plaque rupture is one of the most common causes of acute coronary events. The most common cause of coronary thrombosis is plaque rupture followed by plaque erosion. Thus, the pathogenesis of vulnerable plaques that are prone to rupture has been extensively investigated. Vulnerable plaques usually have a thin-cap fibroatheroma (TCFA), characterized by a large necrotic core with a cover of thin layer of fibrous cap (<65 μm), containing few smooth muscle cells but numerous macrophages (Virmani et al. 2006; Libby et al. 2010; Calvert et al. 2011; Stone et al. 2011).

Besides the typical type of vulnerable plaque that has TCFA, there are two other types of vulnerable plaque: a plaque with superficial erosion and that with calcified nodule. Pathology and clinical studies also demonstrated that thrombus formation at the sites of plaque rupture or erosions may play a critical role in coronary events (Fig. 1.3) (Virmani et al. 2006; Kramer et al. 2010; Nesto et al. 1998; Takano et al. 2005). Virmani et al. (2006) examined over 400 cases of sudden death in the literatures and highlighted differences in the type of thrombi that were observed in 60 % of sudden death cases: plaque rupture in 55–60 %, erosion in 30–35 %, and calcified nodule in

2–7 %. However, it has also been reported that plaque rupture and thrombus formation do not necessarily lead to coronary events (Kramer et al. 2010; Nesto et al. 1998) because plaque rupture and thrombus formation are frequently observed during the development of atherosclerosis (Davies 1996; Hudson and McCaughey 1974). Furthermore, it is reported that vessels with TCFA are not usually associated with severe narrowing but with positive remodeling. It is thus highly possible that a number of other factors and conditions are involved in the pathogenesis of acute coronary syndrome (Yusuf et al. 2004; Arbab-Zadeh et al. 2012).

#### 1.2.3.2 Coronary Spasm

Although atherothrombosis is recognized as an important mechanism of cardiac events in patients with ischemic heart disease, coronary vasoconstriction has received little attention as a cause of acute coronary events, particularly in the Western countries. However, coronary artery spasm is another important mechanism of ischemic heart disease as it causes acute coronary events and sudden cardiac death. Although luminal thrombosis usually develops from any of the three different types of vulnerable plaques mentioned above, coronary spasm could play an important role in triggering coronary vulnerable plaque rupture and erosion. Little et al. (1988) examined 42 consecutive patients who had undergone coronary angiography both before and up to a month after AMI. They found that 29 of the patients had a newly occluded coronary artery and that the artery that was subsequently occluded had less than a 50 % stenosis on the first angiogram in 19 of 29 (66 %) patients, and the stenosis was less than 70 % in 28 of 29 (97 %) (Little et al. 1988). Thus, it is strongly suggested that acute thrombotic response to plaque disruption is attributable to the sudden geometric changes of the vessels with a vulnerable plaque but with relatively preserved lumen. Thus, we may need to change our approach from taking heterogeneous clinical entities together to focusing on clinically different homogeneous groups with a common mechanism (i.e., coronary spasm), considering that coronary spasm is an important therapeutic target of acute coronary syndrome (Maseri et al. 2009). The key mechanism for the coronary spasm (Shimokawa 2000) will be described later in detail.

## 1.3 Vascular Dysfunction as a Predictor for Cardiovascular Events

### 1.3.1 Endothelial Dysfunction

Although the pathogenesis of coronary artery spasm remains to be fully elucidated, endothelial dysfunction and vascular smooth muscle hypercontraction are considered to be the underlying main mechanisms (Maseri et al. 2009). Endothelial dysfunction can be regarded as a clinical syndrome that exhibits systemic manifestation of atherosclerosis and resultant myocardial ischemia (Ross 1999; Shimokawa 1999). Endothelial dysfunction is observed in patients with traditional coronary risk factors even in the absence of angiographic atherosclerotic lesions, and patients with coronary artery disease have severely impaired endothelium-mediated regulation of vascular tone (Cox et al. 1989; Quyyumi et al. 1995; Schachinger et al. 2000). Moreover,

impaired endothelial function predicts the risk of subsequent cardiovascular events (Suwaidi et al. 2000; Halcox et al. 2002). It has been reported that reduced levels of circulating endothelial progenitor cells (EPCs) independently predict atherosclerotic disease progression, thus supporting important roles for endogenous vascular repair to modulate the clinical course of coronary artery disease (Schmidt-Lucke et al. 2005).

Endothelial function can be assessed as a vasodilator response to pharmacological or mechanical stimuli in the clinical settings. The coronary circulation matches blood flow with myocardial oxygen demand by coordinating the vascular resistances within microvasculature, where the endothelium plays an important role (Ross 1999; Shimokawa 1999). The endothelium regulates the tone of the underlying vascular smooth muscle cells (VSMC) by synthesizing and releasing nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), and other endothelium-derived relaxing factors (Ross 1999; Shimokawa 1999) as well as releasing several vasoconstricting factors, such as endothelin, superoxide anions ($O_2^-$), and thromboxane, under certain pathological conditions (Ross 1999; Shimokawa 1999).

## 1.3.2 Modulators of Coronary Vascular Tone

### 1.3.2.1 Endothelium-Derived NO

Under pathological conditions, the balance between endothelium-dependent relaxation and direct VSMC constriction determines vascular tone (Ross 1999; Shimokawa 1999). As an endothelium-derived relaxing factor, NO was originally found in the relaxation of isolated rabbit aorta in response to acetylcholine (ACh) (Furchgott and Zawadzki 1980). Endothelium-derived NO causes VSMC relaxation via binding to guanylate cyclase and increases cyclic guanosine monophosphate (cGMP). Importantly, endothelial cells also play an important role in modulation of vascular tone of coronary microvessels as well as epicardial vessels. However, the response to physical forces (e.g., shear stress) and paracrine mediators may differ among the vessels with various sizes in diameter (Ross 1999; Shimokawa 1999), although it is reported that endothelial cells are substantially involved in the regulation of both epicardial and resistance coronary arteries.

NO is generated during the conversion of L-arginine to L-citrulline by constitutive endothelial NO synthase (eNOS) in endothelial cells under the control by calcium and calmodulin, which depends on molecular oxygen, nicotinamide adenine dinucleotide phosphate (NADH) and its reduced form (NADPH), tetrahydrobiopterin ($BH_4$), adenosine diphosphate (ADP), flavin adenine dinucleotide (FAD), and flavin mononucleotide (FMD) (Moncada 1999; Ignarro et al. 1999). NO diffuses to VSMC and causes relaxation mainly by stimulating soluble guanylate cyclase, catalyzing the production of cGMP. NO mediates vascular relaxation of relatively large conduit arteries, such as aorta and epicardial coronary arteries, which is enhanced by cyclical or pulsatile changes in coronary shear stress (Figs. 1.5 and 1.6) (Takaki et al. 2008). It has been reported that patients with risk factors for coronary artery disease have impaired NO-mediated vasodilatation, possibly due to reduced NO production and/or enhanced inactivation of NO (Moncada 1999; Ignarro et al. 1999).

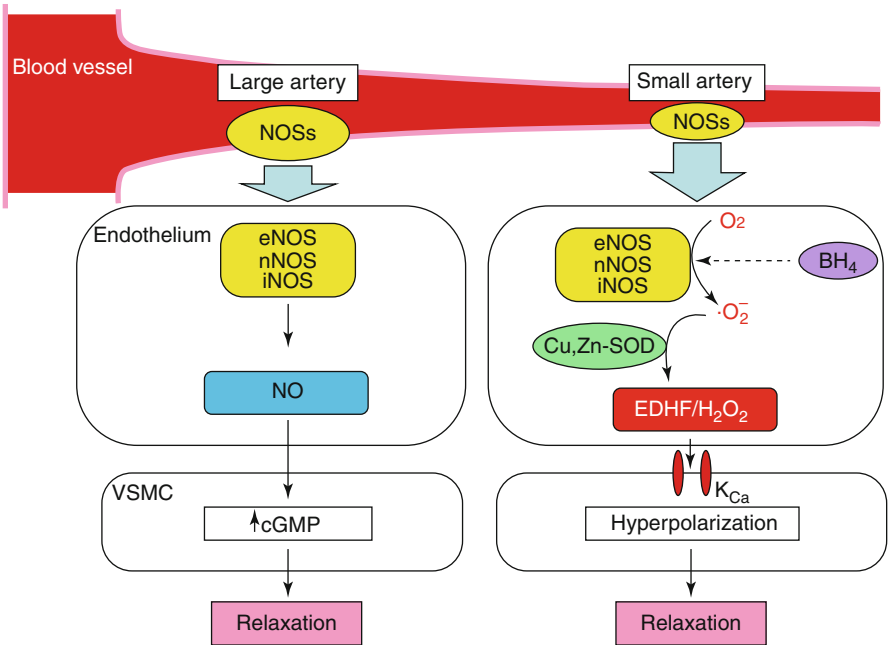


**Fig. 1.4** Different roles of endothelial NO synthase system depending on vessel size. Endothelial NO synthase system plays different roles depending on the vessel size, mainly NO generation in the conduit arteries and EDHF generation in microvessels. *eNOS* endothelial nitric oxide synthase, *nNOS* neuronal nitric oxide synthase, *iNOS* inducible nitric oxide synthase, $BH_4$ tetrahydrobiopterin, *SOD* superoxide dismutase, *EDHF* endothelium-derived hyperpolarization factor, *cGMP* cyclic guanosine monophosphate, $K_{Ca}$ calcium-activated potassium channel (Reproduced from Takaki et al. (2008) with permission)

### 1.3.2.2 EDHF

Feletou and Vanhoutte (1988) and Chen et al. (1988) independently proposed the existence of EDHF based on their finding that a diffusible substance released by the endothelium causes hyperpolarization and relaxation of underlying VSMC. Since then, a number of substances/mechanisms have been proposed for the nature of EDHF, including epoxyeicosatrienoic acids (metabolites of arachidonic P450 epoxygenase pathway) (Fisslthaler et al. 1999; Fleming 2004), $K^+$ ions (Edwards et al. 1998; Edwards and Weston 2004), and electrical communications through myoendothelial gap junctions (Taylor et al. 1998; Griffith et al. 2004).We have previously demonstrated that endothelium-derived hydrogen peroxide ($H_2O_2$) is an EDHF in mouse (Matoba et al. 2000) and human mesenteric arteries (Matoba et al. 2002) and in porcine and canine coronary microvessels (Matoba et al. 2003; Yada et al. 2003). Moreover, we also demonstrated that endothelial Cu, Zn-superoxide dismutase (Cu, Zn-SOD) plays an important role for the synthesis of EDHF/$H_2O_2$ (Morikawa et al. 2003). EDHF has been shown to modulate vascular tone in small resistance arteries *in vitro* (Morikawa et al. 2004) and in human forearm microcirculation *in vitro* (Fig. 1.4) (Masumoto et al. 2001).

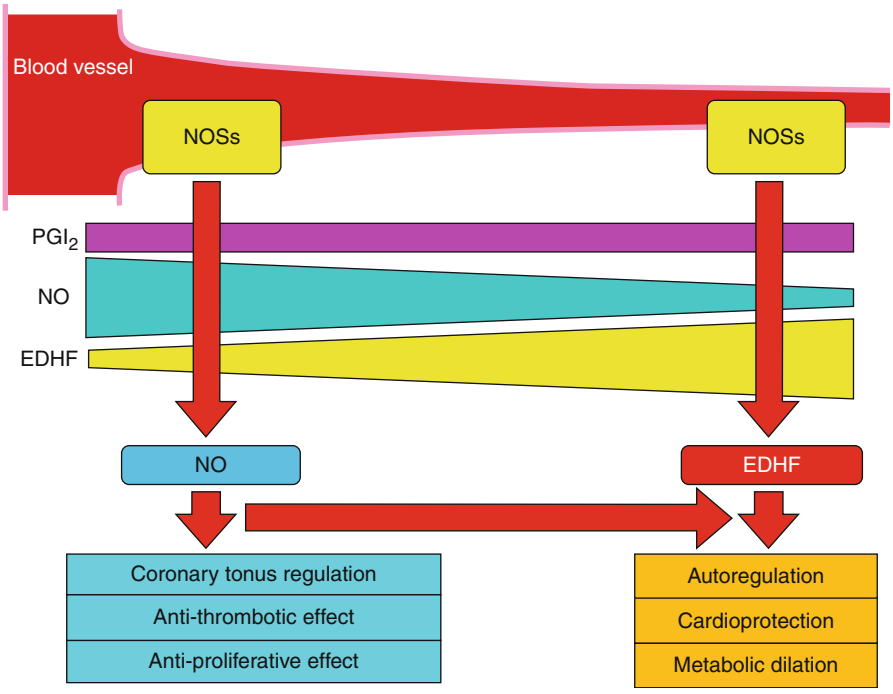


**Fig. 1.5** Different roles of endothelial NO synthase system in the coronary circulation *in vitro*. The endothelial NO synthase system plays an important role in modulation of vascular tone in the epicardial coronary artery as NO-generating system, whereas in coronary microcirculation, it exerts several protective effects as EDHF-generating system in collaboration with NO from the epicardial coronary artery, including coronary autoregulation, protection against myocardial ischemia/reperfusion injury, and metabolic coronary dilatation. *$PGI_2$* prostaglandin $I_2$ (Reproduced from Shimokawa and Yasuda (2008) with permission)

As in the case of NO, EDHF-mediated relaxations are attenuated by several atherosclerotic risk factors (Urakami-Harasawa et al. 1997; Feletou and Vanhoutte 2004). Importantly, we were able to demonstrate that endogenous EDHF/$H_2O_2$ plays important cardioprotective roles in coronary microcirculation *in vitro*, including autoregulation (Yada et al. 2003), protection against ischemia/reperfusion (Yada et al. 2006), and metabolic coronary dilatation (Yada et al. 2007) (Fig. 1.5). In mice lacking all of the three NOS isoforms (triply $NOSs^{-/-}$), both EDHF- and NO-mediated responses are absent (Takaki et al. 2008) and myocardial infarction occurs spontaneously in association with metabolic syndrome manifestations (Nakata et al. 2008), suggesting that endothelial NOSs system appears to play a pivotal role in maintaining cardiovascular homeostasis (Fig. 1.5).

### 1.3.2.3 Rho-Kinase

Enhanced Rho-kinase activity may play an important role in the pathogenesis of both epicardial coronary and microvascular spasm (Fig. 1.6) (Shimokawa 2000;

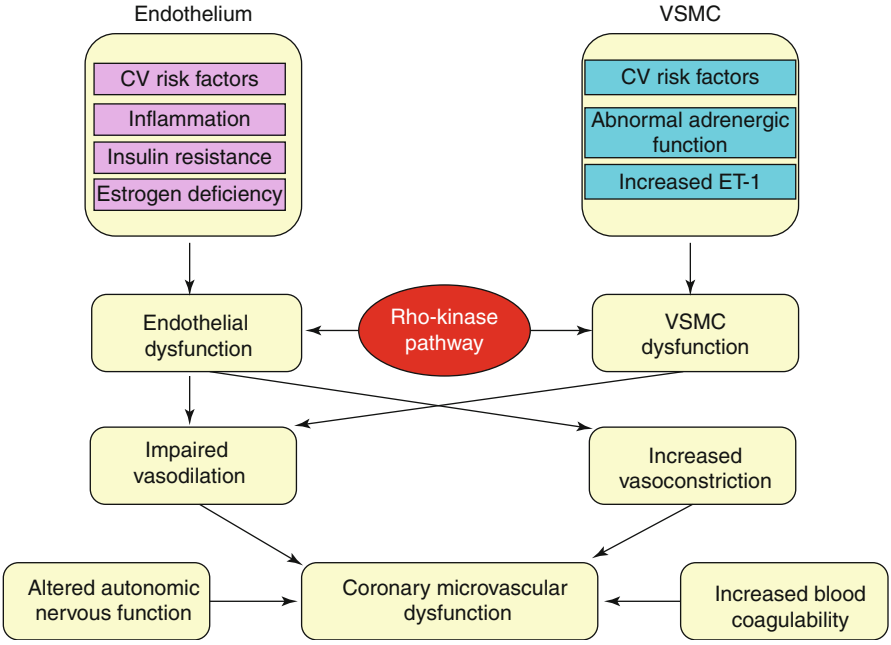


**Fig. 1.6** Pathogenetic mechanisms of coronary microvascular dysfunction. The pathogenetic mechanisms of coronary microvascular dysfunction may be heterogeneous, and many confounding cardiovascular risk factors cause both endothelial dysfunction and VSMC hyperconstriction, where activated Rho-kinase pathway may play an important role. *CV* cardiovascular, *ET-1* endothelin-1 (Reproduced from Shimokawa and Yasuda (2008) with permission)

Shimokawa and Takeshita 2005). Rho-kinase has been identified as an effector of the small GTP-binding protein Rho. Intracoronary administration of fasudil (Asano et al. 1987) or hydroxyfasudil (Shimokawa et al. 1999), pharmacological inhibitors of Rho-kinase, markedly inhibits epicardial coronary spasm in porcine models with various inflammatory stimuli such as angiotensin II, interleukin-1, monocyte chemoattractant protein-1, oxidized low-density lipoprotein, and remnant-like particles *in vitro* (Shimokawa et al. 1996; Katsumata et al. 1997; Miyata et al. 2000; Oi et al. 2004). Indeed, the inhibition of Rho-kinase with fasudil/hydroxyfasudil is associated with the suppression of enhanced myosin light chain (MLC) phosphorylations (both MLC monophosphorylations and diphosphorylations) at the spastic segments of the coronary arteries (Figs. 1.6 and 1.7) (Shimokawa et al. 1996; Katsumata et al. 1997).

Furthermore, Rho-kinase activation is associated with vascular dysfunction involving endothelial dysfunction (Fig. 1.6), as Rho-kinase activation downregulates endothelial NO synthase (Takemoto et al. 2002). We have previously demonstrated that in patients with rest angina, intracoronary administration of ACh induced myocardial ischemia determined by ischemic ECG changes and myocardial lactate production without provocation of large epicardial coronary narrowing or spasm (Fig. 1.8) (Mohri et al. 1998). Hasdai et al. (1997) also demonstrated that coronary blood flow, assessed with the Doppler flow guidewire, was acutely decreased by intracoronary ACh administration without inducing large epicardial coronary

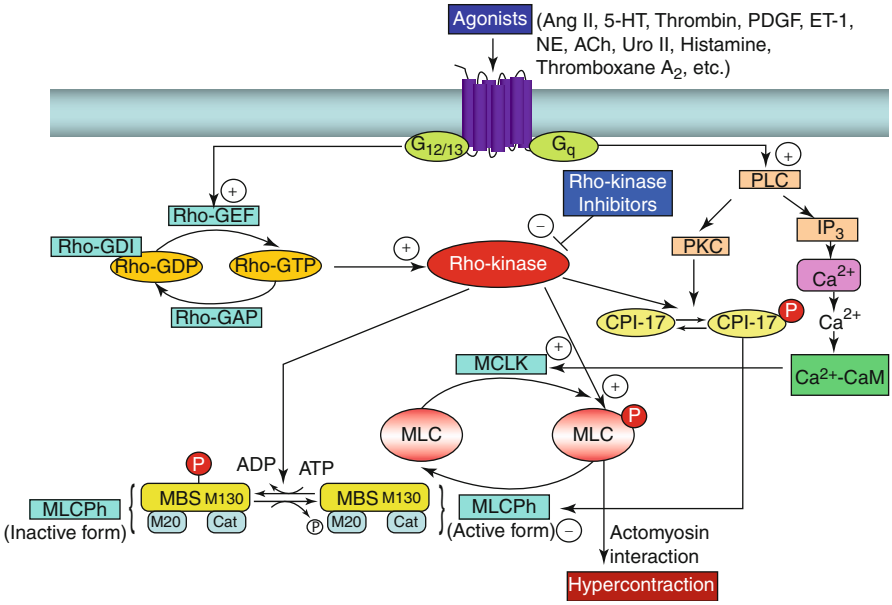


**Fig. 1.7** Role of Rho/Rho-kinase signaling pathway in VSMC hyperconstriction. Contraction is induced by the increased phosphorylation of MLC. The agonist-induced activation of G-protein-coupled receptors leads to the stimulation of MLCK through an increase in intracellular $Ca^{2+}$ concentration and inhibition of MLCPh. Following stimulation by various agonists, the Rho/Rho-kinase-mediated pathway is activated, resulting in the inhibition of MLCPh (through phosphorylation of its MBS), with a resultant increase in MLC phosphorylation. This Rho-kinase-mediated contraction of VSMC can occur independently of intracellular $Ca^{2+}$ levels and is known as "calcium sensitization." Rho-kinase can also increase MLC phosphorylation and contractility by inactivating MLCPh after phosphorylation of CPI-17 or by direct phosphorylation of MLC. Activated $G_{12/13}$ subunits regulate several distinct RhoGEFs. Rho-GEFs activate Rho-GTPases by catalyzing the exchange of GDP from GTP, whereas Rho-GAPs stimulate the hydrolysis of GTP. Rho-GTP binds to the Rho-binding domain of Rho-kinase, then Rho-kinase is activated. *ACh* acetylcholine, *Ang II* angiotensin II, *Cat* catalytic subunit, *CPI-17* protein kinase C (PKC)-potentiated phosphatase inhibitor of 17 kDa, *ET-1* endothelin-1, $IP_3$ inositol (1,4,5)-trisphosphate, *M20* 20-kDa subunit, *MLC* myosin light-chain, *MLCPh* myosin light-chain phosphatase, *NE* norepinephrine, *PLC* phospholipase C, *PDGF* platelet-derived growth factor, *Uro II* urotensin II. Stimulation is denoted by +; inhibition is denoted by – (Reproduced from Shimokawa and Rashid (2007) with permission)

spasm. Although the precise mechanisms still remain to be disclosed, Rho-kinase activation is a strong candidate to be involved in ischemia in microcirculation of coronary artery, because pretreatment with intracoronary fasudil infusion effectively prevented ACh-induced angina and myocardial lactate production in patients with microvascular angina or spasm (Mohri et al. 2003).

### 1.3.3 Microvascular Dysfunction

It has been reported that 20–30 % of patients with angina-like chest pain have no flow-limiting epicardial coronary stenosis or spasm (Proudfit et al. 1966; Kemp et al. 1986),

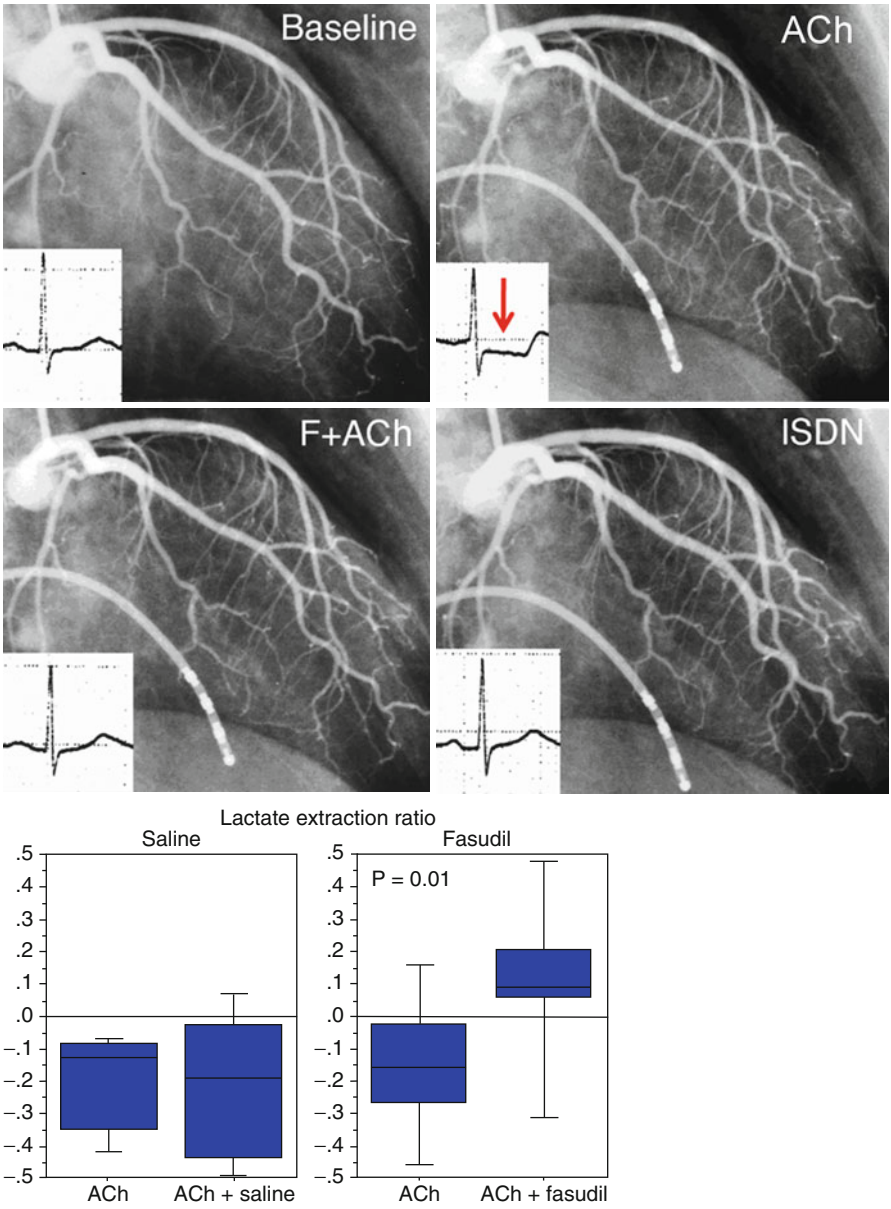


**Fig. 1.8** Clinical findings in a patient with microvascular angina. Representative coronary angiography and ECG recordings (*left*) and group data comparison of the lactate extraction ratio during acetylcholine (*ACh*) infusion with ($n = 13$, fasudil group) and without pretreatment of fasudil ($n = 5$, saline group) (*right*). Intracoronary administration of ACh caused no appreciable vasoconstriction of epicardial coronary arteries, whereas ECG changes and myocardial lactate production indicated the occurrence of myocardial ischemia. Intracoronary pretreatment with fasudil abolished the ACh-induced myocardial ischemia. *F* fasudil, *ISDN* isosorbide dinitrate (Reproduced from Mohri et al. (2003) with permission)

which is often defined as cardiac syndrome X (Kemp 1991) or microvascular angina (Kaski 1998). The mechanisms of this syndrome appear to be heterogeneous but likely involve coronary microvascular dysfunction associated with inadequate coronary vasodilator capacity and/or enhanced coronary vasoconstrictor responses (Crea and Lanza 2004). In patients with microvascular angina, impaired microvascular vasodilator reserve has been repeatedly observed (Opherk et al. 1981; Cannon et al. 1983; Greenberg et al. 1987; Motz et al. 1991). This impaired microvascular vasodilator reserve could be attributable to blunted NO-dependent microvascular dilatation (Motz et al. 1991). It has been recently suggested that an increased synthesis of asymmetric dimethylarginine, which is known to reduce the bioavailability of L-arginine for NO synthase, contributes to the impaired NO activity in those patients (Okyay et al. 2007). Indeed, oral supplementation with L-arginine for 4 weeks improved exercise tolerance in patients with this disorder (Bellamy et al. 1998). In addition to NO, EDHF (Yada et al. 2003, 2006, 2007), Rho-kinase, and several other factors may be involved in the pathogenesis of coronary microvascular dysfunction (Fig. 1.6). For example, increased plasma levels of endothelin-1 (ET-1) were reported in patients with microvascular angina (Kaski et al. 1995; Hoffmann et al. 1998; Cox et al. 1999). Considering that microvascular spasm is the underlying cause of myocardial necrosis in the cardiomyopathic Syrian hamster (Factor et al. 1982), management of microvascular angina is clinically important. Thus, future investigation with drugs such as Rho-kinase inhibitor, fasudil, may be warranted to improve mortality and morbidity of patients with microvascular angina.

## 1.4 Summary

Vasospasm and/or vascular dysfunction plays important roles in the pathogenesis of ischemic heart disease and cardiovascular events. Although vasomotion has been elucidated to be regulated by several mechanisms including NO, EDHF, and Rho-kinase, further investigations are needed to elucidate the pathogenesis of cardiovascular events and to improve mortality and morbidity of patients with ischemic heart diseases.

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# Stroke

# 2

Kazuo Kitagawa

**Abstract**

Stroke is the third to fourth leading cause of mortality in industrialized countries. The etiology of stroke comprises vascular lesions in the cerebral vessels; thus, similar risk factors are involved in both myocardial infarction and stroke. However, small vessel diseases, such as lacunar infarction and intracerebral hemorrhage, are more common in stroke than in myocardial infarction. Recent development of vascular ultrasound and brain magnetic resonance imaging (MRI) has established carotid intima-media thickness (IMT) and cerebral small vessel disease (CSVD) as surrogate markers of incident stroke. The involvement of inflammatory processes has also attracted attention in both cardiovascular and cerebrovascular events. Stratification of patients at high risk for stroke could be improved using surrogate markers such as carotid IMT and CSVD detected by MRI in combination with measurement of blood inflammatory marker levels.

**Keywords**

Risk factors • Carotid intima-media complex thickness (IMT) • Silent cerebral infarction • Inflammation • Thrombolysis

## 2.1 Prevalence and Incidence

In the United States, an estimated 7,000,000 Americans aged older than 20 years have had a stroke, and the overall prevalence of stroke is an estimated 3.0 % (Roger et al. 2011). Each year about 800,000 people experienced a stroke; among these incidences of stroke, 23 % are recurrent attacks. In the United States in 2007, the

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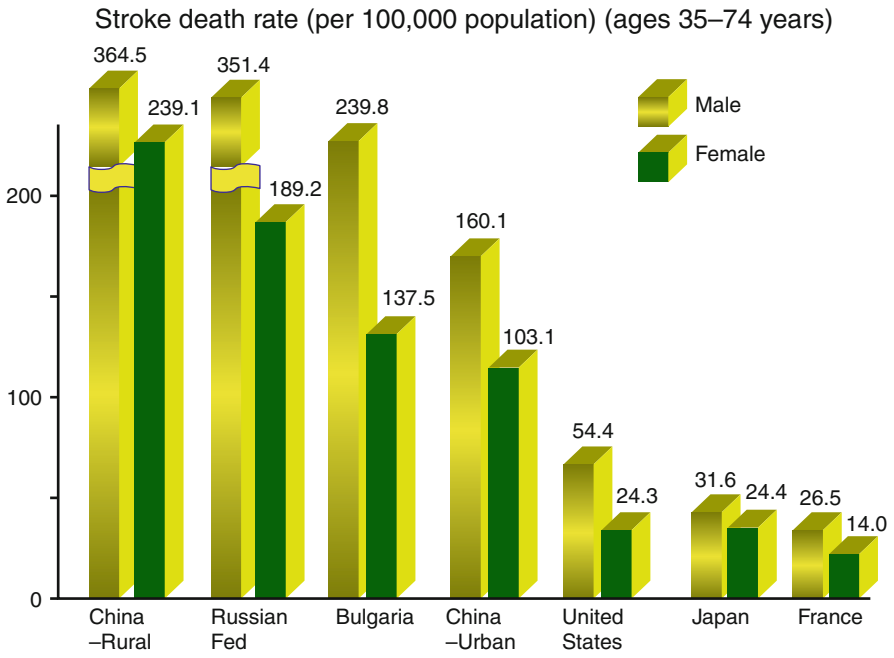


**Fig. 2.1** International stroke death rate (per 100,000 population)

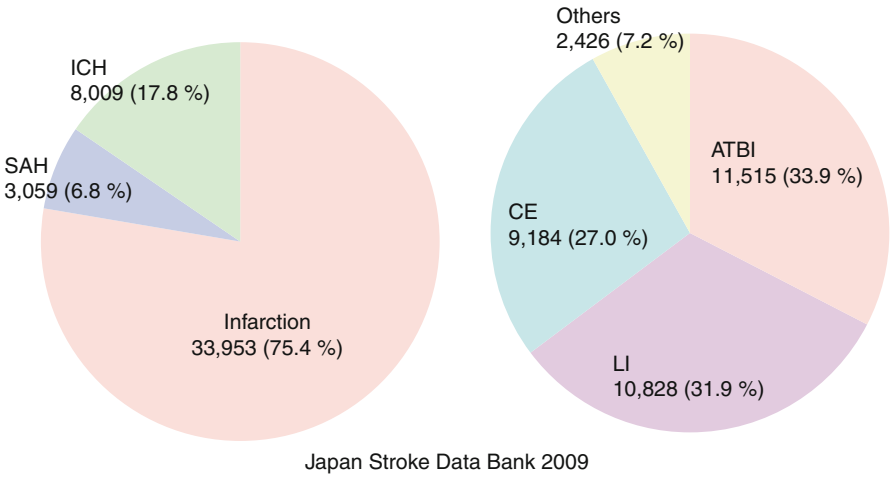


**Fig. 2.2** Stroke classification and subtypes of cerebral infarction in the Japan Stroke Data Bank. *ICH* intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *ATBI* atherothrombotic brain infarction, *LI* lacunar infarction, *CE* cardiogenic embolism

age-adjusted death rate for stroke was 42.2 per 1,000,000 persons, and the direct and indirect cost of stroke was $40.9 billion. Worldwide, death rates are highest in rural China, Russia, and Eastern Europe (Fig. 2.1).

Of all incidence of stroke in the United States, 87 % are ischemic, 10 % are caused by intracerebral hemorrhage, and 3 % are caused by subarachnoid hemorrhage (SAH). According to the Japan Stroke Data Bank, 75 % of new or recurrent strokes in Japan are ischemic, 18 % are due to intracerebral hemorrhage, and 7 % are due to SAH (Fig. 2.2) (Araki et al. 2009). Thus, although there is a trend towards an increase in the incidence of ischemic stroke and a decline in hemorrhagic stroke in Asia, the percentage of hemorrhagic strokes is still higher than that in Western countries. Stroke rates, adjusted for age, have declined over the last 30 years (Redon et al. 2011). However, the presence of an aging population implies that the absolute number of strokes may stabilize or increase over the next two decades.

## 2.2 Stroke Subtypes

Studying the etiology of stroke is essential for better understanding the involvement of risk factors in each subtype of stroke. Previously, the duration of symptoms for longer than 24 h was critical for stroke diagnosis. However, recently developed brain imaging techniques can identify small fresh lesions even if symptoms disappear within 24 h. The definition of ischemic stroke and transient ischemic attack (TIA) is still under debate. However, tissue-based diagnosis is becoming popular for stroke diagnosis (Easton et al. 2009).

Stroke can be classified as cerebral infarction, intracerebral hemorrhage, or SAH (Fig. 2.3). The term cerebral infarction indicates an ischemic stroke caused by occlusion of extracerebral or intracerebral arteries. Intracerebral hemorrhage refers to a hemorrhagic stroke caused by rupture of the cerebral arteries, capillaries, and/or veins. In intracerebral hemorrhage, a hematoma is localized within the brain parenchyma. SAH refers to a hemorrhage at the brain surface. Rupture of cerebral aneurysms is the most important cause of SAH.

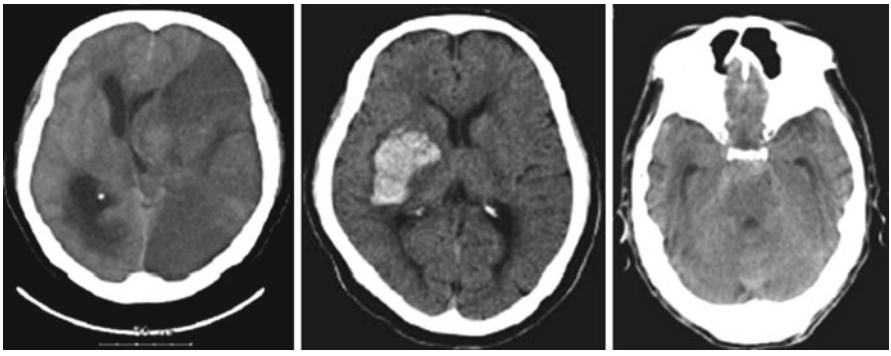


**Fig. 2.3** Computed tomography (CT) findings in cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage

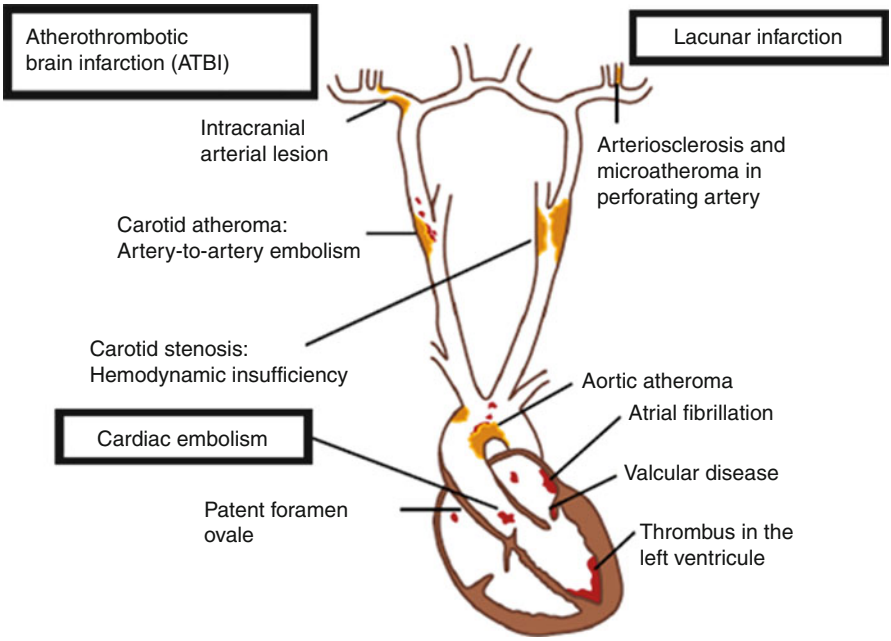


**Fig. 2.4** Etiology of cerebral infarction. From the point of thrombus formation, cerebral infarction is classified as cardiac embolism (fibrin-rich thrombus in the left atrium or venous system) or noncardiac infarction (platelet-rich thrombus in the arterial system)

### 2.2.1 Cerebral Infarction

Cerebral infarction can be classified into three main categories according to etiology and vessel occlusion site (Fig. 2.4): cardiogenic embolism, atherothrombotic brain infarction (ATBI), and lacunar infarction.

In the Japan Stroke Data Bank, about 90 % of all cerebral infarctions are classified as one of these three subtypes (Fig. 2.2). In cardiogenic embolism, an embolus in the cardiac chambers, usually the left atrium (Fig. 2.5a), dislodges and enters into the cerebral arteries along with circulating blood. About 10 % of patients die in the acute stage of cardiac embolism due to massive infarction (Fig. 2.5b). The most important etiology is atrial fibrillation, which accounts for more than 50 % of cardiogenic embolisms. Other embolic sources include patent foramen ovale, myocardial infarction, congestive heart failure, dilated cardiomyopathy, valvular disease, and prosthetic valves.

ATBI is almost identical to large artery disease. Atherosclerosis in extracerebral and intracerebral major arteries causes vessel stenosis and occlusion leading to cerebral infarction. Locations susceptible to atherosclerosis include the carotid bifurcation (Fig. 2.5c), carotid siphon, middle cerebral artery, basilar artery, and extracranial vertebral artery. Plausible mechanisms for stroke onset are embolism (Fig. 2.5d), thrombosis, or hemodynamic failure.

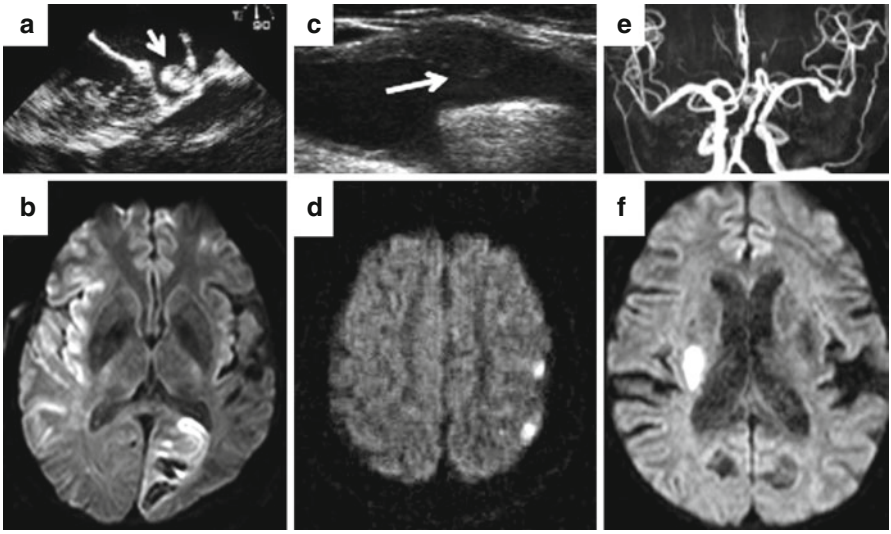


**Fig. 2.5** Ultrasound and magnetic resonance (MR) imaging in three major types of cerebral infarction. (**a**, **b**) Cardiac embolism. (**a**) Transesophageal echocardiography in a patient with nonvalvular atrial fibrillation. Thrombus was found in the left atrium (*arrow*). (**b**) Representative MR diffusion-weighted imaging (DWI) image of cardiac embolism. An ischemic lesion with high-intensity signals was detected in the territory of the middle cerebral artery. (**c**, **d**) Atherothrombotic brain infarction. (**c**) Carotid duplex ultrasonography showing severe stenosis in the carotid bifurcation (*arrow*). (**d**) Multiple embolic infarctions distal to the internal carotid artery were seen upon MR DWI. (**e**, **f**) Lacunar infarction. (**e**) MR angiography showing no occlusive lesions in the major cerebral arteries. (**f**) MR DWI showing a small round infarction in the deep area, corona radiata

Lacunar infarction, or small artery disease, is a small infarction measuring less than 20 mm caused by occlusion of the cerebral perforating arteries. Arteriosclerosis in small cerebral arteries due to lipohyalinosis underlies this type of cerebral infarction. However, microatheroma in the branch portion of the perforating arteries arising from the main cerebral arteries often causes larger infarction than lacunar infarction (Fig. 2.5e, f). This is called branch atheromatous disease (Caplan 1989) and is attracting much attention because of its associated symptom progression and poor motor function outcome.

In addition to these three main subtypes, aortic plaque, cerebral artery dissection, Moyamoya disease, fibromuscular dysplasia, coagulopathy including lupus anticoagulant, and malignancy are other important causes of cerebral infarction.

### 2.2.2 Intracerebral Hemorrhage

Hypertensive hemorrhage is the most common cause of intracerebral hemorrhage, followed by cerebral amyloid angiopathy. Hypertensive damage in cerebral

perforating arteries causes angionecrosis and microaneurysms, which lead to vessel rupture. The basal ganglia, thalamus, pontine, cerebellums, and subcortical areas are frequently affected in hypertensive cerebral hemorrhage. In the elderly, amyloid deposition in cerebral vessels (cerebral amyloid angiopathy) results in subcortical hemorrhage, which is also known as lobar hemorrhage. Other minor causes of intracerebral hemorrhages are cerebral hemangioma, arteriovenous malformation, arteriovenous fistula, venous thrombosis, deficiency of coagulation factors, and use of anticoagulation and fibrinolysis drugs.

### 2.2.3 Subarachnoid Hemorrhage (SAH)

SAH is the most severe form of stroke. Approximately 30–50 % of patients die after suffering from an SAH. Cerebral aneurysm is the most frequent and important etiology underlying SAH. A family history of SAH or cerebral aneurysms doubles the risk of incident SAH. Polycystic kidney disease is known to be a comorbidity of SAH.

## 2.3 Risk Factors: Management of Risk Factors for Primary and Secondary Prevention

The most established risk factors for stroke are age, male gender, hypertension, diabetes mellitus, atrial fibrillation, smoking, and alcohol intake. Obesity, metabolic syndrome, chronic kidney disease, and sleep apnea syndrome have also been recently recognized as risk factors for stroke. The relationship between these factors and stroke differs according to stroke subtype. Hypertension is a risk factor for all types of stroke, including ischemic and hemorrhagic stroke. Elevation of blood pressure beyond 115/75 mmHg increases the risk of stroke (Lewington et al. 2002). Antihypertensive treatment reduces the risk of primary and secondary occurrence of both ischemic and hemorrhagic stroke (Staessen et al. 2001; PROGRESS Collaborative Group 2001). Among the antihypertensive drugs available, inhibitors of the renin-angiotensin-aldosterone system, calcium channel blockers, and diuretics are recommended for stroke prevention. Although the principle of "the lower the better" is recognized in primary stroke prevention, the target of blood pressure in secondary prevention is controversial (Arima et al. 2006; Ovbiagele et al. 2011).

Diabetes mellitus has been consistently shown as a risk factor for cerebral infarction, but the association between diabetes mellitus and cerebral hemorrhage is a subject of debate (Emerging Risk Factors Collaboration et al. 2010a). Although it remains unclear whether the strict control of blood sugar levels reduces the risk of stroke (ACCORD Study Group et al. 2008), blood pressure control and statin treatment in dyslipidemic diabetes patients reduce the risk of stroke (ACCORD Study Group ACCORD Study Group et al. 2010; Colhoun et al. 2004). While aspirin is often used for primary prevention of vascular accident in diabetes patients,

the effect of aspirin in primary stroke prevention has not been established (Ogawa et al. 2008).

Atrial fibrillation is a strong risk factor for ischemic stroke, particularly cardiac embolism. The risk of stroke is increased four- to five-fold by non-valvular atrial fibrillation (NVAF); there is a similar elevation of risk in patients with either paroxysmal or permanent atrial fibrillation (Lip and Tse 2007). The CHADS2 score, which takes into account congestive heart failure, hypertension, age, diabetes mellitus, and stroke/TIA, is useful for risk stratification of NVAF (Gage et al. 2004). If a patient's CHADS2 score is more than 1, anticoagulation drugs are recommended for prevention of stroke and systemic embolism (Ogawa and Hori 2011).

The relation between dyslipidemia and stroke is complex. Epidemiology studies have consistently shown that a low level of total cholesterol and low-density lipoprotein (LDL) cholesterol are associated with cerebral hemorrhage (Noda and Iso 2009). However, although the association of a moderately high level of LDL cholesterol with ischemic stroke is controversial, there is a clear association between LDL cholesterol levels and coronary heart disease (Prospective Studies Collaboration et al. 2007). Rather, a low level of high-density lipoprotein (HDL) cholesterol has been shown to be related to ischemic stroke (Soyama et al. 2003). In contrast to controversies over the association between lipid level and ischemic stroke, statin treatment has been shown to be associated with primary prevention of ischemic stroke by meta-analysis (Baigent et al. 2005). Compared with vehicle treatment, a high dose of statin treatment has been shown to cause a 16 % decrease in stroke recurrence (Amarenco et al. 2006).

Cigarette smoking is associated with cerebral infarction and SAH (Shinton and Beevers 1989). Light-to-moderate intake of alcohol has been shown to be protective against total and ischemic stroke, but heavy alcohol consumption increases the risk of both ischemic and hemorrhagic stroke (Reynolds et al. 2003). Metabolic syndrome has been shown to increase the risk of ischemic stroke as well as coronary heart disease (Iso et al. 2007). The existence of chronic kidney disease, defined on the basis of estimated glomerular filtration rate (eGFR), has also been demonstrated to increase the risk of stroke (Irie et al. 2006). Sleep apnea syndrome is often shown to be a comorbidity of several cardiovascular risk factors such as obesity and hypertension and increases the risk of stroke and all-cause death (Yaggi et al. 2005).

## 2.4 Surrogate Marker for Stroke: Carotid Intima-Media Thickness and Silent Cerebral Infarction

For better prevention of stroke, stratification of high-risk patients could be carried out. Before onset of stroke, patients often show a mild-to-moderate degree of atherosclerosis in the cerebral arteries. For evaluation of asymptomatic cerebral vessel lesions, noninvasive tests such as carotid ultrasound and brain magnetic resonance imaging (MRI) are used, not only in clinical but also in cohort studies.

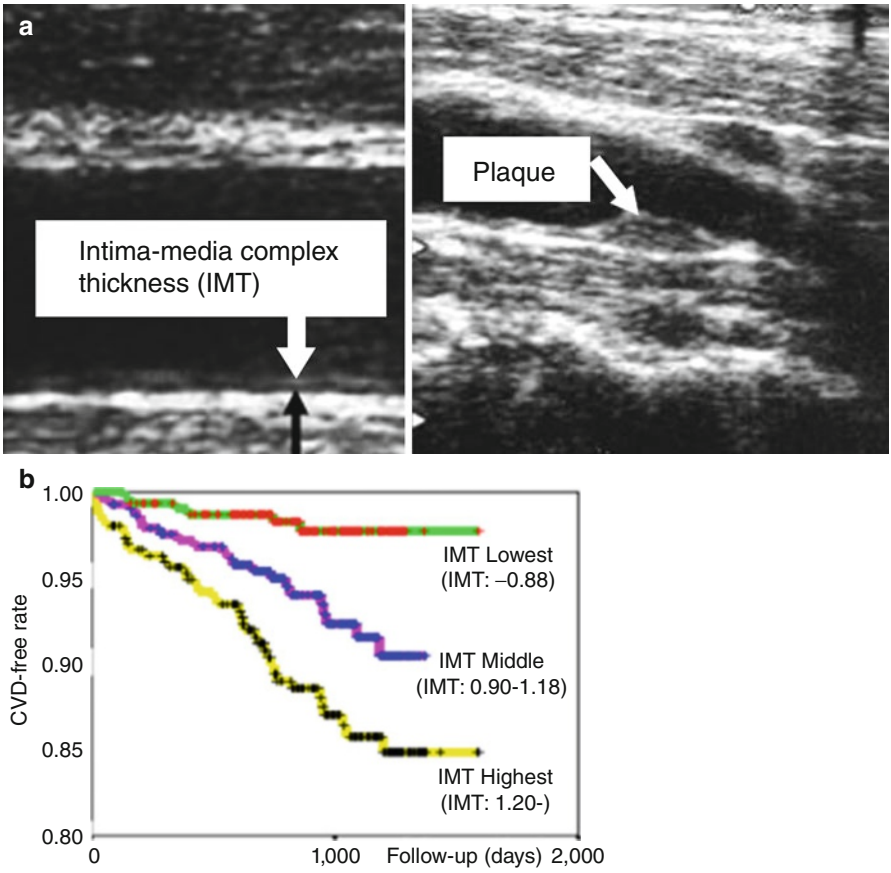


**Fig. 2.6** Carotid ultrasonography and the OSACA2 study. (**a**) The *left panel* shows intima-media complex thickness (*IMT*) in a normal individual. The *right panel* shows a local protruding plaque in the carotid bifurcation. (**b**) Cumulative event-free survival for cardiovascular events in the lowest, middle, and highest third of carotid IMT in 900 outpatients in the OSACA2 study. The relative risk of cardiovascular events in the highest IMT tertile group was 3.6 times greater than that in the lowest tertile group after adjustment for age, sex, risk factors, and a history of cardiovascular disease

### 2.4.1 Carotid Intima-Media Thickness Complex

The early stages of carotid atherosclerosis are evaluated by measurement of carotid intima-media thickness (IMT) using ultrasound (Fig. 2.6a). Carotid IMT has been shown to be associated with a history of cardiovascular disease (myocardial infarction and stroke) (Nagai et al. 2001; Sakaguchi et al. 2003) and risk factors such as diabetes mellitus, hypertension, dyslipidemia, smoking status, and functional variants of certain genes (Humphries and Morgan 2004). More importantly, large-scale population-based cohort studies have consistently shown that an increase in carotid

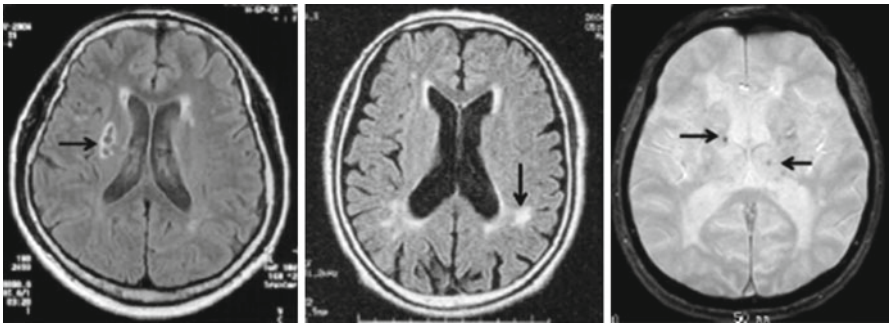


**Fig. 2.7** Cerebral small vessel diseases detected by brain magnetic resonance imaging (MRI). *Arrows* indicate silent infarction, white matter lesions, and cerebral microbleeds, respectively

IMT is independently associated with the risk of both stroke and myocardial infarction (Lorenz et al. 2007). We have also shown that carotid IMT is related to future risk of cardiovascular events independent of management of risk factors according to the guideline (Fig. 2.6b) (Kitagawa et al. 2007). Carotid IMT is a reliable marker for severity of atherosclerosis in the large arteries. Therefore, change in carotid IMT has been widely used as an index for the anti-atherosclerosis effect of several drugs such as statins (Amarenco et al. 2004), antihypertensive drugs (Wang et al. 2006), pioglitazone (Mazzone et al. 2006), and cilostazol (Katakami et al. 2010). However, it remains unclear whether regression of IMT is related to prevention of clinical events.

### 2.4.2 Cerebral Small Vessel Disease and Silent Cerebral Infarction

While carotid IMT represents atherosclerosis in the large arteries, cerebral small vessel disease (CSVD) is evaluated by brain MRI. Asymptomatic CSVD comprises silent cerebral infarction (SCI), white matter lesions (WMLs), and cerebral microbleeds (CMBs) (Fig. 2.7). SCI represents small lacunar infarction due to occlusion of a perforating artery (Vermeer et al. 2007). CMBs represent hemosiderin deposits around the cerebral capillaries due to hypertensive vasculopathy or cerebral amyloid angiopathy (CAA) (Cordonnier et al. 2007). The etiology of WML remains unclear (Román et al. 2002; Debette and Markus 2010). These findings are frequently observed in patients with a history of stroke, but they are also often found in normal elderly people. Age and hypertension are strongly associated with the presence and severity of CSVD. More importantly, CSVD has been shown to be associated with future risk of stroke in several cohort studies. In addition to stroke events, CSVD has been shown to be related to cognitive function and future risk of dementia and cognitive decline (Moorhouse and Rockwood 2008).

## 2.5 Inflammation in the Cerebral Vessels: A New Mechanism Underlying Cerebral Atherosclerosis and Arteriosclerosis?

In addition to traditional risk factors, low-grade inflammation has been attracting much attention in the study of the vascular biology underlying atherosclerosis. Plaque rupture and erosion have been observed in atherothrombotic brain infarction (Ogata et al. 2008). Histology studies have clarified the accumulation of inflammatory cells and expression of inflammation-related molecules within the atheromatous plaque (Krupinski et al. 2006). We have demonstrated that inflammatory cytokines such as interleukin (IL)-6 are released after mechanical plaque rupture during carotid artery stenting (Abe et al. 2010). High-sensitivity C-reactive protein (hsCRP) is a general inflammatory marker and is the most established among inflammatory markers for risk prediction of future myocardial infarction and stroke (Emerging Risk Factors Collaboration et al. 2010b). However, other specific markers of vascular inflammation might be more valuable for risk prediction. Circulating levels of inflammatory markers were shown to be significantly associated with the recurrence of ischemic stroke (Welsh et al. 2008). We have reported the association between inflammatory marker levels (hsCRP, IL-6, IL-18) and the severity, progression, and vulnerability of carotid plaques using ultrasonography (Hashimoto et al. 2001; Yamagami et al. 2004, 2005). Furthermore, independent association between CSVD (SCI, WMLs, and CMBs) and inflammatory marker levels has also been shown (Hoshi et al. 2005; Fornage et al. 2008; Miwa et al. 2011). Therefore, how measurement of inflammatory markers can be combined with the assessment of surrogate markers for risk prediction will be a topic for future research.

Blood inflammatory marker levels may be more important in high-risk patients than in low-risk patients. In 766 outpatients, we showed that circulating IL-6 levels are associated with future cardiovascular disease risk independently of other risk factors and carotid IMT (Okazaki et al. 2010). In this study, higher IL-6 levels were closely associated with future cardiovascular disease risk in the high IMT group, but not in the low IMT group. Ishikawa et al. (2007) also showed that hsCRP levels were associated with future stroke risk in patients with SCI, but not in patients without SCI. The significance of hsCRP for predicting future cardiovascular disease risk may disappear after adjusting for risk factors in the general population (Bos et al. 2006). Thus, future studies are needed to clarify how measurement of inflammatory markers can be better integrated for risk prediction of future cardiovascular disease.

## 2.6 Prevalence of Coronary Heart Disease and Outcome in Stroke Patients

Stroke registries show that around 25 % of patients with stroke have symptomatic coronary events. The REACH Registry, which is the registry examined all over the world, also shows that 30–40 % of stroke patients have coronary heart disease (Steg et al. 2007).

**Table 2.1** NIH Stroke Scale (NIHSS)

| | |
|---|---|
| 1.a. | Level of consciousness (LOC): alert (0), drowsy (1), stuporous (2), coma (3) |
| 1.b. | LOC questions: answers both correctly (0), one correctly (1), neither correctly (2) |
| 1.c. | LOC commands: performs both tasks correctly (0), one task correctly (1), neither task (2) |
| 2. | Gaze: normal (0), partial gaze palsy (1), total gaze deviation (2) |
| 3. | Visual fields: normal (0), partial hemianopia (1), complete hemianopia (2), bilateral hemianopia (3) |
| 4. | Facial palsy: normal (0), minor (1), partial (2), complete (3) |
| 5a. | Left arm: no drift (0), drift before 10 s (1), falls before 10 s (2), no effort against gravidity (3), no movement (4) |
| 5b. | Right arm: no drift (0), drift before 10 s (1), falls before 10 s (2), no effort against gravidity (3), no movement (4) |
| 6a. | Left leg: no drift (0), drift before 5 s (1), falls before 5 s (2), no effort against gravidity (3), no movement (4) |
| 6b. | Right leg: no drift (0), drift before 5 s (1), falls before 5 s (2), no effort against gravidity (3), no movement (4) |
| 7. | Limb ataxia: absent (0), present in upper or lower (1), present in both (2) |
| 8. | Sensory: normal (0), partial loss (1), dense loss (2) |
| 9. | Language: normal (0), mild aphasia (1), severe aphasia (2), mute or global aphasia (3) |
| 10. | Dysarthria: normal articulation (0), mild-to-moderate dysarthria (1), near unintelligible or worse (2) |
| 11. | Neglect: normal (0), mild (1), severe (2) |

Noninvasive multi-slice computed tomography (CT) coronary angiography has demonstrated that about 20 % of stroke patients without a history of coronary artery disease have >50 % asymptomatic coronary artery disease (Calvet et al. 2010). After a first stroke, patients are at high risk for another stroke in the next 2 years, but the 5-year risk of cardiac death is two to three times higher than that of recurrent fatal stroke (Hankey et al. 2000). Therefore, coronary artery disease is considered a significant cause of morbidity and mortality in patients who have had a stroke or TIA. Thus, medical management in stroke survivors includes prevention not only of stroke recurrence but also of new onset of coronary heart disease.

## 2.7 Diagnosis

Acute stroke patients are usually transferred to the hospital with neurological symptoms. The main symptoms of stroke are disturbance of consciousness, weakness or numbness of the extremities and facial muscles on one side, disturbance of visual field, disturbance of speech, headache, vertigo, and dizziness. Once patients arrive at the hospital with the acute onset of neurological signs, they undergo physical and neurological examination within 30 min, blood examination, electrocardiography, chest X-P, and brain CT. For neurological examination for acute stroke patients, the National Institute of Health Stroke Scale (NIHSS) is the most widely used tool worldwide (Lyden et al. 2001) (Table 2.1). The NIHSS has been shown to accurately reflect the severity of stroke.

Plain CT of the brain (Fig. 2.3) is the first step in brain imaging in acute stroke patients. Differentiation between ischemic and hemorrhagic stroke is a critical step in terms of acute treatment. A round or oval type of hyperintensity signal is observed in the brain parenchyma in intracerebral hemorrhage. A hyperintensity signal at the brain surface or basal cistern reflects SAH. However, in cerebral infarction, the signs of infarction are often unclear during the acute stage. It is only clearly visualized several hours after onset, depending on the severity of ischemia and tissue injury. For thrombolytic therapy in the acute stage, careful examination of the brain CT is required. Brain MRI and magnetic resonance angiography (MRA) (Fig. 2.5b, d–f) are the most powerful tools for diagnosis of acute ischemic stroke. Diffusion-weighted imaging (DWI) detects early signs of ischemic damage as hyperintensity signals. Without the use of contrast medium, MRA is useful for detection of vessel occlusion, which is essential for both selection of therapeutic strategy and diagnosis of subtype in cerebral infarction. Carotid duplex B-mode ultrasound (Fig. 2.5c) is routinely used for detection of vessel occlusion and stenosis in the carotid bifurcation, internal carotid artery, and vertebral artery.

Cerebral angiogram is an invasive technique used for the evaluation of cerebral vessel lesions. Although this technique is the gold standard, the recent development of MRA and CT angiography has limited its use for the purpose of diagnosis. However, it is essential when using an endovascular approach to recanalization of the occluded vessel in acute ischemic stroke.

## 2.8 Treatment

Tissue plasminogen activator (tPA) is the only agent proven to be effective for brain protection in acute ischemic stroke. Although treatment with tPA within 3 h of onset was approved since 1995 (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995), tPA treatment within 4.5 h of onset has been approved after careful examination in most countries (Hacke et al. 2008). tPA treatment increases the rate of good outcome by 50 %, but the incidence of symptomatic hemorrhage also increases with tPA treatment (5–10 % versus less than 1 % with vehicle treatment). Due to time limitation on the commencement of treatment and the poor rate of recanalization by tPA (40–50 %), endovascular treatment for mechanical thrombectomy has been developed in recent years. Patients with evidence of occlusion in a major cerebral artery may be subject to mechanical thrombus retrieval within 8 h after onset, regardless of prior tPA treatment (Nogueira et al. 2009). However, evaluation by MRI including DWI is preferable in order to evaluate the extent of the ischemic lesion before endovascular intervention.

In the acute stage of stroke, both systemic conditions (blood pressure, body temperature, respiratory state, etc.) and neurological signs are labile (Adams et al. 2007; Morgenstern et al. 2010). Stroke care units consist of a room exclusively for acute stroke patients and a team comprised of physicians, nurses, and rehabilitation staff. The most prevalent complications in the acute stage are infection, gastrointestinal bleeding, and disuse atrophy. Careful observation of body temperature, sputa,

cough, and urine is effective for treatment of infection at an early stage. Rehabilitation in the acute stage of stroke includes maintenance of range of motion in each joint and prevention of disuse muscle atrophy. Initiation of rehabilitation at the acute stage is important for functional outcome several months later.

Besides thrombolytic therapy, the antiplatelet drug such as aspirin has been shown to be slightly but significantly protective in the acute stage of ischemic stroke (International Stroke Trial Collaborative Group 1997). The effect of intravenous administration of heparin is controversial, because its antithrombotic beneficial effect may be overcome by the increased risk for hemorrhage. In Japan, intravenous administration of argatroban, a direct inhibitor of thrombin (LaMonte et al. 2004), and edaravone, a free radical scavenger (Edaravone Acute Infarction Study Group 2003), are approved for acute ischemic stroke.

In cases of massive cerebral infarction, surgical decompression has been shown to be beneficial in patients with consciousness disturbance and signs of central or uncal herniation (Adams et al. 2007). For massive hematoma, surgical evacuation is recommended in patients with consciousness disturbance and signs of compression of the brain stem after cerebellar and subcortical hemorrhage. Indication for surgical treatment after putamen hemorrhage is controversial (Morgenstern et al. 2010).

## 2.9 Secondary Prevention of Stroke

Secondary prevention of stroke includes management of the risk factors for all stroke subtypes described above, antithrombotic therapy for cerebral infarction, and surgical or endovascular treatment for occlusive vascular lesions in selected patients.

### 2.9.1 Antithrombotic Therapy in Cerebral Infarction

The strategy of antithrombotic therapy differs between subtypes of cerebral infarction (Fig. 2.4). In cardioembolic stroke, an anticoagulation drug is the first choice. Warfarin treatment, resulting in an increased prothrombin time-international normalized ratio (PT-INR) such as 2–3, reduced the occurrence and recurrence of stroke by 64 % (Hart et al. 2007). In the elderly, a PT-INR of 1.6–2.6 is recommended because warfarin treatment with a PT-INR > 2.6 increased the risk of cerebral hemorrhage in elderly patients (Yasaka et al. 2001). Recently, novel antithrombin (dabigatran) and anti-factor Xa (rivaroxaban, apixaban) drugs have been approved for prevention of stroke and systemic embolism in patients with NVAF (Connolly et al. 2009; Patel et al. 2011; Granger et al. 2011). Treatment with novel anticoagulants showed at least equivalent or superior effects on prevention of stroke and systemic embolism and was associated with a significantly lower rate of intracerebral hemorrhage when compared with warfarin treatment. In contrast, aspirin treatment has no preventive effect on cerebral embolism in NVAF patients (Sato et al. 2006).

In non-cardioembolic ischemic stroke, antiplatelet drugs are the first choice for prevention of stroke recurrence. Aspirin, an inhibitor of cyclooxygenase, and

clopidogrel, an antagonist of the P2Y12 receptor, are the most popular drugs in this class. In a meta-analysis of patients with a history of ischemic stroke, aspirin treatment lowered stroke risk by about 20 % (Antithrombotic Trialists' ATT Collaboration et al. 2009). In the CAPRIE trial, clopidogrel treatment was shown to reduce vascular events by about 9 % compared with aspirin treatment (CAPRIE Steering Committee 1996). In Asian countries, cilostazol, an inhibitor of phosphodiesterase (PDE) III, is approved for prevention of recurrence of ischemic stroke. In the CSPS2 trial, cilostazol treatment lowered stroke occurrence by 25 % compared with aspirin treatment in patients with cerebral infarction (Shinohara et al. 2010). It is particularly interesting that the rate of intracranial hemorrhage in the cilostazol group was less than half that of the aspirin group. In the United States and Europe, a combination of aspirin and dipyridamole, an inhibitor of PDE V, has been approved and is widely used based on the ESPRIT trial (ESPRIT Study Group et al. 2006). Novel P2Y12 receptor blockers, prasugrel and ticagrelor, have been approved for acute coronary syndrome and are under clinical trial for prevention of stroke recurrence (Wiviott et al. 2007; Wallentin et al. 2009).

### 2.9.2 Surgical and Endovascular Treatment

Extracranial stenosis of the internal carotid artery in patients with recent TIA or stroke is an important cause of recurrent ischemic stroke. Previous randomized controlled trials have proved that carotid endarterectomy (CEA) is superior to medical therapy alone for prevention of recurrent stroke in symptomatic patients (European Carotid Surgery Trialists' Collaborative Group 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991). However, the annual risk of ischemic stroke distal to an asymptomatic carotid stenosis is less than 1 % with contemporary medical treatment (Abbott 2009). Indications for carotid revascularization in asymptomatic patients should be carefully considered because the benefit of CEA for asymptomatic carotid stenosis is small and is very dependent on low operative risk. A less invasive endovascular technique, carotid artery stenting (CAS), has been highlighted as an alternative to CEA. Both CEA and CAS are effective and safe when performed by highly qualified surgeons and interventionists, but there are risks of stroke and myocardial infarction during the periprocedural period: the former risk was higher with CAS and the latter risk was higher with CEA (Brott et al. 2010).

## 2.10 Transient Ischemic Attack (TIA)

TIAs have recently been attracting attention because this condition has become regarded as a neurological emergency. Previously, patients who showed focal neurological signs lasting less than 24 h were diagnosed with TIA. However, the definition of TIA has changed after the development of MRI DWI (Easton et al. 2009). About 40 % of patients who were previously diagnosed with TIA had DWI-positive

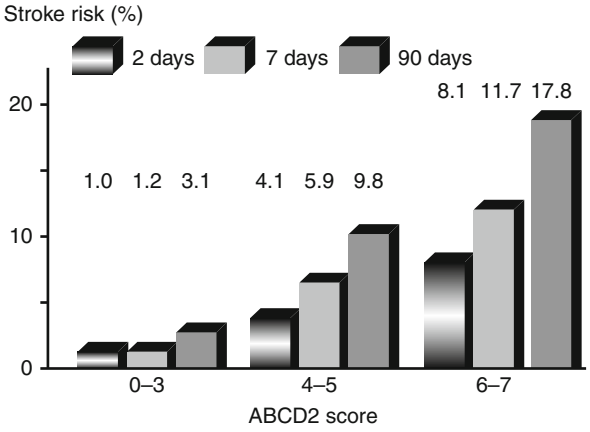


**Fig. 2.8** ABCD2 score and subsequent stroke risk at day 2, day 7, and day 90 after transient ischemic attack (*TIA*). ABCD2 score: age 60 years or older (1 point), blood pressure elevation on first assessment after TIA (1 point; systolic > 140 mmHg or diastolic > 90 mmHg), clinical features of TIA (unilateral weakness, 2 points, or speech impairment without weakness, 1 point), duration of TIA (> 60 min, 2 points, or 10–59 min, 1 point), and diabetes (1 point)

lesions (Ay et al. 2005). Thus, a tissue-based definition of TIA as transient neurological symptoms without any evidence of ischemic lesion is now recommended. The etiology of TIA is similar to that of cerebral infarction and includes cardiac and noncardiac origins. The risk for subsequent stroke associated with TIA is stratified by ABCD2 score (Johnston et al. 2007) (Fig. 2.8) according to the following criteria: age 60 years or older (1 point), blood pressure elevation on first assessment after TIA (1 point if systolic >140 mmHg or diastolic >90 mmHg), clinical features of TIA (unilateral weakness, 2 points; speech impairment without weakness, 1 point), duration of TIA (>60 min, 2 points; 10–59 min, 1 point), and diabetes (1 point). Although ABCD2 score is applied easily in clinics, several important findings such as atrial fibrillation, occlusive vascular lesions, and new ischemic lesions upon DWI are not included. TIA patients experience stroke within 7 days in 5–10 % of cases unless appropriately treated. The EXPRESS study (Rothwell et al. 2007) and the SOS-TIA trial (Lavallée et al. 2007) showed that accurate diagnosis and treatment with antiplatelet, statin, and antihypertensive drugs within a day after TIA onset dramatically reduced stroke occurrence by about 70 %. Thus, within the first few days, TIA should be treated as an emergent condition.

## 2.11 Summary and Perspective

Due to the neurological signs seen in stroke patients, management of stroke is mostly performed in neurology and neurosurgery departments. However, the etiology of stroke is mostly ascribed to cerebral vascular lesions including the large arteries (atherosclerosis), small arteries (arteriosclerosis), and capillaries

(blood–brain barrier permeability). Therefore, a common vascular etiology may underlie the vascular lesion formation associated with stroke, myocardial infarction, and peripheral artery disease. Current strategies to prevent stroke include management of risk factors, antithrombotic drugs, and revascularization for occlusive cerebral artery disease in selected patients. Stratification of high-risk patients by surrogate markers, such as carotid IMT and CSVD detected by brain MRI, could be useful for strict management of risk factors. The involvement of inflammation in cerebral vessel lesion development needs to be further clarified from both basic and clinical aspects. Furthermore, the significance of blood inflammatory marker measurement for risk stratification should be clarified by cohort studies as well as intervention trials in the future.

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# Heart Failure: Management and Prevention of Heart Failure Based on Current Understanding of Pathophysiological Mechanisms

3

Masao Endoh

**Abstract**

Heart failure is a clinical syndrome due to cardiac contractile dysfunction resulting from various underlying cardiovascular disorders, including ischemic heart disease (IHD), hypertension, and cardiomyopathies caused by genetic abnormalities. Cardiac pump dysfunction reduces cardiac output (forward failure), increases venous pressures (backward failure), and is accompanied by molecular abnormalities, i.e., cardiac and vascular remodeling, which cause progressive deterioration of the failing heart. Heart failure can be viewed as an end stage of final common pathway by which various etiologies damage the heart to cause disability and premature death. In developed countries, the incidence of heart failure is increasing, associated with an increase in IHD brought about by population aging and overall adaptation of a Western diet. Risk factors that finally lead to heart failure are composed of a wide range of events exacerbating cardiovascular disorders, including hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking, aging, and gender (male>female). The prevention of heart failure is strongly related to the attempt to reduce or avoid these risk factors which fasten the process of IHD by facilitating atherosclerosis. Health-related quality of life of the patients is impaired by subjective symptoms and decreased exercise tolerance with a high frequency of cardiac sudden death due to lethal arrhythmias. The abnormalities in the lungs, kidneys, liver, skeletal muscle, and some other organs dominate in the clinical picture, even though these tissues are victims of impaired cardiac pump function. The compensatory mechanisms driven to reverse these abnormalities constitute the feature of heart failure as general physical disorders. The characteristics of progressive deterioration of the

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failing heart associated with cardiac remodeling and shortened life expectancy are crucial target for the treatment. Future approaches and achievements of genome-wide association studies and novel informatics applied to genomic, proteomic, and clinical information will be likely to accelerate advancement of understanding and pharmacological and genetic therapy in the field of prevention and management of heart failure.

**Keywords**

Angiotensin converting enzyme (ACE) inhibitors • Angiotensin II $AT_1$ receptor blockers (ARBs) • Aldosterone • Brain natriuretic peptide (BNP) • β-Blockers • Cardiac contractility • Cardiac remodeling • Cardiomyopathy • $Ca^{2+}$ handling • Myofilament $Ca^{2+}$ sensitivity • Endothelin • Force-frequency relationship • Frank-Starling mechanism • LV ejection fraction • Neurohumoral activation • Novel cardiotonic agents • Obstructive sleep apnea (OSA) • Phosphodiesterase 3 (PDE3) • Renin-angiotensin-aldosterone system (RAAS) • Vasopressin

## 3.1 Introduction

Heart failure is a clinical syndrome caused originally by cardiac contractile dysfunction resulting from various types of underlying cardiovascular disease states, including ischemic heart disease, systemic and pulmonary hypertension, valvular diseases, cardiomyopathies due to genetic abnormalities in heart muscle, and congenital cardiac diseases. Cardiac contractile dysfunction reduces cardiac output, increases venous pressures, and is accompanied by molecular and other abnormalities, i.e., cardiac and vascular remodeling, which cause progressive deterioration of the failing heart. Therefore, heart failure is not a disease, but instead is a syndrome that can be viewed as an end stage of the final common pathway by which various etiologies damage the heart to cause disability of patients and premature death.

Risk factors that lead to heart failure are composed of a wide range of elements exacerbating cardiovascular disorders, including hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking, aging, and gender (male > female). Therefore the prevention of heart failure is strongly related to the attempt to reduce or avoid these pieces of risk factors that fasten the process of ischemic heart diseases by facilitating atherosclerosis.

Health-related quality of life (QOL) of heart failure patients is impaired by subjective symptoms and decreased exercise capability with a high frequency of cardiac sudden death due to lethal arrhythmias, which markedly aggravates the prognosis of the disease.

Because the most obvious abnormality is impaired pump function, heart failure was initially viewed simply as a hemodynamic disorder. Emphasis on pump malfunction was highlighted due to the fact that until the mid-twentieth century the most common cause of this syndrome was structural, notably rheumatic valvular disease.

Descriptions of heart failure reach back to the ancient Greek (Katz 2008). At the beginning of the nineteenth century, various types of cardiac enlargement were recognized to play a crucial role in determining the prognosis of heart failure. In the

1960s and 1970s, the focus of cardiovascular physiology shifted to myocardial contractility and its regulation, which led heart failure to be viewed largely as a hemodynamic syndrome characterized by depressed contractility that could be effectively reversed by digitalis and diuretics. Later, in the 1970s, when it was noted that cardiac relaxation is likewise impaired, decreased lusitropy is recognized as an important item to define heart failure.

In the beginning of the 1980s, an extensive effort to develop novel cardiotonic agents that can replace digitalis and catecholamines, both of which have serious adverse effects, has been accumulated. As a consequence, selective phosphodiesterase 3 (PDE3) inhibitors, including amrinone, milrinone, olprinone, and enoximone, were developed for the treatment of cardiac contractile dysfunction in heart failure patients. These agents succeeded to effectively improve the health-related QOL and exercise capability in patients with heart failure but failed to improve the prognosis of heart failure patients but even abbreviated the life span due to cardiac sudden death by increased incidence of serious ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation (Movsesian 2000).

In the late 1980s, when long-term clinical trials with the novel cardiotonic agents revealed the gloomy prognosis of heart failure patients, the progressive deterioration of the failing heart associated with cardiac remodeling and shortened life expectancy became crucial targets for pharmacological treatment. It became evident that, in addition to the hemodynamic abnormalities caused by impaired pump performance, cardiac remodeling must be recognized as the important abnormality that causes the heart to deteriorate.

Meanwhile, it became evident that the clinical picture of heart failure is commonly dominated by abnormalities in other organs. For example, an accumulation of fluid in the lung behind a failing left ventricle (LV) forces effort for the work of breathing, impairs gas exchange, and leads to shortness of breath due to the LV backward failure. Low cardiac output also affects renal function to retain salt and water in the body, which adds to the clinical disability of the patients and can cause renal and hepatic failure. In addition, the profound weakness noted in a large number of heart failure patients is also related to a skeletal muscle myopathy. These abnormalities in the lungs, kidneys, liver, skeletal muscle, and some other organs dominate the clinical picture, even though these tissues are victims of impaired pump function originated from cardiac contractile dysfunction. The compensatory mechanisms of the body driven to reverse these abnormalities represent the feature of heart failure as general physical disorders.

Based on the paradigm shift due to progress in the understanding of pathophysiology and improvement of pharmacotherapy of the disease, heart failure is currently defined as a hemodynamic abnormality, causing the clinical signs and symptoms that result from impaired cardiac function pumping the blood from veins to arteries, the consequences of which are reduced cardiac output, increased venous pressure, and compensatory increase in neurohumoral activation, accompanied by molecular abnormalities, including cardiac and vascular remodeling, which cause progressive deterioration of the failing heart (Katz and Konstam 2009).

**Table 3.1** Disorders that cause heart failure

| |
|---|
| *Disturbances of heart muscle* |
| Ischemic heart disease |
| Myocarditis |
| Cardiomyopathies (dilated, hypertrophic, constrictive, *sarcoidosis, etc*.) |
| Metabolic disorders such as diabetes mellitus |
| Neuronal and muscular disorders |
| Myocardial depression by pharmacological agents |
| Collagen disease |
| Alcoholism |
| Tumor infiltration |
| Aging |
| *Mechanical insults* |
| Hypertension |
| Valvular diseases |
| Congenital heart diseases |
| Cardiac tamponade |
| Constrictive myocarditis |
| *Abnormalities of cardiac rhythmicities or conduction disturbances* |

## 3.2 Disorders That Cause Heart Failure

Cardiovascular and other disorders that cause heart failure are summarized in Table 3.1. Among them, ischemic heart disease, hypertension, valvular diseases, and nonischemic cardiomyopathies are most frequent. Genetic predisposition may in many cases contribute to the risk for cardiomyopathy (Morita et al. 2005). Comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia as well as obesity and smoking are important risk factors to trigger and exacerbate cardiac remodeling and heart failure. Heart rate plays an important role in triggering and exacerbating heart failure. Due to impaired preload reserve, inotropic reserve, or both, the regulation of stroke volume adjustment by increasing heart rate is limited in heart failure patients. Tachycardia is especially deleterious for heart failure patients due to a reduction of stroke volume and an increase in ventricular diastolic pressure and myocardial oxygen demand. Persistent tachycardia is an important stimulus for progressive ventricular remodeling and dysfunction associated with impaired myocyte $Ca^{2+}$ handling.

It is currently recognized that obstructive sleep apnea is an important risk factor for exacerbation of heart failure (Kasai and Bradley 2011). Intermittent upper airway obstruction with associated hypoxemia can lead to a form of cor pulmonale with pulmonary hypertension, right ventricular dilatation and dysfunction, right heart failure, and fluid retention. It can likewise cause supraventricular (including atrial fibrillation) and ventricular arrhythmias. It is also associated with LV heart failure, probably due to myocardial hypoxia, tachyarrhythmias, and ventricular interdependent effects. Patients experience snoring, nighttime sleeplessness, daytime sleepiness and frequent napping, and nightmares.

Certain drugs should be preferably avoided in heart failure patients to prevent aggravation of heart failure symptoms. Intake of alcohol and cocaine is associated with myocardial injury and/or cardiomyopathy. Alcoholic cardiomyopathy appears to be idiosyncratic, occurring in some patients with only moderate alcohol intake but in a fraction of patients with long history of heavy alcohol ingestion. COX-inhibiting NSAIDs should be avoided in most patients with heart failure, since these agents aggravate heart failure symptoms by vasoconstriction, hypertension, reduced GFR, and sodium and water retention (Bleumink et al. 2003). In heart failure patients, NSAIDs can be replaced by acetaminophen, opiates, and steroids. Cardiomyopathy-inducing drugs include the cancer chemotherapeutic agents anthracyclines and trastuzumab, and the newer tyrosine kinase inhibitor. Antagonists of TNF-α and thiazolidinedione insulin sensitizers have been implicated in exacerbating heart failure.

## 3.3 Classification of Heart Failure

### 3.3.1 Acute and Chronic Heart Failure

Acute heart failure is a complex syndrome resulting from activation of diverse neurohumoral regulatory processes due to emergent hemodynamic abnormalities. In most cases, these abnormalities are triggered primarily by serious cardiac contractile dysfunction. It includes acute lung edema, cardiogenic shock, and acute aggravating phase of chronic heart failure and characterized by sudden occurrence of heart failure syndrome. Such processes result from various causes including inability of cardiac pump function due to acute myocardial infarction and valvular disease, tachy- or bradyarrhythmia, diastolic dysfunction due to hypertrophic cardiomyopathy, and inability of compensatory neurohumoral and Frank-Starling mechanism leading to immediate hemodynamic failure (Endoh and Hori 2006).

On the other hand, chronic heart failure develops gradually following occurrence of disorders. In the Guidelines of the Japanese Circulation Society, chronic heart failure is defined as "the pathological state of impaired pump function due to chronic myocardial contractile dysfunction, in which cardiac output is insufficient to meet blood volume for supplying oxygen requirement of important peripheral organs, and blood congestion in lung or systemic veins disturbs vital activities for living of the patients."

### 3.3.2 High-Output and Low-Output Heart Failure

In heart failure patients with reduced LV ejection fraction, cardiac output is generally decreased. In the minority of patients with heart failure, cardiac output is increased compared with normal subjects, and this is triggered by an increase in oxygen consumption of peripheral organs in conditions of, e.g., hyperthyroidism, anemia, and arteriovenous shunt. In high-output heart failure, cardiac pump function is unable to maintain the balance of oxygen consumption and supply that results in heart failure symptoms even in the presence of increased cardiac output.

### 3.3.3 Right and Left Ventricular Heart Failure

In left ventricular failure, blood congestion occurs mainly in the pulmonary circulation leading to pleural effusion and lung edema, while in right ventricular failure, the congestion is mainly induced in the systemic circulation system (e.g., peripheral edema, hepatic congestion). As systemic neurohumoral activation and cardiac remodeling affect the whole heart, global heart failure is often observed in advanced (end-stage) disease.

### 3.3.4 Systolic and Diastolic Heart Failure

Heart failure symptoms are often associated with a reduced left ventricular ejection fraction. However, in the last two decades, attention has risen for a considerable number of patients with signs of heart failure and congestion but (nearly) normal LV ejection fraction (heart failure with preserved ejection fraction, HFPEF). These patients present with echocardiographic or hemodynamic abnormalities during diastole, i.e., during relaxation of the myocardium and filling of the left ventricular cavity. In recent population-based studies, roughly half of the patients with clinical signs of heart failure present with preserved EF (Owan and Redfield 2005). Among these patients, aged women with underlying comorbidities such as hypertension, diabetes mellitus, and renal impairment represent a typical constellation. Atrial fibrillation not only elicits loss of contractile activity of atrial muscle but also exacerbates diastolic dysfunction in heart failure patients due to tachycardia.

## 3.4 Epidemics

In developed countries, the incidence of heart failure patients is increasing, associated with an increase in ischemic heart disease brought about by population aging and overall proliferation of European and American lifestyle and also with improved survival of an acute coronary event resulting in ischemic cardiomyopathy. It is expected that the incidence of heart failure will be increasing further. In the USA over 500 million patients are suffering from heart failure, and every year a half million patients are newly diagnosed with heart failure. While heart failure is not a natural manifestation of the senescent heart, its prevalence increases with age with 10 % of the Western population >75 years of age affected (Jessup and Brozena 2003). Three hundred thousand patients are dying due to heart failure every year, which are increasing year by year. In Framingham study in which ordinary domestic population is targeted, it is reported that the age-dependent morbidity of chronic heart failure patients is 800 in 50–59 years old, 2,300 in 60–69 years old, 4,900 in 70–79 years old, and 9,100 in over 80 years old (per 100,000 people). In Japan, there is no definite statistics of heart failure, but it is supposed that there are almost a million patients with chronic heart failure, a number that is increasing as in European and American countries, so this tendency will be strengthened in the future.

## 3.5 Pathophysiology of Heart Failure

The cellular mechanisms that promote progression of heart failure include cardiac contractile dysfunction, neurohumoral activation, and cardiac remodeling, with hypertrophy, interstitial fibrosis, and apoptosis in the myocardium (Cohn et al. 2000). In order to compensate the cardiac contractile dysfunction due to myocardial stress, damage, or maladaptive remodeling, neurohumoral factors are activated, including the activation of sympathetic nerves leading to tachycardia, increase in cardiac contractility and relaxation, and vasoconstriction. The activation of renin-angiotensin-aldosterone system (RAAS) leads to vasoconstriction, salt-water retention, and myocardial remodeling. In addition, cytokines such as TNF-α, endothelin, and oxidative stress characterized by excessive oxygen free radicals are activated to facilitate cardiac remodeling to promote myocardial damages and to further impair cardiac pump function, constituting *circulus vitiosus*. The *circulus vitiosus* occurring in such a manner plays a central role in development and progress in severity of heart failure symptoms.

### 3.5.1 Contractile Failure and Diastolic Failure

The main mechanism of heart failure is contractile dysfunction, which is assessed by the ventricular function curve or the pressure–volume relationship (Fig. 3.1) (Katz 2011). The left ventricular pressure–volume relationship reflects the Frank-Starling mechanism that is the intrinsic cardiac contractile regulatory mechanism, in which the stretch or lengthening of cardiac muscle fiber to the optimum overlapping of thin and thick filament produces an immediate increase in contractile force. This mechanism plays a crucial role in immediate adjustment of cardiac contractility in response to increase in venous return. It corresponds to the length-tension relationship in the isolated cardiac muscle preparation.

During the cardiac contraction-relaxation cycle, the left ventricular pressure–volume loop runs in counterclockwise direction, the left upper point corresponding to end systole (maximal developed LV pressure during systole). The slope of end-systolic pressure–volume relation obtained when left ventricular preload is altered over a wide range is a measure of left ventricular contractility, with an increased slope reflecting facilitated inotropy, while a decreased slope indicates reduced inotropy as observed with cardiac contractile dysfunction.

The end-diastolic pressure–volume relation reflects the left ventricular diastolic function. Therefore, the ventricular pressure–volume relationship is useful to differentiate the contractile dysfunction and diastolic dysfunction.

In the myocardium, cardiac myocytes constitute a pseudo-syncytium and excitation and contraction follow an all-or-none rule. Contractile dysfunction can be related to (1) macroscopic remodeling (i.e., chamber dilatation/hypertrophy leading to altered regional strain and timing of contraction), (2) changes in the extracellular matrix (i.e., an altered composition of extracellular collagen leading to abnormal passive stiffness and recoil), (3) loss of functional cardiomyocytes (apoptosis,

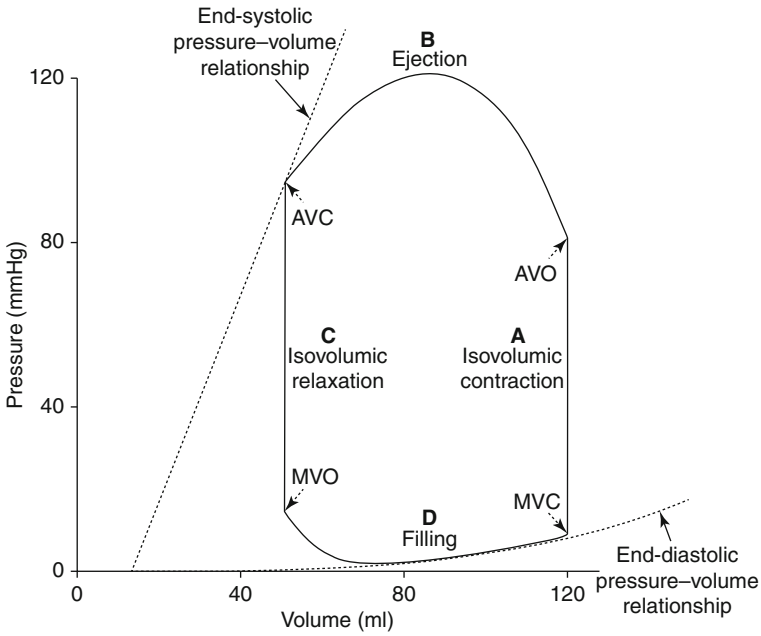


**Fig. 3.1** Pressure–volume loop generated by a normal left ventricle. The loop is constrained by the end-diastolic pressure–volume relationship, which is determined by the lusitropic state of the ventricle, and the end-systolic pressure–volume relationship. When the systole begins, the mitral valve closes (*MVC*) and pressure increases rapidly during isovolumic contraction (*A*). Ejection (*B*) begins when the aortic valve opens (*AVO*) and the ventricle meets its afterload, the aortic pressure. Systole ends when ventricular pressure and volume reach the end-systolic pressure–volume relationship. After aortic valve closure (*AVC*) separates the afterload (aortic pressure) and the ventricular chamber, blood can neither enter nor leave the ventricle; as a result, relaxation begins under isovolumic conditions (*C*). When left ventricular pressure falls below that in the left atrium, the mitral valve opens (*MVO*) and blood flows from the atrium into the ventricle during the phase of filling (*D*). The cycle ends when ventricular pressure and volume reach the end-diastolic pressure–volume relationship (Cited from Katz 2011)

necrosis), and (4) contractile dysfunction of the cardiomyocyte itself. At the cardiomyocyte, $Ca^{2+}$ signaling, including beat-to-beat changes in cytosolic $Ca^{2+}$ assessed experimentally as $Ca^{2+}$ transients, myofilament $Ca^{2+}$ sensitivity, or combination of both, plays a key role in contractile dysfunction. This is due to the fact that the $Ca^{2+}$ binding to troponin C triggers a series of processes leading to cardiac force generation by disinhibition of troponin I-induced suppression of thin and thick filament interaction.

In the failing cardiomyocytes, the dysfunction of regulatory proteins involved in $Ca^{2+}$ mobilization from the intracellular store, the sarcoplasmic reticulum (SR), involves the SR $Ca^{2+}$-release channels (ryanodine receptors), SERCA2a (SR $Ca^{2+}$ pump ATPase), phospholamban that regulates activation of SERCA2a depending on the phosphorylation state, and alterations in the $Ca^{2+}$-induced $Ca^{2+}$-release (CICR) mechanism (Hasenfuss and Pieske 2002).

Acidosis that can occur in acute heart failure following ischemia/reperfusion of ventricular myocardium decreases myofilament $Ca^{2+}$ sensitivity by affecting specific amino acids of troponin I responsible for controlling $Ca^{2+}$ sensitivity of thin and thick filament interaction. Alteration of myofilament $Ca^{2+}$ sensitivity occurring in chronic heart failure is controversial, because in chronic heart failure, the decrease in troponin I phosphorylation due to downregulation of β-adrenoceptors during the course of development of heart failure results in an increase in myofilament $Ca^{2+}$ sensitivity (Layland et al. 2005).

The aggravated Frank-Starling mechanism is associated with a reduced peak of $Ca^{2+}$ transients that is ascribed to a decrease in SR $Ca^{2+}$ store and release due to downregulation of SERCA2a and impaired function of ryanodine receptors, which can be reversed by cyclic AMP-mediated facilitation of intracellular $Ca^{2+}$ handling that leads to elevated peak of $Ca^{2+}$ transients.

In addition, the positive force-frequency relationship in ventricular myocardium disappears or reversed in chronic heart failure. These pieces of experimental observation imply that the dysregulation of $Ca^{2+}$ handling (upstream mechanism) may play a key role in contractile dysfunction in chronic heart failure, the detailed underlying mechanism of which is still elusive.

Diastolic dysfunction is due to either cellular abnormalities that impair myocyte relaxation (retardation of $Ca^{2+}$ uptake and/or $Ca^{2+}$ leak from ryanodine receptors in diastolic phase), cardiac structural abnormalities leading to reduced ventricular cavity volume (concentric hypertrophy induced by hypertension, hypertrophic cardiomyopathies), increased myocardial stiffness (fibrosis, aging, amyloidosis), or pericardial diseases that impede filling.

### 3.5.2 Activation of Neurohumoral Factors

Compensatory mechanisms are activated maximally to overcome the hemodynamic disorders brought about by underlying cardiovascular diseases that lead to chronic heart failure. Activation of sympathetic nerve and RAAS and the release of cytokines play crucial roles in promoting disease progression and shaping the long-term prognosis of chronic heart failure, including symptoms, cardiovascular remodeling, and transition from hypertrophy to heart failure (Packer 1992).

Sympathetic activation mainly results in tachycardia, increase in cardiac contractility and relaxation, peripheral vasoconstriction, and renin release. Long-term stimulation of β-adrenoceptors results in downregulation of β-adrenoceptors leading to the abrogation of β-adrenoceptor-mediated regulation. Stimulation of α-adrenoceptors is coupled to activation of signaling for hydrolysis of PIP2 through activation of $G_{q/12}$ proteins to generate diacylglycerol and subsequent activation of protein kinase C (PKC) and inositol 1,4,5-trisphosphate ($IP_3$), which are partly responsible for promoting cardiac hypertrophy and remodeling. Cardiac oxygen consumption is increased by cardiac β-adrenoceptor stimulation and by an increase in cardiac afterload with peripheral vasoconstriction induced by α-adrenoceptor stimulation. Cardiac β-mediated effects, such as increased cardiac contractility and

relaxation and tachycardia, as well as α-mediated peripheral vasoconstriction in heart failure, are responsible for the short-term adaptive responses as the case with exercise and circulatory shock. But in the long term, they become maladaptive and result in increased cardiomyocyte cytosolic $Ca^{2+}$ leading to serious arrhythmias that can cause cardiac sudden death, increased cardiac energy demand associated with cardiac myocyte necrosis, and decreased cardiac output by energy deficit and increased afterload (Sabbah 2004).

Activation of RAAS elicits short-term regulation, including vasoconstriction, aldosterone release, and sodium/water retention, and long-term regulation leading to promotion of cardiovascular remodeling. In addition to plasma renin-angiotensin system (RAS), tissue RAS in the myocardium plays an important role in progress in heart failure, i.e., in aggravation of heart failure symptoms caused by cardiomyocyte hypertrophy and increase in cardiac oxygen consumption (Unger and Li 2004). Proliferation of intimal and medial vascular smooth muscle cells, myocardial interstitial fibrosis due to proliferation of fibroblasts, and increased collagen synthesis result in a decrease in cardiac reserve and promote myocardial ischemia.

### 3.5.3 Myocardial Remodeling

In conditions of LV pressure overload, physical and mechanical factors play an important role in promoting cardiac hypertrophy. A mechanical stimulus (stretch or myocardial strain) is perceived by a putative pressure/stretch sensor located in the plasma membrane and conducted intracellularly through an elevation of perinuclear $Ca^{2+}$ concentration in micro-domain to trigger genetic signaling, the information for the detailed process of which is still fragmentary and elusive. Proliferative (transcriptional) signaling in sarcomeres mediates (1) cell thickening causing adaptive hypertrophy and (2) in long term likewise maladaptive hypertrophy in association with cell elongation, dilatation, remodeling and increased wall stress, increased cardiac energy demand and decreased energy supply with cardiac myocyte necrosis, and apoptosis, leading to exacerbation of chronic heart failure (Braunwald and Bristow 2005). In long-term and end-stage heart failure, proinflammatory signaling mediates cachexia and skeletal muscle myopathy. Both proliferative and proinflammatory responses develop slowly and generally persist until the patient dies.

In hypertrophied heart, the interstitial fibrosis and collagen are produced by interstitial fibroblasts. Angiotensin II (Ang II) plays a crucial role in triggering the signal for facilitation of collagen production. Ang II induces proliferation of fibroblasts and promotes biosynthesis of type I and type III collagen. In addition Ang II induces secretion of cytokines such as endothelin and TGF-β from fibroblasts, which promote further cardiac fibrosis by acting on fibroblasts themselves in an autocrine/paracrine manner.

In addition to cardiac functional stimulation, $\beta_1$-adrenoceptor activation is involved also in hypertrophic responses and induction of apoptosis, which contributes to the deterioration of the failing heart. Cardiac $\beta_2$-adrenoceptors are coupled to both $G\alpha_s$ and $G\alpha_i$ proteins, activation of the latter being antiapoptotic to act

protective in the failing heart, where $\beta_2$-adrenoceptors are upregulated in contrast to $\beta_1$-adrenoceptors. $\beta_2$-Adrenoceptors mediate a vasodilator effect in vascular smooth muscle, though the dominant vascular response to norepinephrine is vasoconstriction mediated by $\alpha_1$-adrenoceptor activation.

Aldosterone promotes likewise cardiac fibrosis by increasing collagen production. Cardiac interstitial fibrosis attenuates compliance (distensibility) and contributes to dysfunction of cardiac adaptation by promoting diastolic dysfunction.

## 3.6 Clinical Symptoms

Heart failure symptoms can be differentiated in backward failure, that is, pulmonary congestion with respiratory discomfort (dyspnea, coughing) due to LV failure and peripheral edema due to blood congestion in vital organs by RV failure, and in forward failure that manifests as fatigue and latitude due to insufficient perfusion of organs, particularly skeletal muscles by LV failure.

### 3.6.1 Dyspnea (Shortness of Breathing)

Shortness of breathing (dyspnea) is a predominant symptom of backward failure of the LV. Accumulation of fluid in the pulmonary veins stiffens the lungs and leads to fluid transudation into the pulmonary interstitium and lymphatics. The increase in respiratory effort is seen when the elevated pulmonary venous pressure causes the lungs to become stiff and inelastic, and the oxygen exchange across the alveolar membranes is impaired. Dyspnea is exacerbated by pulmonary interstitial edema and weakness of the respiratory muscles. Dyspnea begins as the increased respiratory effort during exercise, proceeding to shortness of breath with very light exercise and even at rest when heart failure becomes more serious. When severe, LV failure causes pulmonary edema that can drown the patient. The ventilatory efficiency can be quantified during cardiopulmonary exercise testing as $VE/VCO_2$ slope, i.e., the relationship between ventilation and exhaled $CO_2$. Increased $VE/VCO_2$ slope is strongly related to worse prognosis in heart failure patients (Poggio et al. 2010).

Dyspnea generally becomes more severe when the heart failure patient lies down, since central blood volume (venous return) is increased by the blood drained from the lower extremities via the leg veins and partly by elevation of diaphragm. Therefore, the patient feels to breathe more easily in the characteristic posture sitting on the bed holding the knees (orthopnea). The sudden onset of severe shortness of breath occurs in a patient after several hours of sleep in the night (paroxysmal nocturnal dyspnea) with pink foamy sputum and rales (cardiac asthma). In addition to the same mechanism for orthopnea, transfer of interstitial fluid from the lower extremities and abdomen to the vein and lowering of sympathetic nerve tone and sensitivity of respiratory center during sleeping contribute to the dyspnea.

Low cardiac output contributes also to exertional dyspnea by increasing anaerobic metabolism in exercising skeletal muscle (Coats et al. 1994).

### 3.6.2 Peripheral Edema

As a backward failure of the RV, an elevation of jugular vein pressure causes fluid to be transudated into the soft tissues leading to typically soft, painless, and dependent peripheral edema in lower extremities, namely, the ankles and legs, where the gravity helps to force fluid out of capillaries into the soft tissues. It is a predominant sign of venous congestion and increased venous hydrostatic pressure. The edema is associated with engorgement of veins in the neck and thoracic wall and increased body weight. Edema appears in sacral and back region in long-term bed rest. Long-lasting edema is associated with bright and hardened skin and reddish swelling and pigmentation.

However, it has been noted that the most important cause of edema is salt and water retention by the kidney, rather than the high venous pressure caused by impaired pumping of blood out of the venous system. Retention of sodium rather than water is the major cause of the expanded extracellular fluid volume in heart failure, water retention being largely due to sodium retention. Renal fluid retention in heart failure occurs by the selective constriction of renal efferent arterioles, increased renal vein pressure, increased sodium reabsorption by renal tubules, and increased renal water reabsorption by collecting ducts. Neurohumoral mediators, such as norepinephrine, Ang II, vasopressin, and endothelin, selectively constrict glomerular efferent arterioles. Aldosterone and vasopressin directly increase sodium and water reabsorption by tubular epithelium and collecting ducts, respectively, and thereby contribute to fluid retention.

Backward failure of the RV causes the body cavities to fill with usually thin and colorless fluid (dropsy, anasarca): accumulation of fluid in the pleural spaces (pleural effusion), peritoneal cavity (ascites), and pericardium (pericardial effusion).

### 3.6.3 Weakness, Fatigue, and Lethargy

Fatigue is one of the most common and troublesome problems in heart failure patients. In addition to hypoperfusion of skeletal muscle due to decreased cardiac output, skeletal muscle myopathy caused by disuse, malnutrition, inflammation, apoptosis, and molecular abnormalities, including changes in myosin isoforms and mitochondrial dysfunction, are major causes of fatigue (Coats et al. 1994). Impaired mitochondrial oxidative ATP regeneration leads to increased anaerobic lactate production and to acceleration of systemic acidosis during exercise and reduced skeletal muscle performance. Cytokines and other inflammatory mediators also play causal roles in skeletal muscle myopathy.

### 3.6.4 Other Symptoms

Anorexia and nausea occur due to blood congestion in intestine, liver, and pancreas (gastrointestinal discomfort). Diarrhea and vomiting are seen with intestinal congestion. In the RV failure, right and/or middle hypochondrium pain is often recognized.

Decrease in renal blood flow results in oliguria. When the patient who has a decreased renal flow and is standing at work during the daytime lays in supine position at night, venous return to the heart is increased leading to increased filling and release of natriuretic peptides and nocturia.

## 3.7 Therapeutic Relevance of Compensatory Mechanisms

Hemodynamic abnormalities are triggered primarily by cardiac pump dysfunction. However, various signal transduction processes and messenger molecules are activated as compensatory mechanisms for impaired pumping of blood. These include RAAS, norepinephrine, endothelin, atrial and brain natriuretic peptides (ANP and BNP), and cytokines. Dysfunction of Frank-Starling mechanism is responsible for aggravation of lung congestion and progression of hypoxemia, which is associated with constriction of large veins due to an excessive increase in cardiac preload (RV backward failure) and low cardiac output due to afterload mismatching that is associated with constriction of peripheral resistance vessels (LV forward failure).

The primary purpose of pharmacological therapy of chronic heart failure is (1) a decrease in mortality and morbidity of the patients and (2) an improvement of health-related QOL and exercise capability. The difficulty of the treatment is that both are not simultaneously or consistently achieved, particularly because clinical trials imply that the former is not always associated with the latter. This is in contrast to the pharmacological treatment of acute heart failure, which aims at immediate reversal, cessation, or retardation of the various serious clinical symptoms that are primarily caused by cardiac contractile dysfunction.

Pharmacological therapy of chronic heart failure is mainly focused on the control of compensatory mechanisms triggered by hemodynamic dysfunction, involving regulation of increased circulating blood volume mainly due to body water and sodium retention. The neurohumoral response, which provides the compensatory mechanism to minimize the hemodynamic consequences, becomes not well suited to deal with the long-term problems caused by cardiac pump failure, fails to improve the situation, and adds further to the long-term problems in heart failure patients.

### 3.7.1 Autonomic Nervous System

The most important mediator of the cardiac β-adrenoceptor stimulation induced by arterial underfilling is the baroreceptor response, which causes sympathetic stimulation and decreases parasympathetic tone. Norepinephrine released from sympathetic nerve endings binds to cardiac $\beta_1$-adrenoceptors and mediates cardiac stimulatory responses. It should be noted that cardiac contractile stimulation in the failing heart is associated with arrhythmogenic effects and an increase in energy expenditure, resulting in exacerbation of contractile dysfunction and myocardial cell death. In chronic heart failure, underfilling of the arterial system (despite venous

congestion) lasts for a lifetime, which makes the increase in heart rate, contractility, and relaxation help to maintain cardiac output in response to cardiac $\beta_1$-adrenoceptor stimulation maladaptive. Since the failing heart is mostly energy starved, continuous cardiac $\beta_1$-stimulation contributes to contractile dysfunction due to increased cardiac energy utilization and myocardial cell death. On the other hand, arteriolar vasoconstriction by α-stimulation helps to maintain arterial blood pressure, but increases LV afterload, and contributes to a decrease in cardiac output and an increase in myocardial energy demand. Other serious maladaptive effects of vasoconstriction in end-stage heart failure patients are clinical deterioration caused by a decrease in perfusion of skeletal muscle, kidneys, liver, and other organs. The most important mediator of vasoconstriction is norepinephrine, but in addition plasma levels of Ang II, endothelin, and vasopressin are elevated in chronic heart failure, which also contributes to vasoconstriction. Chronic sympathetic activation directly affects myocardial remodeling (Lohse et al. 2003). In cardiomyocytes, $\beta_1$-, $\beta_2$-, and also $\beta_3$-adrenoreceptors are expressed. Most of the maladaptive effects of increased sympathetic tone, including cardiomyocyte hypertrophy and apoptosis, are attributed to $\beta_1$-adrenoceptor signaling, whereas experimental data even suggest a potential benefit of $\beta_2$-agonists (in combination with $\beta_1$-blockers) in heart failure (Talan et al. 2011).

### 3.7.2 Renin-Angiotensin-Aldosterone System (RAAS)

RAAS is among the most powerful mechanisms affecting cardiovascular function possessing causal links to hypertension, cardiac hypertrophy, interstitial fibrosis, and cell proliferation. RAAS elicits functional responses including vasoconstriction and a decrease in fluid excretion by the kidneys through aldosterone secretion. Ang II mediates these responses via activation of $AT_1$ receptors. Ang II is an octapeptide formed from angiotensin I by proteolytic reactions in the circulation (lung) and several tissues by ACE and/or chymase. Proteolysis of Ang II generates biologically active heptapeptide angiotensin III and hexapeptide angiotensin IV. Angiotensin III is proinflammatory and causes vasoconstriction via $AT_1$ receptor activation. In the first step of Ang II signaling, renin is released from juxtaglomerular apparatus when kidneys become ischemic and/or in response to $\beta_1$-adrenoceptor stimulation. Renin is a protease that forms angiotensin I by catalyzing the hydrolysis of angiotensinogen. Activation of $AT_2$ receptors induces vasodilatation and growth inhibition. Ang II stimulates secretion of aldosterone, vasopressin, catecholamines, and endothelin, which contribute to vicious cycles in heart failure patients.

Aldosterone is a steroid hormone produced by the zona glomerulosa of the adrenal cortex. It acts on the distal tubules to increase sodium reabsorption and excretion of potassium and hydrogen ions, the latter of which are responsible for hypokalemia and metabolic alkalosis seen in severe heart failure. Physiologically, aldosterone secretion is stimulated by ACTH released from pituitary gland with low blood volume and also by hyperkalemia. In chronic heart failure, different endogenous

mediators, such as Ang II, catecholamines, vasopressin, and endothelin, stimulate aldosterone release. Aldosterone as well as Ang II stimulate fibrosis and mediate maladaptive proliferative responses in chronic heart failure patients. Beside the systemic RAAS, locally regulated RASs have been identified in various tissues, also in the heart (Neri Serneri et al. 1996). Differential regulation of Ang II activity in the heart and even in distinct myocardial regions may contribute to contractile dysfunction, arrhythmias, and adverse remodeling in advanced heart failure (De Mello and Frohlich 2011).

## 3.8 Prevention and Therapeutic Strategy

Management of heart failure aims on prolonging the survival of the patient and to maximize health-related QOL, the latter including all the factors that affect both symptomatic profile and functional status. Symptoms such as dyspnea, lightheadedness, or edema and physical disability for exercise, such as climbing stairs, and sleep disturbance all negatively impact on health-related QOL. Much debate centers on the relative value of living longer versus feeling better. Greater weight is currently placed on the treatment for prolonging survival rather than for improving health-related QOL. This is mainly due to the higher statistical rigidity of the design and conduct of cardiovascular clinical trials with mortality endpoint, while the indices for convincing symptom or functional status improvement are more elusive.

While both acute and chronic heart failure share the cardiac contractile dysfunction as the common basic mechanism, therapeutic strategy purposes are quite different from each other, even though the pharmacological treatments for urgent relief of the symptoms in individual patients are overlapping to some extents. Generally, cardiac contractile dysfunction that threatened the life of patients with acute heart failure requires emergent treatment, while in chronic heart failure long-term cardioprotective and/or cardiac unloading therapy is currently recognized to be more beneficial than the inotropic therapy for improving prognosis.

## 3.9 Paradigm Shift of Therapeutic Strategy

In the early 1980s, the pharmacological treatment of chronic heart failure has been targeted to improvement of cardiac pump function due to contractile dysfunction, since heart failure has been viewed as a uniformly fatal condition that varies only moderately in progression speed of cardiac functional and symptomatic deterioration, which play a key role as etiology of initiation and progress of heart failure. In those days heart failure has been treated with digoxin to increase contractility, diuretics to decrease preload, and bed rest to unload the cardiac pump. An extensive effort began to develop novel cardiotonic agents that act through novel mechanism of action to replace digitalis and catecholamines generally employed to reverse contractile dysfunction but associated with serious unfavorable adverse effects, including pharmacokinetic disadvantages and arrhythmogenesis. It has been intuitively

believed that the improvement of health-related QOL by cardiotonic agents directly results in a decrease in mortality and morbidity of heart failure patients. However, after an extensive effort for almost 10 years, it became evident that the novel agents such as PDE3 inhibitors (amrinone, milrinone, enoximone, and vesnarinone) and the β-adrenoceptor partial agonist xamoterol unexpectedly failed to demonstrate long-term clinical benefits, even though intravenous injections of these agents succeeded in improving health-related QOL and exercise capability in patients with acute heart failure. By contrast, the agents such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II $AT_1$ receptor blockers (ARBs), and β-adrenoceptor blockers that have no positive inotropic effect, but have cardioprotective effects by suppressing the neurohumoral modulation induced by cardiac pump dysfunction, provided evidence in clinical trials of improving the natural history of the chronic heart failure patients. Thereafter, the pharmacological treatment of heart failure patients was rapidly shifted from the inotropic to cardiac protective therapy, the latter being able to suppress the remodeling of myocardium, including cardiac hypertrophy and fibrosis, in addition to eliciting favorable hemodynamic action with cardiac unloading. A paradigm shift of the pathophysiology of heart failure occurred after recognizing an importance of interdependent systemic (neurohumoral) and cardiovascular (structural remodeling and functional modification) components.

Although the mortality and morbidity of patients with chronic heart failure are still very high, cardiac protective therapy by means of ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists, as well as cardiac unloading by diuretics and vasodilators, has been shown to exert favorable effects on the prognosis of chronic heart failure patients in large-scale clinical trials (Hunt et al. 2005). While there are publications reporting that the inodilators with myofilament $Ca^{2+}$ sensitizing action, such as levosimendan and pimobendan, are able to improve significantly the prognosis of heart failure patients in small- and middle-size clinical trials, supporting evidence has still been fragmentary and not currently confirmed in large-scale clinical trials (Endoh 2008). This is partly because of complex characteristics of heart failure, in which etiology, stage, and hemodynamic state of the patients are quite inhomogeneous.

## 3.10 Treatment of Acute Heart Failure

The purpose of pharmacological therapy of acute heart failure is immediate reversal, cessation, or retardation of the various clinical symptoms caused by cardiac contractile dysfunction. Successful therapy is able to improve the subjective symptoms, hypoxemia and acute circulatory failure, and to normalize the hemodynamic abnormalities.

In acute lung edema, immediate improvement of hemodynamic abnormalities is achieved by a decrease in preload by means of nitrates (intravenous or sublingual), intravenous furosemide, and intravenous morphine. In a recent randomized trial, ultrafiltration was inferior to diuretic therapy in decompensated heart failure with impaired renal function (Bart et al. 2012). The endogenous ANP and BNP have the potential to improve renal function and coronary perfusion and decrease arterial

pressure. Nesiritide is a recombinant human BNP that has been evaluated in acute heart failure in recent trials and showed a slight improvement in symptoms (but not mortality) in some but not all clinical trials (Gassanov et al. 2012). Mineralocorticoid (aldosterone) receptor antagonists should be initiated or continued during acute heart failure if renal function permits.

When a decrease in cardiac output in addition to lung congestion is serious, the treatment with cardiotonic agents, including PDE3 inhibitors (milrinone, amrinone, olprinone), sympathomimetic amines (norepinephrine, dopamine, dobutamine, denopamine), and (in rare reports) direct adenylyl cyclase activators (forskolin and its water-soluble derivative colforsin daropate), is used. In more severely affected patients who are resistant to ordinary therapy, artificial respiration, intra-aortic balloon pumping, percutaneous cardiopulmonary support, and left ventricular assist device have often to be applied. Even more important than cardiac-output increase is respiratory management for improvement of hypoxemia and elevated carbon dioxide by means of noninvasive positive pressure ventilation, such as continuous positive-airway pressure or bilevel positive-airway pressure.

In the treatment of cardiogenic shock, the initial therapy is crucial: without immediate assessment of curable pathogenic etiology and appropriate interventions, mortality is >85 %. Immediate stabilization of clinical symptoms and hemodynamic parameters is required. In order to determine the cause of the relative and absolute lowering of LV filling pressure, differential diagnosis of the cause of hypotension is essential. In 10–15 % of patients with acute myocardial infarction, loss of body fluid is manifest, but this is also encountered in patients with lung embolism, RV myocardial infarction, or cardiac tamponade. When excessive LV overload is not identified, transfusion of saline can be initiated. If the hypotension continues even after saline infusion, administration of inotropic and vasoconstrictor agents, including dopamine, dobutamine, norepinephrine, and vasodilatative PDE3 inhibitors, is necessary.

In the aggravating phase of chronic heart failure, clinical symptoms due to volume overload, lung congestion with an increase in LV filling pressure, and low cardiac output are manifest. Monitoring of ongoing therapy is necessary to stabilize the subjective and hemodynamic symptoms. It is especially important to address aggravating factors, such as inappropriate therapy, infection, arrhythmias, lung embolism, stress, renal insufficiency, essential cardiac disorders, and other conditions (e.g., anemia, malnutrition, pregnancy, diabetes mellitus). Some patients suffering from acute myocardial infarction proceed to chronic heart failure through cardiac hypertrophy, energy starvation, cardiomyocyte degeneration, and apoptosis.

## 3.11 Treatment of Chronic Heart Failure

Clinical feature of chronic heart failure is characterized by cardiac contractile dysfunction by impaired Frank-Starling mechanism and force-frequency relationship, maladaptive neurohumoral signal transduction processes, and cardiac and vascular pathological remodeling associated with proliferative responses including interstitial fibrosis, increased collagen content, and myocardial cell death.

**Table 3.2** New York Heart Association functional classification

| | |
|---|---|
| Class I | No limitation of physical activity; ordinary physical activity causes no discomfort |
| Class II | Slight to moderate limitation of physical activity; ordinary physical activity causes discomfort |
| Class III | Moderate to great limitation of physical activity; less than ordinary physical activity causes discomfort |
| Class IV | Unable to carry on any physical activity without discomfort |

From the Criteria Committee of the New York Heart Association (1942)

**Table 3.3** Stages of chronic heart failure

| | |
|---|---|
| The stages presented within the joint guideline of the American Heart Association and American College of Cardiology are as follows: | |
| Stage A | Patients at high risk for heart failure in the absence of structural heart disease |
| Stage B | Asymptomatic patients with structural heart disease |
| Stage C | Patients with prior or current symptoms of heart failure |
| Stage D | Patients with advanced cardiac disease and refractory clinical heart failure |

Prevention and management of chronic heart failure are targeted to improvement of prognosis by prolongation of survival and improving health-related QOL. For evaluation of drug effects on mortality and morbidity of the patients, it is crucial to define appropriately patient subsets based on functional, structural, and clinical characteristics. Many clinical trials have categorized patient clinical status based on the NYHA classification (Table 3.2). Recent clinical practice guidelines have recognized limitations in NYHA classification including the frequency of shifts in either direction in patient classification and adopted a broader categorization based on a pattern of advancing cardiac and clinical functional impairment (Table 3.3; Hunt et al. 2005).

### 3.11.1 LVEF and Volumes

Clinical trials and treatment recommendations generally categorize patients based on LVEF. Patients are described as having systolic or diastolic heart failure based on whether the EF is low (e.g., <35 or 40 %: systolic failure) or preserved (diastolic heart failure). However, there are limitations to this categorization, which might have seriously affected the outcome of clinical trials on mortality and morbidity. LVEF is determined principally by the degree of LV remodeling with dilatation rather than the extent of reduced myocardial contractility. Abnormalities in both contraction and relaxation are generally present in chronic heart failure patients, regardless of EF. Furthermore, underlying disease states are not identified by LVEF. The reduction of LVEF is most commonly caused by ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. On the other hand, the most common cause of patients with preserved LVEF is hypertensive cardiovascular disease (HCVD) though many other causes exist in the latter, including familial hypertrophic cardiomyopathies. Reduced LVEF can be therefore recognized principally as a marker of LV remodeling with dilatation.

Patients with reduced LVEF can be treated with ACE inhibitors and ARBs that prevent or reverse adverse ventricular remodeling, rather than increasing myocardial contractility. Patients with HFPEF do not respond as well to the established therapy of HF with reduced EF. In these latter patients, current therapy is directed toward preventing or reversing the underlying cardiac abnormalities, including myocardial hypertrophy and interstitial fibrosis, by treating the underlying comorbidities (e.g., diabetes, hypertension, metabolic syndrome).

Patients who do not express heart failure symptoms but have LV eccentric (dilatation) or LV concentric hypertrophy (due mostly to long-standing hypertension) are recognized as conditions requiring treatment to prevent development and progression of clinical heart failure by normalization of blood pressure. Administration of multiple agents is often required for adequate hypertension management. Pathological LV hypertrophy directly drives the expression of disease, generating cardiac functional impairment to promote clinical heart failure.

The most prevalent cause of heart failure without a dilated LV cavity is HCVD. In these patients, it is crucial to clarify the following: whether suffering from a long-lasting hypertension, the family history suggestive of hypertrophic cardiomyopathy, RV dysfunction out of proportion to LV heart failure, intermittent LV ischemia or hibernating myocardium, obstructive mitral or aortic valvular disease, and constrictive or restrictive heart disease, e.g., myocardial infiltration or pericardial thickening. Management of HCVD is to treat hypertension and prevent or regress LVH by ACE inhibitors or ARBs, to refine volume management by sodium restriction and thiazide or loop diuretics, to maintain diastolic filling time by a decrease in heart rate, and to diminish or prevent ischemia with $Ca^{2+}$ antagonists, ACE inhibitors, or ARBs (Georgiopoulou et al. 2010).

### 3.11.2 Asymptomatic Patients with LV Dilatation

Increased LV volume, particularly LVEDV, represents a major independent risk factor for subsequent adverse clinical outcomes in patients with myocardial infarction (MI). LV cavity dilatation generally associated with reduced LVEF constitutes stage B in the absence of symptomatic heart failure (Table 3.3, Hunt et al. 2005). The most probable cause is ischemic heart disease, but cocaine or excessive alcohol use and family history suggestive of a familial dilated cardiomyopathy have to be taken into consideration. The treatment designed to prevent the progression of adverse ventricular remodeling and to reduce the likelihood of symptomatic heart failure with ACE inhibitors or ARBs and β-blockers is required. These agents, including enalapril and carvedilol, have been shown to elicit beneficial effects to reduce mortality and/or morbidity in patients with reduced LVEF. Use of implantable cardioverter-defibrillator (ICD) should be considered in patients with moderate to severe reduction in LVEF (<30 %) who are more than 30 days after an MI. Between 2003 and 2004, it has been recognized that 20–40 % of acute heart failure patients suffer from diastolic dysfunction, with systolic functions essentially within the normal range (LVEF > 40–50 %). These patients are preferentially treated with

cardioprotective agents, such as ACE inhibitors, ARBs, aldosterone antagonists, β-blockers, and diuretics and vasodilators (nitrates, human ANP (carperitide), and BNP (nesiritide), which decrease oxygen consumption by causing cardiac unloading) (Braunwald and Bristow 2000).

### 3.11.3 Pharmacological Therapy

Pharmacological therapies of chronic heart failure patients succeeded to prolong survival, improve symptom status and health-related QOL, and arrest or reverse the progression of adverse cardiac remodeling and dysfunction. Normalization of LVEF and LV volumes is frequently observed with ACE inhibitors, ARBs, and β-blockers in patients with dilated cardiomyopathy. Nowadays, the therapeutic tools are capable of improving the lives of patients with heart failure and of those at risk (Braunwald and Bristow 2000). The present mechanistic paradigms, including ventricular remodeling and neurohumoral activation, will undoubtedly evolve in the coming years. They form a solid basis for moving forward along a pathway to further clinical advances through the novel pharmacological tools based on the sound pathophysiological paradigm and the conduct of well-designed clinical trials with them.

As the basis of pharmacological therapy, three pathophysiological characteristics are worthy focusing: neurohumoral activation, ventricular remodeling, and cardiovascular-renal syndrome (Braunwald and Bristow 2000).

#### 3.11.3.1 Neurohumoral Activation and Ventricular Remodeling

Activation of neurohumoral systems, particularly the RAAS and adrenergic nervous system, is closely related to therapeutic advances in heart failure. Most drugs, including ACE inhibitors, ARBs, aldosterone antagonists, and β-blockers, documented to improve the natural history of heart failure act through interface of these systems. Activation of these systems contributes to cellular and interstitial changes that drive ventricular remodeling, which applies to restructuring of cardiac architecture leading to LV dilatation and hypertrophy. These structural changes are associated with myocyte hypertrophy and an increase in interstitial collagen. Remodeled myocardium displays various abnormal functional alterations, including $Ca^{2+}$ handling, receptor-mediated signaling, metabolism, and contraction and relaxation, which exacerbate contractile dysfunction. Increased interstitial collagen is associated with increased myocardial stiffness, while improved clinical outcomes in successful treatment were associated with slowing or reversal of progression of pathologic remodeling. These findings support the view that the ventricular remodeling plays a central role in driving the natural history of chronic heart failure, and the clinical benefits are driven at least in part through modulation of ventricular remodeling and prevention of myocardial cell death (Braunwald and Bristow 2000).

#### 3.11.3.2 Cardiorenal Syndrome

It has currently been recognized that renal and vascular factors contribute to the pathogenesis and clinical expression of heart failure, which is termed cardiorenal

syndrome or cardiovascular-renal syndrome (Hatamizadeh et al. 2013; Ronco et al. 2008). Clinically, it is often not readily distinguishable whether it is primarily chronic renal failure that drives cardiac hemodynamic compromits (as postulated for cardiorenal syndrome type 4 in a new classification) or vice versa (as in cardiorenal syndrome type 2) (Ronco et al. 2008). Factors such as neurohormones, hypertension, diabetes, and lipid derangement, which contribute to underlying cardiac disease, also promote vascular and renal disorders. Endothelial dysfunction and recessive arterial stiffness contribute to the symptoms of heart failure through impaired reactive vasodilatation and inability to handle an intravascular volume load, while, conversely, heart failure promotes endothelial dysfunction. Impaired sodium handling and increased renin production promote the progression of clinical expression of heart failure, while, conversely, heart failure impairs renal function and sodium excretion and promotes renin production. Thus, cardiac, vascular, and renal pathology and functional impairment conspire in a complex series of *circulus vitiosus*. Therefore, it is highly likely that direct renal and/or vascular effects of the agents such as ACE inhibitors, ARBs, and nitrates contribute importantly to their benefits in patients with heart failure. Patients with chronic kidney disease and heart disease are at increased risk for life-threatening arrhythmias (Padeletti et al. 2011), aggravated by an increased propensity for electrolyte imbalance and – in dialysis patients – larger intravascular volume changes.

### 3.11.4 Sudden Cardiac Death

Patients with heart failure and pathologic LV dilatation are prone to ventricular arrhythmias and sudden cardiac death, since ventricular tachycardia and fibrillation is a common mode of death. Amiodarone is often used to suppress ventricular arrhythmias, but the reduction of the frequency of sudden cardiac death with this agent has not yet been shown in well-controlled clinical trials, while implantable cardioverter-defibrillators significantly reduced the mortality rate (see Chap. 4).

## 3.12 Treatment of Underlying Cardiovascular Diseases

In management of heart failure patients, it is of extreme importance to consider and address etiologic and exacerbating factors and potentially remediable causes, including ischemic heart disease, hypertension, valvular disease, and other disorders.

### 3.12.1 Ischemic Heart Disease

Ischemic heart disease is a major cause responsible for heart failure in the developed world. Energy starvation caused by ongoing ischemia adversely impacts both diastolic and systolic function. In addition, patients with ischemic heart disease may manifest chronic heart failure due to loss of myocardium secondary to

prior infarction or chronic low-flow ischemia (hibernation). Progressive reactive hypertrophy and fibrosis in noninfarcted zones after infarction contribute to cardiac dysfunction and ventricular dilatation. Chronically ischemic myocardium manifests abnormal $Ca^{2+}$ handling, increased stiffness, and functional abnormalities in both systolic and diastolic phases (Swynghedauw 1999). Furthermore, ischemic heart disease may result in mitral valve dysfunction due to papillary muscle dysfunction and functional impairment related to left ventricular remodeling and dilatation.

### 3.12.2 Hypertension

Hypertension represents the most important risk for the development of heart failure among healthy individuals. It can directly provoke heart failure symptoms by elevating LV afterload and so is a critical cause in triggering and enhancing acute exacerbation of heart failure. Hypertension promotes myocyte hypertrophy and abnormalities in contraction, relaxation, and compliance. It is an important risk factor for ischemic heart disease, a major cause of heart failure, and in addition contributes to heart failure syndrome by increasing vascular resistance and impedance, reducing vascular capacitance, and impairing endothelial function. Therefore, management of hypertension is an essential strategy designed to prevent heart failure and to treat patients with both acute and chronic heart failure, which reduces the risk for development of heart failure. A general approach to hypertension management includes sodium restriction, diuretics, ACE inhibitors, ARBs, β- and α-blockers, $Ca^{2+}$ antagonists, vasodilators, and/or aldosterone antagonists. In clinical trials targeting patients with atherosclerosis or diabetic nephropathy, ACE inhibitors or ARBs have reduced the frequency of subsequent heart failure events, leading to credence to the attractiveness of choosing this class of agents in managing hypertension, even in patients without overt symptoms, for prevention of heart failure.

In patients with clinical heart failure or reduced LVEF, agents with demonstrated benefit on long-term clinical outcomes (ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists) represent important elements of an antihypertensive treatment regimen. The combination of hydralazine and isosorbide dinitrate has been shown to be beneficial in improving clinical outcomes and symptoms of heart failure (Hunt et al. 2005). Diuretics should be used wherever there is evidence of or a propensity toward volume overload. Sodium restriction represents a major constituent of treatment for most patients with heart failure, particularly those with hypertension.

### 3.12.3 Valvular Diseases

Rheumatic heart disease was the major etiologic cause of heart failure in a large proportion of patients, with congenital aortic valve disease and endocarditis likewise representing significant contributing causes in mid-twentieth century in the developed world. However, these diseases have been mostly cured and disappeared

with the development of chemotherapy by antibiotics and surgical treatments. Thus, valvular heart disease contributes only to a small proportion of heart failure patients. Pharmacological treatment of mitral stenosis includes maintenance of sinus rhythm, heart rate reduction with β-blockers and $Ca^{2+}$ antagonists or digoxin, appropriate fluid management, prophylaxis of endocarditis, and anticoagulation.

## 3.13 Education and Counseling

Education and counseling of patients with or at risk for heart failure and particularly during initial treatment of heart failure are extremely important for the patient management. These include diet and exercise and careful monitoring for early signs and symptoms of clinical worsening and fluid status. Noncompliance to medication and dietary prescription represents serious obstacles to patient management. Weight gain and early symptoms of clinical worsening are major causes of urgent hospitalization. Successful general care plans include regular education efforts to overcome these sources of treatment failure. Key components of an educational initiative are understanding of the patient's condition at individually appropriate levels, emphasis on compliance to medication and dietary prescription, avoidance of toxic substances such as cocaine or heavy alcohol drinking, and awareness of the early signs of clinical worsening. These should be reinforced at every occasion as a part of disease management effort.

### 3.13.1 Diet

Sodium restriction is most important for dietary management in patients with heart failure. The degree of sodium restriction should match to that of sodium retention in individual patients. Fluid retention is the single most prevalent cause for clinical worsening and hospitalization. Dietary sodium intake directly negates the effectiveness of most diuretics that act by reducing renal tubular sodium reabsorption. In addition, dietary sodium restriction is important for hypertension treatment. Attention to sodium restriction has been inadequate because too strong emphasis is placed on a heart-healthy diet with low cholesterol and low saturated fat. It is recommended to limit dietary sodium to 2–3 g daily, in patients with the clinical syndrome of heart failure, with further restriction to 2 g daily for patients with moderate to severe heart failure (The Heart Failure Society of America 2006 Comprehensive Heart Failure Guideline). Restriction of cholesterol and saturated fat intake should be considered as with all patients at risk for cardiovascular events, which is more important in patients with atherosclerotic cardiovascular disease and less important in patients with more advanced degrees of heart failure. It is increasingly recognized that heart failure is associated with morbid obesity, for which key contributing factors are obstructive sleep apnea, hypoxemia, and pulmonary hypertension. For the management of obesity-related heart failure, multidimensional approach can be considered, including dietary and psychological counseling, tailored exercise, treatment of obstructive sleep apnea, and surgical procedures.

### 3.13.2 Exercise

Bed rest to attenuate physical activity has been an important element for management of patients with chronic heart failure up to 30 years ago, because exercise tends to impose excess stress on the failing heart and thereby accelerates the progress of heart failure. However, it was then recognized that cardiovascular risk is reduced in individuals engaged in regular exercise compared with those being sedentary. In addition, clinical benefits of regular exercise training were shown in controlled trials in ischemic heart disease or heart failure patients. Furthermore, exercise has been shown to improve exercise capacity in patients with heart failure. In addition, a meta-analysis has indicated a net reduction in adverse clinical outcomes with exercise training in patients with heart failure (van der Meer et al. 2012). Recent data suggests that patients with HFPEF also profit from exercise programs (Edelmann et al. 2011).

Benefits of exercise on blood pressure, lipid profile, body fat and insulin sensitivity, thrombogenicity, autonomic nerve activity, and resting myocardial oxygen demand have been suggested as underlying mechanisms for exercise-induced improvement in clinical outcomes in patients with heart failure. Exercise has been shown to reverse endothelial dysfunction in patients with heart failure through periodic increases in endothelial laminar shear, resulting in increase in NO production, reduction of oxidative stress, stimulation of vasodilatation, and alteration of endothelial gene expression to induce endothelial cytoskeletal remodeling. Exercise may also improve vascular function and hemodynamics and prevent adverse vascular remodeling and coronary ischemia through alteration of arterial flow pattern. Exercise has favorable effects likewise on skeletal muscle, which functions abnormally in patients with heart failure, and has also favorable psychological effects, improving patients' affect and general well-being.

## 3.14 Summary and Perspectives

For overall management of the patient with heart failure to prevent, retard, and reverse the progress in severity of heart failure symptoms, it is necessary to assess the patient's condition as finely and precisely as possible. Frequent and continuous clinical patient monitoring and attention to patient compliance to dietary and medication for underlying diseases have currently been developed based on sound understanding of pathophysiology underlying the disease by taking a carefully thought-out scientific measures. Measurements of daily alterations in body weight are crucial for evaluation and for administration of diuretics in response to early signs of fluid overload and worsening symptoms. During visits of patients to the hospital, signs of heart failure and fluid loading, particularly jugular venous pressure and status of edema, should be routinely assessed. Measurements of serum concentrations of electrolytes, urea nitrogen, and creatinine are particularly warranted in patients experiencing fluid status fluctuation and undergoing diuretic dose adjustment and those receiving combination therapy with ACE inhibitors, ARBs, β-blockers, and/

or aldosterone blockers. Measurements of BNP and NT-proBNP can be a valuable adjunct to clinical assessment of fluid status and heart failure severity, which can help in reducing hospitalization rates and improving clinical outcomes.

Understanding of the pathophysiological basis of heart failure at various levels, including genetic, molecular, and cellular bases of cardiac hypertrophy, contractile dysfunction, and interstitial fibrosis, has been extended in the last three decades. These increasing pieces of knowledge provide therapeutic targets worthy for development of novel pharmacological strategies for treatment of heart failure patients. Ongoing trials for novel strategies targeting specifically cardiac myocytes include the following: modulation of signaling pathways for maladaptive hypertrophy; improvement of maladaptive $Ca^{2+}$ handling, particularly related to SR function; and myofilament $Ca^{2+}$ sensitization. One currently clinically tested approach in gene therapy in advanced heart failure is to increase SERCA2a in cardiac myocytes to restore the SR $Ca^{2+}$ handling and improve contractile function and relaxation. Myocardial cell-based therapies, including injection of skeletal muscle myoblasts or pluripotent stem cells into myocardial scar areas, have not yet reached a consistent beneficial outcome. Further effort for improvement of experimental procedures and selection of appropriate patients may be necessary to achieve more consistent clinical beneficial outcomes.

Other targets of pharmacological treatment include the myocardial mesenchymal tissue, e.g., to reduce the myocardial stiffness by modulation of the pathological extracellular matrix composition, and the correction of renal and vascular conditions contributing to progression and clinical expression of heart failure.

Personalized medicine, constituting specific treatments for individual patients based on identified phenotype and genotype, is increasingly gaining interest. Future approaches and achievements of genome-wide association studies and novel informatics applied to genomic, proteomic, and clinical information will be likely to accelerate advancement of understanding and pharmacological and genetic therapy in the field of prevention and management of heart failure patients.

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# Cardiac Arrhythmias

# 4

Frank R. Heinzel and Burkert M. Pieske

**Abstract**

Cardiac arrhythmias can be classified into brady- and tachyarrhythmias. Bradyarrhythmias are related to sinus node dysfunction, higher degree AV block, or a combination of these. If reversible causes are ruled out (i.e., myocardial ischemia, concomitant drugs), symptomatic bradyarrhythmias often require implantation of a pacemaker. Tachyarrhythmias are divided into supraventricular (SVT) and ventricular tachycardias (VT). Regular paroxysmal SVTs are mostly related to congenital malformations of the specialized conduction system (accessory or dual pathways) and often can be causally treated by ablation therapy. The most common irregular SVT in clinical practice is atrial fibrillation (AF), which is observed in about 10 % of the elderly population. AF may be highly symptomatic (palpitation, heart failure due to reduced cardiac output) but especially in elderly patients with comorbidities also occurs unnoticed. In patients with AF, the risk for systemic thromboembolism (e.g., stroke) is increased and anticoagulation is mostly warranted. VTs carry an increased risk of hemodynamic compromise and sudden cardiac death. Immediate medical or electrical cardioversion to sinus rhythm is often the therapy of choice and implantation of a cardioverter defibrillator is indicated for high-risk patients. Pathophysiologically, tachyarrhythmias are based on (1) increased automaticity, (2) triggered activity, and/or (3) electrical reentry. Cardiac remodeling is an important predisposing factor for acquired arrhythmias. Cardiomyopathies are often characterized by increased apoptosis, necrosis, and fibrous (scar) tissue infiltration, leading to conduction abnormalities and providing a substrate for reentry as the most common mechanism of acquired arrhythmias. Myocardial heterogeneity in cardiac repolarization is typical for congenital arrhythmias related to genetic ion channel defects

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(e.g., long QT syndrome) but is also observed in cardiac remodeling. Ectopic (premature) beats do occur in healthy hearts but are more common in diseased hearts where they can trigger sustained arrhythmias based on the pathological myocardial substrate. Cytosolic $Ca^{2+}$ and $Na^{+}$ overload as it occurs in cardiomyocytes during ischemia and in heart failure can be aggravated by neurohumoral/sympathetic activation and promotes triggered premature beats (afterdepolarizations). Current antiarrhythmic therapy is mainly aimed to reduce sympathetic activation (beta-blockers), $Na^{+}$ or $Ca^{2+}$ influx (class I and IV antiarrhythmics), or prolonged repolarization (class III), with the most potent antiarrhythmics acting as multichannel blockers. New therapeutic approaches comprise drugs with (atrial) tissue selectivity and new targets ($Ca^{2+}$ stabilizers, upstream therapy).

**Keywords**
Ion channels • Reentry • Afterdepolarizations • Triggered activity • Automaticity • Sudden cardiac death • Atrial fibrillation • Ventricular tachycardia • Substrate • Trigger • Antiarrhythmic • Beta-blockers • Long QT syndrome • Myocardial remodeling

## 4.1 Cardiac Rhythm

In the heart, electrical activation of the cardiac myocytes triggers contraction in a calcium-dependent process termed excitation contraction coupling. As established by Henry Pickering Bowditch in 1871, cardiac (unlike skeletal) muscle follows the all-or-nothing principle, indicating that local electrical activation will induce contraction of the whole heart. In the healthy heart, activity of the sinus node determines the rate of electrical activation and thus contraction of the heart. Importantly, electrical activation of the heart goes beyond rhythmic impulse generation, as timely electrical activation of the atria and synchronous activation of the ventricles determine the efficacy of the heart as a pump and depend on the sequential activation of fast and slow conduction in myocardial tissue. Organized electrical activation is observed in the embryonic stage long before the heart has differentiated into its final shape emphasizing the role of differential electrical conduction system in the heart's development and function (Van Mierop 1967). However, in cardiac remodeling, altered electrical conduction in the diseased ventricle is the most common cause for regional short circuits (reentry tachycardias, see Sect. 4.6.3) that dominate heart rate.

Cardiac arrhythmias represent a transient or persistent disturbance in cardiac rhythm. Initiation of arrhythmias is often the result of an individual predisposition and an acute triggering event (Fig. 4.1).

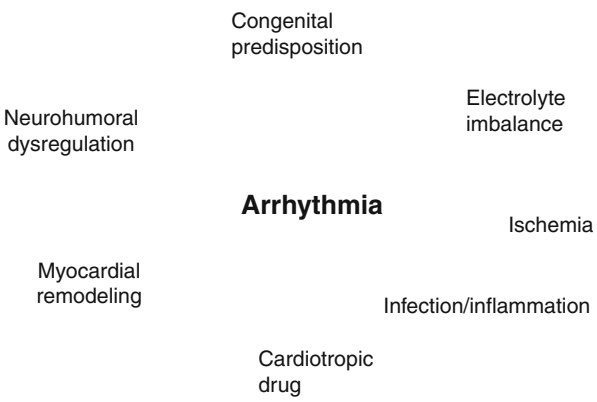


**Fig. 4.1** Factors predisposing for arrhythmias

## 4.2 Regular Heart Rate

Physiologically, cardiac rhythm originates from specialized cardiac cells located in the sinus node (primary pacemaker). As opposed to the vast majority of cardiac myocytes ("working myocardium"), these pacemaker cells are able to spontaneously generate action potentials. The pacemaking mechanism involves the interplay of several sarcolemmal ion channels (including the selectively expressed pacemaking "funny" current, $I_f$) as well as intracellular $Ca^{2+}$ cycling ("$Ca^{2+}$ clock," Lakatta et al. 2010), resulting in a slow depolarization during the resting phase (phase 4) of the action potential (Fig. 4.2).

Heart rate during sinus rhythm is in the range of 60–100/min at rest and is modulated by the sympathetic and parasympathetic nervous system. In trained individuals, sinus rhythm with lower heart rates at rest (between 40 and 60/min) may be physiologic. In case of inability of a diseased sinus node to generate an electrical pulse (as in sick sinus syndrome), cells from the specialized electrical conduction system of the heart, i.e., the atrioventricular junctional cells (secondary pacemaker) or His-Purkinje system (tertiary pacemaker), and even working myocardium can trigger heartbeats, albeit at successively lower rates (escape rhythms).

Heart rate is modulated by the autonomic nervous system, with vagal influence dominating at rest. Increased heart rate at rest (>80–85/min) is associated with increased morbidity and mortality in population-based trials and represents an independent risk factor in patients with arterial hypertension, ischemic cardiac remodeling, and also pulmonary disease. Experimentally, increased resting heart rate induces maladaptive myocardial as well as vascular remodeling (Custodis et al. 2010). Lowering resting heart rate to values below 70/min, either by beta-adrenoceptor antagonists or by selective blockade of the $I_f$ current (ivabradine), reduces morbidity and mortality and has evolved to an established therapeutic strategy in patients with heart failure and ischemic cardiomyopathy.

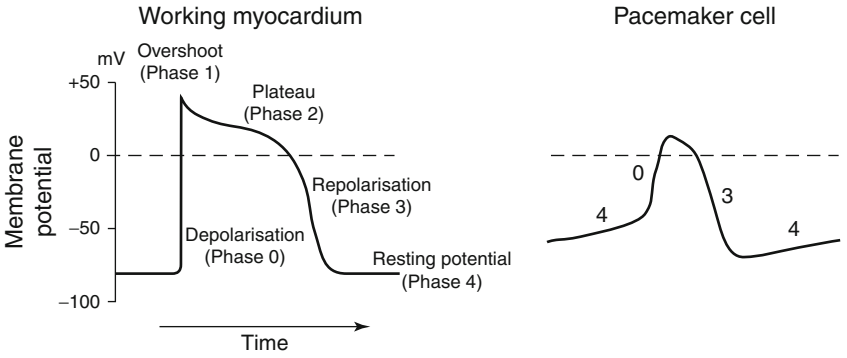


**Fig. 4.2** Action potential of working myocardium (*left*) and an impulse-generating pacemaker cell (*right*)

Heart rate variability (HRV), i.e., the circadian variability in the beat-to-beat interval, reflects the autonomous control of the heart. In cardiac remodeling and heart failure, a reduction in HRV is associated with increased mortality and an increased incidence of arrhythmias, even though the predictive value of HRV in primary prevention of arrhythmogenic events in clinical practice is limited by the strong influence of confounding comorbidities.

## 4.3 Classification of Arrhythmias

The classification of arrhythmias in clinical practice is oriented towards the rapid assessment of the associated risk of cardiac arrest and identification of immediate treatment strategies to restore compromised cardiac output. Arrhythmias are divided by rate into bradyarrhythmias (<60/min) or tachyarrhythmias (>100/min), according to the resulting ventricular heart rate. Cardiac arrest defines a state of mechanical inactivity similarly observed during asystole (no ventricular electrical activity) or ventricular fibrillation (chaotic electrical activity).

Arrhythmias are further classified according to their origin: Supraventricular arrhythmias involve ventricular activation via the specialized conduction system of the heart, are usually better tolerated by the patient, and carry a low risk of cardiac arrest. Supraventricular arrhythmias are generally more common than ventricular arrhythmias. Ventricular arrhythmias on the other hand often occur in patients with underlying structural heart disease and imply an abnormal ventricular activation pattern further compromising cardiac function. The risk of sudden cardiac death in ventricular arrhythmias is increased. Arrhythmia duration ranges from single irregular ("premature") atrial (PAC) or ventricular (PVC) contractions to sustained (>30 s) and incessant/persistent arrhythmias. Arrhythmias can compromise cardiac output as a result of a reduced heart rate (bradyarrhythmias), reduced stroke volume (tachyarrhythmias), and/or a less efficient contraction sequence (ectopy).

## 4.4 Clinical Manifestation

Patients with arrhythmias usually experience palpitations, often associated with anxiety, dizziness, dyspnea, and sometimes retrosternal discomfort even in the absence of coronary artery disease. Presyncope and syncope (transient loss of consciousness) may occur, if the arrhythmia is associated with hemodynamic compromitation. Arrhythmias with longer duration may manifest in fatigue, exercise intolerance, and overt heart failure. Sudden cardiac death (SCD) is defined as an unexpected death attributed to a cardiac cause that occurs within 1 h of the onset of symptoms. SCD has an estimated risk of 1–2/1,000 in the general population (Zipes 2005), is more common in patients with structural heart disease (see Sect. 4.7.2), and is largely (~80 %) attributed to ventricular arrhythmias. Ventricular arrhythmias associated with an increased risk of SCD (most of them are) are often termed malignant arrhythmias.

### 4.4.1 Premature Beats

PACs and PVCs are the most prevalent arrhythmias and do not necessarily imply an increased risk for SCD or disease progression. Forty to seventy percent of an otherwise healthy population have one or more PVCs in a 24 h Holter (Kostis et al. 1981; Bjerregaard 1982); almost 90 % have PACs. More than 200 PACs or PVCs/24 h or complex (i.e., repetitive or multiform) extra beats, however, are rarely seen in otherwise healthy individuals (≤5 % of cases, Bjerregaard 1982). Premature beats are the initiating event for reentry tachycardias in predisposed individuals. Single ectopic beats are often asymptomatic. However, the perception of palpitations varies greatly between individuals and is only weakly associated with objective measures of arrhythmia incidence. Thus, as may be expected, patients that tend to somatize more report a higher disease burden with arrhythmias (Barsky 2001). Premature beats may trigger reentry arrhythmias. However, in the CAST trials, an effective reduction of PVCs (initially >6/h) with antiarrhythmics of the Vaughan-Williams class I (encainide, flecainide, moricizine) in post-MI patients was associated with increased mortality. This indicates that the reduction of PVCs has to be weighed against potential drug-related proarrhythmic effects, in the case of these class I antiarrhythmics, a deceleration of ventricular conduction time probably predisposing for macroreentrant arrhythmias.

### 4.4.2 Tachyarrhythmias

Mechanistically, tachyarrhythmias are classified as focal (ectopic) tachycardias if electrical activation arises from a group of spontaneously depolarizing atrial or ventricular cardiomyocytes. The sinus node itself may also give rise to tachyarrhythmias (as observed in sick sinus syndrome, see Sect. 4.4.3.1). In contrast, reentry tachycardias are due to myocardial conduction abnormalities leading to circus

movement of electrical activation along a defined path. The beat-to-beat interval is therefore very regular. Fibrillation (atrial or ventricular) is the most complex form of arrhythmia, while seemingly chaotic electrical activity during fibrillation may be sustained by focal and/or reentry mechanisms.

#### 4.4.2.1 AV and AV Nodal Reentry Tachycardias

AV reentry tachycardia (AVRT) and AV nodal reentry tachycardia (AVNRT) belong to the group of paroxysmal supraventricular tachycardias (pSVT), characterized by a sudden onset and sudden termination. These tachyarrhythmias are based on a congenital predisposition and often observed in otherwise healthy hearts. The rhythm during tachycardia is usually fast (on average around 180/min, with up to 260/min). In AVRT, the reentry cycle driving the arrhythmia involves an accessory pathway (AP) between the atria and the ventricle, representing a congenital abnormality. During sinus rhythm, electrical activity may be conducted faster by the AP than the AV node, leading to preexcitation of ventricular tissue as reflected by a short PQ interval and a characteristic delta wave in the ECG. During tachycardia, circus movement results from antegrade (atrioventricular) conduction via one and retrograde (ventriculoatrial) conduction via the other pathway. The combination of preexcitation and paroxysmal tachycardias defines the Wolff-Parkinson-White (WPW) syndrome. AVRT tachycardias mostly (95 %) have a narrow QRS complex (antegrade condition via AV node). While generally benign, WPW syndrome carries an increased risk of SCD (~0.1 %), which is higher in familial WPW. This is attributed to an increased incidence of atrial fibrillation with fast conduction to the ventricles via the AP leading to VF. The prevalence of AP is increased in patients with congenital heart disease.

AVNRT is the most frequent pSVT (~60 %) and often manifests in the fourth decade of life. Here, the circus movement involves a fast- and a slow-conducting pathway in the atrial tissue feeding into the compact AV node, followed by rapid conduction to the ventricles via the His-Purkinje system. AVNRT and AVRT can be treated by catheter ablation with a high success rate.

#### 4.4.2.2 Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia associated with increased morbidity and mortality. The overall prevalence of AF in the Western world is 0.4–2 %. As AF is more common in the elderly (see Sect. 4.6.1), this number is expected to increase (double) in the next 30 years due to the demographic trend. Lifetime risk at an age of 40 years to develop AF is ~25 %. During AF, rapid, seemingly chaotic electrical activity of the atria is sporadically conducted to the ventricles leading to a completely irregular heart rhythm. Ventricular rate is often tachyarrhythmic, but may be normocardiac or bradyarrhythmic depending on the electrical properties of the AV node and concomitant medical therapy. AF leads to the loss of atrial contraction and thus reduced left ventricular (LV) filling, which can reduce cardiac output, especially in conditions of preexisting reduced LV function, and worsen symptoms of heart failure. AF can occur sporadically, lasting seconds to days (paroxysmal AF). AF lasting longer

**Table 4.1** Patient characteristics summarized in the CHA2DS2-VASc score as risk factors for stroke in the presence of atrial fibrillation (AF) and as risk factors for manifestation of AF (see references)

| | Risk factor for stroke in the presence of AF | Score | Increase in risk factor for AF | References |
|---|---|---|---|---|
| C | Chronic HF | 1 | 6–18× 30–40 % of CHF pts | Benjamin et al. (1994)<br>Nabauer et al. (2009) |
| H | Hypertension | 1 | 1.4–2.1× | Healey and Conolly (2003)<br>Benjamin et al. (1994) |
| A | Age ≥ 65 | 1 | 2.6× vs. age>40 years | Feinberg et al. (1995) |
| D | Diabetes | 1 | 40 % | Huxley et al. (2011) |
| S | Stroke or TIA | 2 | ~25 % of stroke pts have AF | Marini et al. (2005) |
| V | Vascular disease (coronary, peripheral, cerebral) | 1 | 1.4–2× | Benjamin et al. (1994)<br>Goto et al. (2008)<br>Bloch Thomsen et al. (2010) |
| A | Age ≥ 75 | 1 | 2.4× vs. age 65–74 years | Psaty et al. (1997) |
| Sc | Sex (female gender) | 1 | No (males) | Michelena et al. (2010) |

than 7 days or requiring immediate cardioversion to SR is defined as persistent AF. AF for more than 1 year but with the therapeutic goal to convert to SR has been termed long-standing persistent AF. In many patients, episodes of AF tend to become more frequent and longer over time, as AF itself induces changes in the atrial myocardium that promote and sustain the arrhythmia ("AF begets AF," Wijffels et al. 1995; see Sect. 4.5). If successful restoration of SR is considered unlikely and therapeutic strategy is focused on normalizing heart rate ("rate control"), AF is considered "permanent."

In patients with AF, slow flow or stasis of blood in the atria together with altered properties of the atrial endocardial surface and cytokine-mediated activation of the coagulation cascade increases the risk of cardiac thrombi, systemic embolism, and stroke. In fact, 25 % of all otherwise unexplained ("cryptogenic") strokes are attributed to cardiac thromboembolism related to AF. Strokes caused by AF are more often large and fatal, as compared to noncardiac strokes; silent cerebral infarcts can be detected by MRI imaging in about 15 % of all AF patients.

The risk of stroke is strongly dependent on coexisting patient characteristics and comorbidities as summarized by the CHADS-VASc score (Table 4.1). The annual risk for stroke ranges from 1.3 % with CHADS-VASc score of 1 to 15.2 % with CHADS-VASc score of 9 (European Heart Rhythm Association et al. 2010). The risk of stroke is similarly elevated in patients with paroxysmal and persistent AF. In fact, short episodes of AF (>6 min) are sufficient to raise the risk of stroke significantly (ASSERT trial, Healey et al. 2012). Additional, less established risk factors for stroke in AF patients include chronic obstructive lung disease and renal failure. In younger patients (<60) with no additional risk factors ("lone" AF), the

risk of stroke is low (~1.3 % in 15 years; European Heart Rhythm Association et al. 2010). Anticoagulation therapy is recommended in patients with CHADS-VASc ≥ 1 and can significantly reduce stroke risk.

In population-based studies and clinical trials, up to 40 % of patients with AF episodes are asymptomatic (Oliner and Ballantine 1968; Disertori et al. 2011) indicating a large dark number of patients with undiagnosed AF and increased risk of stroke. Interestingly, most of the factors predisposing for stroke in the presence of AF are also risk factors for the manifestation of AF (see Table 4.1), indicating that close rhythm monitoring may be beneficial in patients with high CHADS-VASc score even in the absence of a history of AF. However, the prevalence of AF in patients with manifest cardiovascular disease is higher (~13 %) than in patients with cardiovascular risk factors only (6 %, REACH Registry; Goto et al. 2008).

#### 4.4.2.3 Atrial Flutter

Atrial flutter is a supraventricular reentry tachycardia, where the activation path circles around an anatomical structure in the atria with a very regular rate of 250–300/min. In common-type atrial flutter (type I atrial flutter), the reentry cycle is located in the right atrium and involves the cavo-tricuspid isthmus. The electrical activation usually proceeds in a counterclockwise direction, leading to the diagnostically relevant negative *P* waves in the inferior ECG leads (II, III, aVF). Type I flutter with clockwise wave propagation is less common (10 % of patients with atrial flutter, Bun et al. 2012). Other types of atrial flutter are located around atrial scar tissue, the pulmonary veins, or mitral valve. Atrial flutter is most often observed in patients with concomitant heart disease (coronary artery disease, cardiomyopathy, hypertensive heart disease, following surgery or catheter ablation) but may also occur in otherwise healthy individuals. Also patients with AF receiving class I antiarrhythmics are predisposed to develop atrial flutter. Similar to AF, atrial flutter is thrombogenic and requires anticoagulation. Atrial flutter occurs in 25–35 % of AF patients. Common-type atrial flutter can be curatively treated by catheter ablation with a high (95 %) success rate.

#### 4.4.2.4 Focal Atrial Tachycardia

Focal AT is defined as a regular AT starting at a small atrial region and spreading centrifugally across the atria (Saoudi et al. 2001). Non-sustained focal AT is a common finding in Holter ECGs and often asymptomatic. Sustained AT is generally rare in adults but accounts for 10–23 % of supraventricular tachycardias in otherwise healthy children and is more common in congenital heart disease. The most efficient therapy is catheter ablation of the focus. ATs from three or more different atrial regions (multifocal AT, MAT) lead to an irregular arrhythmia (foci with different cycle length). MAT is a rare arrhythmia (0.1–0.4 % in hospitalized patients, Scher and Arsura 1989) and is often associated with pulmonary disease, coronary artery disease, or heart failure. Treatment with current antiarrhythmic drugs or ablation is not effective and strategies aim to treat the comorbidities.

#### 4.4.2.5 Monomorphic Ventricular Tachycardia

Monomorphic ventricular tachycardia (VT) mostly occurs in patients with structural heart disease and is then based on electrical reentry around an anatomical structure (myocardial scar or aneurysm). VTs present as regular wide/broad QRS complex tachycardia in the ECG. Dissociation of atrial (*P* waves) and ventricular activity (QRS) and other ECG criteria are used to confirm the diagnosis of VT. Over 90 % of monomorphic VTs are associated with coronary artery disease. Non-sustained VTs (<30 s) are often asymptomatic and then generally do not require specific therapy. However, their occurrence should trigger further diagnostics to evaluate the patient for disease progression (ischemia). Sustained or symptomatic VTs in most cases require implantation of a defibrillator (ICD) to reduce the risk of SCD, as monomorphic as well as polymorphic VT can degenerate into VF leading to SCD. In individual patients, the incidence of VT can be reduced by pharmacological therapy (mainly beta-blockers and class III antiarrhythmics; see below), but in clinical trials current antiarrhythmic therapy has been proven less effective than ICD in reducing morbidity and mortality in selected patient cohorts.

#### 4.4.2.6 Polymorphic Ventricular Tachycardia and Ventricular Fibrillation

Polymorphic VT and VF also most commonly occur in patients with coronary artery disease. Polymorphic VT/VF is also seen in patients with hereditary ion channel dysfunction (long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), idiopathic VF), drug-induced QT prolongation, and otherwise structurally normal hearts or electrolyte imbalance (hypokalemia or hypomagnesemia). Torsades-de-pointes tachycardia, a specific form of polymorphic VT, is characteristic for conditions of prolonged QT. Polymorphic VT often degenerates into VF but may also terminate spontaneously. Symptomatic polymorphic VT/VF is an indication for ICD therapy when other reversible causes (i.e., acute ischemia due to coronary stenosis) have been ruled out.

### 4.4.3 Bradyarrhythmias

Bradyarrhythmias result from sinus node dysfunction or atrioventricular block (AVB). Sinus node dysfunction reflects impaired pulse formation in the sinus node or failing conduction from the sinus node cells to the atrial myocardium (sinoatrial block).

#### 4.4.3.1 Sick Sinus Syndrome

Sick sinus syndrome (SSS) is a unifying term for different forms of sinus node dysfunction leading to sinus bradycardia, sinus arrest, or sinoatrial exit block (Bigger and Reiffel 1979). SSS mostly affects the elderly patient and is equally distributed among men and women (Lamas et al. 2000). It may in some cases be related to

structural heart disease (ischemia, myocarditis, cardiomyopathies) but is often termed "idiopathic." Generally, SSS is only treated when patients are symptomatic, mostly warranting implantation of a pacemaker. SSS is associated with other atrial arrhythmias such as sinus tachycardia, atrial fibrillation, paroxysmal supraventricular tachycardias, and atrial flutter. In 60 % of patients, SSS is associated with tachyarrhythmias (Adán and Crown 2003), commonly summarized as "tachy-brady syndrome."

#### 4.4.3.2 AV Block

In AV block (AVB), conduction from the atria via the AV node/His-Purkinje system to the ventricles is delayed (AVB I), blocked for single beats (AVB II), or blocked completely (AVB III). AVB I and AVB II subtype Wenckebach (progressively increasing AV conduction times before the block) are usually benign, whereas AVB II subtype Mobitz (sudden block of conduction for single beats) and AVB III (both termed high-degree AV block, hdAVB) carry an elevated risk for cardiac arrest. Electroanatomically, hdAVB is mostly located distal to His bundle (infrahisian block).

The prevalence of hdAVB is increased in patients with diabetes mellitus (odds ratio 3.1, Movahed et al. 2005) and hypertensive heart disease. hdAVB is a frequent complication of acute myocardial infarction with a reported incidence of up to 13 %, depending on the location of the infarct. A recent study suggests that the incidence has decreased (to ~3 %) with the advent of more effective revascularization therapy (Gang et al. 2012). However, also recently, hdAVB has been reported to occur during later stages (>21 days) after acute myocardial infarction in ~10 % of patients, contributing to increased morbidity (Gang et al. 2011). hdAVB historically has been the first and remains a standard indication for implantable pacemakers.

#### 4.4.3.3 Chronotropic Incompetence

Chronotropic incompetence (CI) is not an arrhythmia in the stricter sense, but reflects the inability of the sinus node to increase heart rate with increased activity or demand. While resting heart rate remains stable with aging, the maximal heart rate with exercise decreases, largely related to a decrease in exercise tolerance. As a reference, the maximal expected heart rate in a patient is often estimated as 220 bpm – age (in years), yet more elaborated approaches have been described (Brubaker and Kitzman 2011). The lower limit cutoff for an appropriate rise in heart rate with peak exercise is not uniformly defined. Values between 70 % and more commonly 80–85 % of the predicted maximal heart rate during exercise test have been used (Adán and Crown 2003). CI is fairly common in heart failure (~30 % of patients according to one study, Witte et al. 2006) and may be aggravated by concomitant beta-adrenergic receptor blocker therapy. Other proposed pathomechanisms include downregulation of the beta-adrenergic signaling cascade and responsiveness as well as structural remodeling of the sinus node in HF (Sanders et al. 2004).

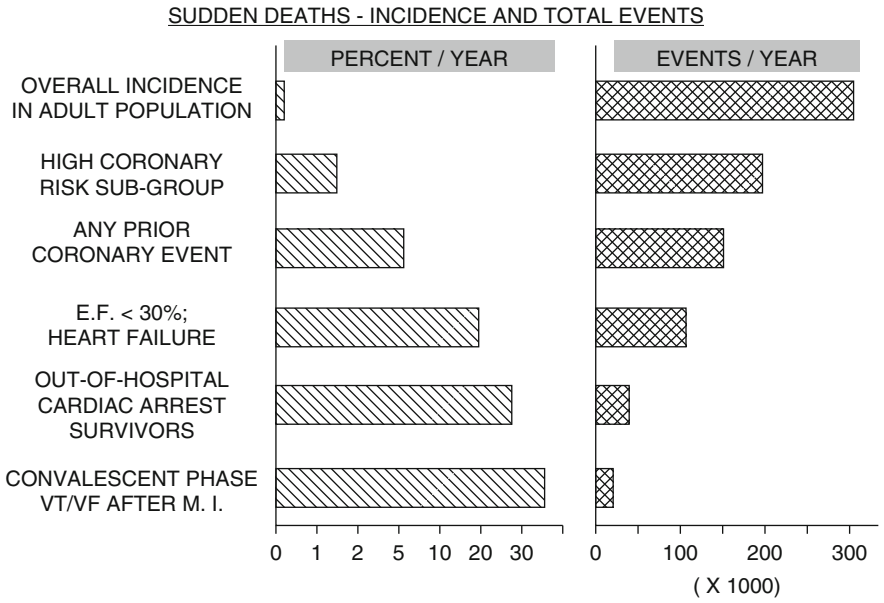


**Fig. 4.3** Sudden death: incidence overall and in subpopulations at risk. High-risk patients are the minority in the overall number of sudden death in the general population (From Myerburg et al. 1997)

### 4.4.4 Sudden Cardiac Death

SCD due to coronary artery disease is the most important cause of death in the adult population of the industrialized countries, and VF is the most common first recorded underlying rhythm (in 75–80 % of cases, Hookana et al. 2011), whereas bradyarrhythmias and asystole are found in ~15–20 %. The interpretation of the causative rhythm is complicated by the fact that VT/VF at some point will convert into asystole, and bradycardia as a result of advanced AV block may trigger VF. The overall incidence of SCD is ~1/1,000/year (Priori et al. 2002). In the United States, SCD comprised up to 15 % of total mortality (Podrid and Myerburg 2005) and similar values (21 % in men and 14.5 % in women) were reported in Europe (Priori et al. 2002). As SCD often occurs in patients with CAD, the risk factors that evolved for SCD match the risk factors for atherosclerosis, i.e., age, smoking, diabetes, male gender, hypertension, and hyperlipidemia. The risk of SCD is related to the degree of structural heart disease. In patients with symptomatic heart failure, chronically severely impaired left ventricular ejection fraction (<35 %) is the strongest indicator for increased mortality due to malignant arrhythmias and indicates primary prophylaxis of SCD with an ICD (Zipes et al. 2006). However, while this group carries the highest risk, in absolute numbers, their contribution to the overall incidence of SCD is small (see Fig. 4.3 from Myerburg et al. 1997), leaving a large group of patients with preserved LV function at risk for SCD.

## 4.5 Diagnosis

Basis for the diagnosis of rhythm abnormalities is the electrocardiogram (ECG). The highly amplified electrical signals recorded from the surface of the skin represent a summation of electrical field vectors arising from differences in the membrane potential during the cardiac cycle. ECGs allow the differentiation between atrial and ventricular arrhythmias in most cases based on the width of the QRS complex reflecting the ventricular activation sequence. Further analysis of *P* wave (atrial activation) and QRS morphology in the standard 12-lead surface ECG helps to narrow down further the region of ectopic activity. Twenty-four hours to 7 days Holter ECGs and surface electrode event recorders (up to 30 days) are used to document episodic arrhythmias, whereas subcutaneously implanted event monitors allow continuous rhythm monitoring for currently up to 3 years. ECG ergometry is useful to document stress-induced tachyarrhythmias or conduction deficits as well as for risk stratification (in certain cardiomyopathies and in patients with accessory pathways). Ultimately, management of patients with recurrent symptomatic arrhythmias may necessitate an electrophysiologic study with intracardial mapping and stimulation protocols to induce the arrhythmia, determine the exact mechanism and location, and potentially ablate myocardial structures involved.

## 4.6 Pathomechanisms of Arrhythmogeneity

Electrophysiological mapping of intracardial spread of electrical activity allows distinguishing arrhythmias driven by repetitive focal (ectopic) activity from reentry tachycardias with circus movement of electrical activation involving larger parts of the myocardium. Focal arrhythmias can be explained by enhanced impulse formation either by automaticity (spontaneous depolarization) or triggered activity (depolarization following a regular beat). Some of the arrhythmias classified as focal in origin, however, may not depend on locally enhanced impulse formation but reflect small, localized reentry cycles (“microreentry”).

### 4.6.1 Automaticity

Cells from the His-Purkinje system slowly depolarize during phase 4 of the AP (Fig. 4.1), albeit at a slower rate as sinus node cells. In conditions of ischemia or cell injury (e.g., myocardial infarction) as well as during increased beta-adrenergic stimulation, enhanced automaticity may occur in these cells leading to focal arrhythmias, such as accelerated idioventricular or junctional rhythm. In similar conditions, working myocardium may regain the capability of periodic depolarizations during phase 4, leading to abnormal automaticity, as is observed, e.g., in multifocal atrial tachycardias (Carmeliet 1999). While most ventricular tachycardias are reentry tachycardias, a small subset of monomorphic ventricular tachycardias triggered by

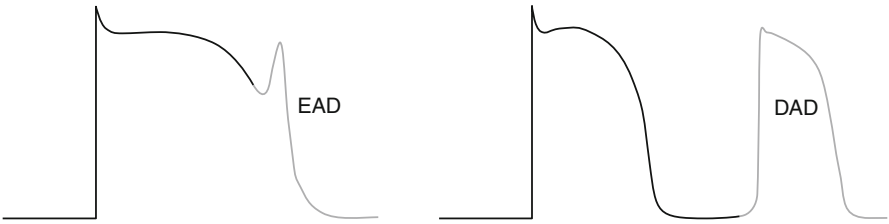


**Fig. 4.4** Triggered activity: early afterdepolarizations (*EAD*) occur before and delayed afterdepolarizations (*DAD*) after repolarization of the regular action potential is completed

enhanced activity in Purkinje cells has recently received greater attention as these arrhythmias can be cured by focal ablation of the arrhythmogenic Purkinje cells (Nogami 2011).

### 4.6.2 Triggered Activity

Triggered activity comprises transient membrane depolarizations that are linked to a normal action potential, which are divided into early (EAD) or delayed (DAD) afterdepolarizations. EADs occur during repolarization (phase 2 or phase 3 of the action potential) and lead to a deceleration or transient reversal of repolarization. DADs occur in phase 4 when repolarization to the resting potential has been completed (Fig. 4.4).

#### 4.6.2.1 Delayed Afterdepolarizations

Delayed afterdepolarizations (DAD) in cardiomyocytes occur as a result of high intracellular $Ca^{2+}$ load. The classical model of intracellular $Ca^{2+}$ overload is digitalis toxicity (Fig. 4.5). Digitalis inhibits the sarcolemmal $Na^+/K^+$ ATPase, resulting in intracellular $Na^+$ accumulation (1). $Na^+$ is exchanged with $Ca^{2+}$ by the sarcolemmal $Na^+/Ca^{2+}$ exchanger (2). Excess $Ca^{2+}$ transported into the intracellular store (sarcoplasmic reticulum, SR) (3) leads to diastolic SR $Ca^{2+}$ leak (4). Increased cytosolic $Ca^{2+}$ triggers transsarcolemmal $Na^+$ influx via the $Na^+/Ca^{2+}$ exchanger reflected by a transient inward current ($I_{ti}$) (5). If the depolarization of the membrane by $I_{ti}$ reaches the activation threshold of the fast $Na^+$ channels, an irregular action potential is generated.

Increased SR $Ca^{2+}$ leak is also observed in experimental and human chronic heart failure, related to alterations in the properties of the SR $Ca^{2+}$ release channel, the ryanodine receptor (RyR, Fig. 4.5). In heart failure, reduction in $I_{K1}$, a current that repolarizes and stabilizes the resting membrane potential during diastole, can facilitate $Ca^{2+}$-induced arrhythmias (Pogwizd and Bers 2004). Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but well-studied hereditary arrhythmia, where mutations to the ryanodine receptor (in autosomal dominant CPVT type 1) or the SR $Ca^{2+}$ binding protein calsequestrin (autosomal recessive CPVT 2) lead to increased SR $Ca^{2+}$ leak, DADs, bigeminus, and characteristic

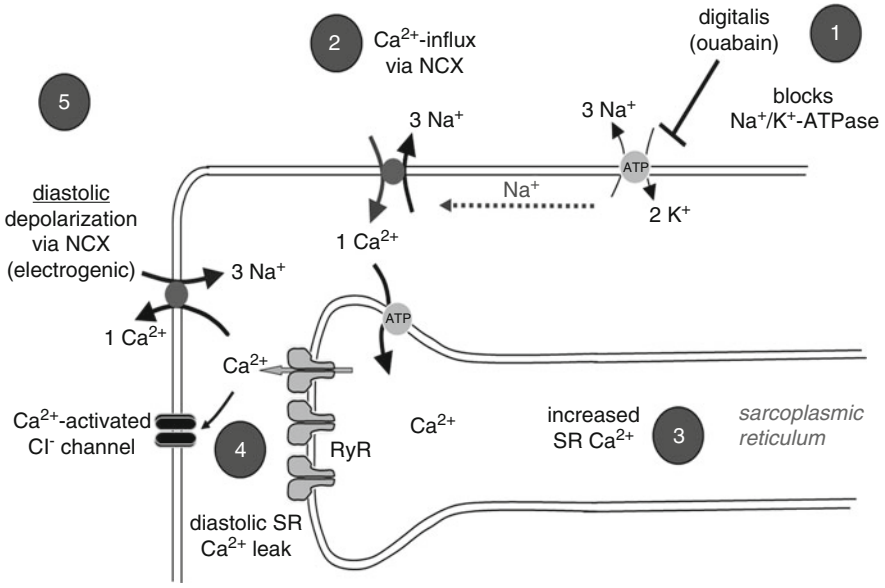


**Fig. 4.5** Mechanisms of digitalis-induced delayed afterdepolarizations. *SR* sarcoplasmic reticulum, *NCX* $Na^+/Ca^{2+}$ exchanger, *RyR* ryanodine receptor

bidirectional polymorphic ventricular tachycardias, identical to what is observed with digitalis. In light of a common pathomechanism in hereditary and acquired arrhythmias, decreasing $Ca^{2+}$ leak from the SR in cardiac remodeling is currently investigated as a potential new therapeutic target (Sacherer et al. 2012).

#### 4.6.2.2 Early Afterdepolarizations

EADs result from a transient inward current mainly through (re)activation of sarcolemmal L-type $Ca^{2+}$ channels (January and Riddle 1989) and $Na^+$ channels (Boutjdir et al. 1994), but there may be a role for NCX-mediated inward current as well (Volders et al. 2000). EADs occur in the setting of increased AP duration (APD). APD prolongation can result from acute changes in electrolytes (hypokalemia, hypomagnesemia), from remodeling of transsarcolemmal ion channels (e.g., downregulation of rectifying potassium channels, increase in late sodium current), as well as from alterations in intracellular $Ca^{2+}$ release (longer $Ca^{2+}$ transient) (Volders et al. 2000). APD prolongation facilitating EADs is also induced by an increased cycle length (pause) of the preceding beat; this mechanism is called pause-dependent triggered activity; EADs (rather than DADs) are provoked in conditions of alpha- and beta-adrenergic stimulation in combination with rapid pacing rate. In the surface ECG, EADs may be apparent as *T*-wave alterations and *U*-waves.

#### 4.6.2.3 Arrhythmias Initiated by Triggered Activity

Atrial tachycardias based on triggered activity rarely occur in clinically stable patients but are observed in the presence of acute adrenergic stimuli, either endogenous (acute illness) or exogenous (adrenergic agents, caffeine, theophylline; Josephson 2008).

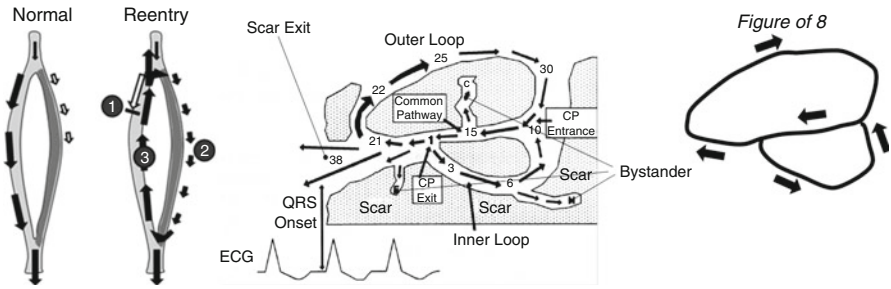


**Fig. 4.6** Mechanisms of reentry. *Left*: reentry requires two differentially conducting pathways that are joined at the beginning and end. *Middle* and *right* (Adapted from Stevenson et al. (1993) and El-Sherif et al. (1982)): in diseased ventricular tissue, the substrate for reentry may be more complex, e.g., following a "figure-of-8" pattern. See text for details

Triggered atrial arrhythmias are also observed during atrial ischemia (Nishida et al. 2011) and are thought to contribute to atrial fibrillation (see Sect. 4.6.5).

In ischemic cardiomyopathy, ventricular arrhythmias are mostly initiated by reentry mechanisms (see Sects. 4.6.3 and 4.7.2). In nonischemic cardiomyopathy, however, monomorphic focal arrhythmias that arise from triggered activity are more often observed (Pogwizd et al. 1998). Idiopathic arrhythmias from the ventricular outflow tract in otherwise structurally normal hearts are also based on triggered activity (O'Donnell et al. 2003). Torsades-de-pointes tachycardia, which is characteristic for hereditary and acquired long QT syndromes (prolonged APDs), is based on EADs, whereas catecholaminergic polymorphic ventricular tachycardias are initiated by DADs.

### 4.6.3 Reentry

Reentry tachycardias are the most common regular tachyarrhythmias. The mechanism of reentry has first been described in detail for AV reentry tachycardias (see Sect. 4.4.2.1). In these conditions, (congenitally) preformed conduction pathways run in parallel to the normal AV nodal activation sequence connecting the atria to the ventricle. These pathways possess different conduction velocities (Fig. 4.6) and refractoriness (i.e., recovery time after activation) than the physiological AV conduction. Reentry tachycardias initiate when a unidirectional block prevents activation of one pathway (Fig. 4.6, left), allowing conduction along the second pathway (2) and retrogradely along the first pathway (3), thus closing the circle. Initiation and maintenance of the reentry arrhythmia strongly depends on the relationship between the conduction velocities and recovery times of these antegradely and retrogradely conducting pathways. Often these arrhythmias occur in response to changes in autonomous tone (i.e., with exercise or before falling asleep), as this affects myocardial conduction velocities. Typically (but not always), these supraventricular reentry tachycardias can be terminated by increasing the parasympathetic tone (vagal nerve stimulation by "Valsalva" maneuvers).

Ventricular reentry tachycardias are most commonly seen in structurally diseased hearts. Circus movement of electrical activity occurs around islets of fibrotic tissue (often, infarct scar). According to a common model, rather than forming a simple circle, electrical activation is slowed down along a central common pathway (CP) of viable but dysfunctional myocardium. Upon exiting the diseased area, electrical activation returns to the CP entrance in clockwise and counterclockwise direction, thus forming two synchronous circuits in a "figure-of-8" (Fig. 4.6, right; El-Sherif et al. 1982). Often myocardial scars are interwoven with viable tissue leading to a more complex arrangement of conducting and nonconducting tissue forming the arrhythmogenic substrate (Fig. 4.6, middle; Stevenson et al. 1993). Other models agree with a more dynamic distribution of reentry circles resulting in rotating 2D vortices of electrical activation. Independent of the underlying model, typical features of reentry tachycardias are that they are usually regular, monomorphic, and easily inducible by short coupled extra stimuli during programmed electrical stimulation in an electrophysiological study.

### 4.6.4 Cellular Heterogeneity in the Arrhythmogenic Substrate

Even in the normal heart, epicardial, endocardial, and mid-myocardial cells have distinct electrophysiological properties. For instance, the latter, "M-cells," are characterized by longer AP duration and higher susceptibility to class III (potassium-inhibiting) antiarrhythmics (Antzelevitch and Fish 2001). Additionally, heterogeneity in cardiomyocyte orientation, cell-to-cell coupling (connexin 43 expression), and distribution of fibrous tissue contribute to the spatial transmural dispersion of repolarization (Glukhov et al. 2010). In LV hypertrophy, epicardial APs are more prolonged than endocardial, probably related to alterations in $I_{to}$, $I_{Ca}$, and NCX density (Bryant et al. 1997; Shipsey et al. 1997; McIntosh et al. 1998). Also, in heart failure, APD prolongation is more heterogenously distributed. The spatial dispersion of repolarization may alter with heart rate. In the inherited long QT syndrome 3 (increased $Na^+$ channel activity), a very pronounced dispersion of AP duration during bradycardia facilitates triggered activity.

In addition, temporal dispersion of repolarization is reflected in beat-to-beat changes in AP duration in the same cell. Electrical alternans describes a periodic change between short and long APs from beat to beat. In experimental conditions, AP alternans is often observed at higher pacing rates and has been linked to intracellular $Ca^{2+}$ overload. In patients, temporal dispersion of cardiomyocyte repolarization is reflected by alterations in the amplitude of the *T*-wave in the surface ECG (*T*-wave alternans, TWA). In clinical studies, TWA has been used to predict susceptibility to ventricular arrhythmias and SCD in patients with ischemic and nonischemic cardiomyopathy or inherited arrhythmias (e.g., Brugada syndrome). However, further studies are needed to establish the role of TWA in clinical decision making (Narayan 2006).

### 4.6.5 From Cellular Depolarizations to Arrhythmias

Several of the arrhythmogenic mechanisms outlined before are often acting together to initiate and sustain arrhythmias. Mostly, arrhythmias are triggered by an ectopic beat as a result of triggered activity, which may then induce a monomorphic reentry tachycardia around scar tissue or a torsades-de-pointes reentry tachycardia sustained by intramyocardial heterogeneity of repolarization.

Cardiomyocytes are connected by gap junctions resulting in electrotonic coupling. In this syncytium, a depolarizing cell acts as a source of electrical charge, which will be conducted to neighboring cardiomyocytes acting as a "sink" for this charge. Based on the source-sink concept, it can be concluded that a single arrhythmogenic cell may by far not be sufficient to trigger a propagating AP throughout the myocardium (Xie et al. 2010). Recent evidence suggests that arrhythmogenic activity in neighboring cardiomyocytes can be "synchronized" by adrenergic stimuli to create a depolarizing source that can overcome the sink (Myles et al. 2012). An increase in fibrous tissue during structural remodeling can additionally passively reduce the number of surrounding cardiomyocytes acting as a sink and also forms a potential basis for electrotonic interaction between cardiomyocytes and myofibroblasts that may promote depolarizations and thus arrhythmias (Rohr et al. 1997; Myles et al. 2012).

## 4.7 Conditions of Increased Arrhythmogeneity

A variety of comorbidities and patient characteristics have been associated with arrhythmias. In the following, major risk factors for arrhythmias identified in large clinical studies are discussed.

### 4.7.1 Endogenous Triggers

As outlined above, arrhythmias may be triggered by stress or other alterations in autonomous tone. The sympathetic nervous system is a well-known trigger of arrhythmias. In cardiomyocytes, beta-adrenergic receptor stimulation increases cytosolic cAMP and downstream signaling pathways, such as protein kinase A-mediated phosphorylation of the sarcolemmal $Ca^{2+}$ channel and an increase in the sarcoplasmic reticulum $Ca^{2+}$ load. While these effects mediate positive inotropy, they also predispose for $Ca^{2+}$-mediated triggered arrhythmias (see Sect. 4.6.2.1). In chronic heart failure but also in other systemic diseases such as sepsis, sympathetic tone is increased predisposing for arrhythmias.

The renin-angiotensin-aldosterone system (RAAS) is another important neurohumoral axis in cardiac remodeling. Angiotensin II (AT II) is a potent vasoconstrictor and has also been implicated in atrial and ventricular arrhythmias. The cellular pathomechanisms of ATII-mediated arrhythmogeneity are complex and have not

been fully elucidated but likely involve $Ca^{2+}$- and reactive oxygen species (ROS)-dependent signaling (Zhao et al. 2011). While RAAS antagonists (angiotensin receptor blockers, angiotensin converting enzyme inhibitors) effectively reduce ventricular arrhythmias and SCD in patients with heart failure, their use in the absence of heart failure to prevent AF (so-called upstream therapy) has so far proven unsuccessful (Savelieva et al. 2011).

### 4.7.2 Arrhythmias in Structurally Diseased Hearts

#### 4.7.2.1 Acute and Chronic Myocardial Ischemia

Acute ischemia leads to cardiomyocyte depolarization, intracellular $Ca^{2+}$ and $Na^{+}$ overload, and $K^{+}$ efflux in cardiomyocytes (Ehlert and Goldberger 1997), promoting triggered activity (EADs, DADs). Electrical dispersion of repolarization additionally contributes to an increased propensity for arrhythmias (Janse and Wit 1989), largely reentry tachycardias in the early phase (phase 1a) of ischemia. In the later phase (1b, more than 10 min ischemia), endogenous catecholamines further facilitate arrhythmias. Clinically, in the acute phase of MI, polymorphic and torsades-de-pointes tachycardia is often observed, usually not associated with QT prolongation in the surface ECG.

Ischemic heart disease (IHD) refers to chronic left ventricular dysfunction related to ischemia on the basis of coronary artery disease. The incidence of arrhythmias – atrial and ventricular – is increased in IHD. In patients with IHD, an increased prevalence of PVCs is related to an increased risk of SCD. Based on this observation, Lown has introduced a classification of PVCs based on their frequency and morphology (Lown and Wolf 1971). However, the positive predictive and discriminative value of PVCs alone to detect SCD is low (5–15 %; Crawford et al. 1999), and the Lown classification is no longer used for risk stratification in clinical practice. To date, the extent of left ventricular dysfunction (ejection fraction) remains the strongest predictor of malignant arrhythmias and SCD in clinical practice.

#### 4.7.2.2 Heart Failure

Roughly half of the patients with chronic heart failure die of SCD. Heart failure predisposes to ventricular tachyarrhythmias (see Sect. 4.4.4). A variety of intracellular signaling cascades related to neurohumoral activation are activated in advanced heart failure independent of the origin of cardiac remodeling. Endogenous catecholamines, angiotensin II, endothelin, and other hormones and paracrine mediators promote arrhythmias in cardiac myocytes. Independent of these changes in the *in vivo* milieu, cardiomyocyte remodeling in heart failure alters the cellular phenotype. At the cellular level, prolonged cytosolic $Ca^{2+}$ transients, $Ca^{2+}$ leak from the sarcoplasmic reticulum, and AP prolongation are commonly observed, the latter also attributed to a reduction in repolarizing potassium currents ($I_{Ks}$, $I_{Kr}$, $I_{K1}$) and increase in NCX but also to late sodium influx through the fast sodium channels (Aiba and Tomaselli 2010). Less selective cation channels (i.e., TRPC channels)

and stretch-activated channels promote agonist-induced or mechanical stress-induced ectopic activity. Structural (scar, fibrosis) and functional (stretch, ischemia) conduction abnormalities contribute to the maintenance of sustained arrhythmias. In patients with heart failure, currently, the only clinically widely accepted predictor of ventricular arrhythmias and sudden cardiac death is the extent of LV contractile impairment as quantified by the LV ejection fraction (EF). Patients with chronically severely reduced LV function (EF < 35 %) should receive an implantable cardioverter defibrillator (ICD) for primary prevention of SCD, as current antiarrhythmic pharmacological therapy has proven inferior to ICD therapy in improving survival.

#### 4.7.2.3 Nonischemic Cardiomyopathies

In dilative cardiomyopathy (DCM), ventricular tachyarrhythmias are mostly reentry tachycardias. However, as opposed to IHD, myocardial fibrosis is more diffuse. The spectrum of arrhythmogenic substrates is more heterogenous and may involve focal tachycardias, epicardial reentry circuits, and macroreentry involving the His-Purkinje system. Risk stratification for SCD is more challenging in these patients as ventricular tachyarrhythmias show a low inducibility during electrophysiological studies.

In patients with hypertrophic cardiomyopathy (HCM), the annual risk of SCD is ~1 %, with large interindividual variation related to patient characteristics (such as LV septum thickness). SCD may be the first disease manifestation (Elliott et al. 2006). HCM is the most common reason for SCD in competitive athletes. Many patients with HCM do not survive the first arrhythmogenic event, and additional risk factors have been defined to identify asymptomatic patients at increased risk (such as positive family history, unexplained syncope, pathologic exercise test, pronounced hypertrophy, and non-sustained VTs). In 50–70 % of patients, HCM can be attributed to one of the currently known mutations coding for sarcomeric genes.

### 4.7.3 Genetic Predisposition

Genetic predisposition to arrhythmias has been studied best in a group of rare ion channel defects with monogenetic inheritance. These channelopathies are characterized by an increased incidence for arrhythmic sudden cardiac death in otherwise apparently structurally normal hearts. Most common (~1/5,000 individuals, Kass and Moss 2003) are the long QT (LQT) syndromes, a heterogenous group of point mutations with loss-of-function defects of potassium channels (the most prevalent types LQT1 and LQT2 but also very rare LQT5-7) or gain-of-function defects of the fast sodium channel (LQTS 3) (Zipes et al. 2006). However, also cytoskeletal anchoring proteins (LQT4) can be involved. LQT syndromes are characterized by a prolonged QT interval in the resting ECG and a predisposition for torsades-de-pointes-type polymorphic VT and VF. LQT syndrome often manifests already in childhood with unexplained syncope. Recently, rare conditions of

arrhythmias associated with an extraordinarily short QT interval (QTc < 350 ms) have been identified (Patel et al. 2010). As in LQT, causes for secondary alterations in the QT interval such as alterations in serum electrolytes (potassium), acid–base status, or catecholamines and other drugs (digitalis) have to be excluded. On the cellular level, a reduction in $Ca^{2+}$ or $Na^{+}$ inward current or an increase in $K^{+}$ outward current can shorten APD. In accordance, several loss-of-function and gain-of-function mutations in these respective ion channel genes have been described in affected families. As in LQT, the disparity of repolarization is increased in short QT syndrome. Other monogenetically inherited arrhythmias include catecholaminergic polymorphic ventricular tachycardia (see Sect. 4.6.2.3), some forms of the Brugada syndrome, and arrhythmogenic cardiomyopathies such as arrhythmogenic right ventricular dysplasia (ARVD) and hypertrophic cardiomyopathy (see Sect. 4.7.2.3).

Monogenetically inherited single point mutations to ion channels, however, have only been able to explain a minority of arrhythmias with familiar clustering. Common arrhythmias, e.g., AF, or a predisposition for ventricular tachycardias during ischemia, have been linked with several predisposing genetic variations (modifier genes) and in most cases are likely polygenetic. Genome-wide association studies (GWAS) are being used to link abnormalities in heart rhythm or ECG morphology with gene polymorphisms, with variable success. A more comprehensive systems biology approach may be required to identify and manage patients with genetic predisposition for arrhythmias (Grace and Roden 2012).

### 4.7.4 Age

The number of ectopic PACs and PVCs increases with age in the healthy population (Kostis et al. 1981; Bjerregaard 1982) as well as in patients following myocardial infarction, where age is also associated with a higher prevalence of VTs (Josephson et al. 1995). Older patients have a higher dispersion of repolarization (Saadeh 2004) which may promote arrhythmias. Sinus node dysfunction is a typical disease of the elderly with an average age at diagnosis of 68 years. The prevalence of AF is strongly associated with age (Fig. 4.7, modified from Feinberg et al. 1995). The incidence of SCD increases with age in parallel with the increase in coronary artery disease but is relatively lower in patients above age 70 years due to competing causes of death (Zipes et al. 2006).

### 4.7.5 Gender

Women have a higher resting heart rate than men and this is independent of differences in autonomous tone (Jose and Collison 1970; Burke et al. 1996). Additionally, typical ECG findings associated with female gender include a slightly longer QT interval (~20 ms longer than in men) as described early by

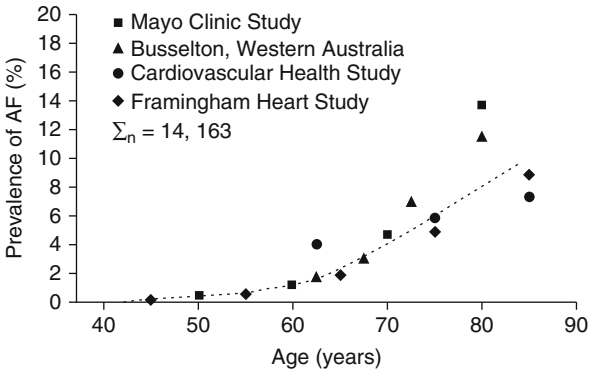


**Fig. 4.7** Increase in the prevalence of atrial fibrillation (*AF*) with age in population-based studies (Modified from Feinberg et al. (1995))

Bazett (1920) and confirmed by others (Molnar et al. 1996). This difference in QT interval may be driven by the higher testosterone levels in men (Zhang et al. 2011). For AV node reentry tachycardia, the gender ratio is about 2:1 (female to male, Rodriguez et al. 1992; Liuba et al. 2006). The reason for this difference is not completely understood but may be related to differences in the refractory periods of the fast- and slow-conducting properties of the AV nodal input (Liuba et al. 2006). Accessory pathways are more commonly seen in men than in women, with a 1:2 female to male gender ratio, and this applies to overt as well as concealed AP (Rodriguez et al. 1992). Men with WPW are more likely to develop AF and VF than women with AP, probably related to the overall increased incidence of AF in men. The incidence of focal AT is evenly distributed between men and women (Rodriguez et al. 1992). With respect to ventricular tachycardias, women are more likely to develop TdP tachycardia (Lehmann et al. 1996; Makkar et al. 1993), possibly related to the slightly longer QT interval in women which manifests especially at lower heart rates (Kligfield et al. 1996; Rautaharju et al. 1992).

### 4.7.6 Arterial Hypertension

An acute elevation in arterial blood pressure can trigger PVCs, PACS, as well as atrioventricular block (Sideris et al. 1987, 1988). In chronic arterial hypertension, the risk of atrial arrhythmias is increased, even more if hypertension is associated with LV hypertrophy (Loaldi et al. 1983), indicating a causative role for increased LV and consecutively left atrial pressure. Increased LV mass is associated with an increased risk for SCD (Haider et al. 1998). In patients with arterial hypertension, a higher QTc dispersion is observed (Saadeh 2004). This is consistent with experimental data, as in hypertrophied myocardium prolongation of the AP, and refractoriness is the most commonly observed electrophysiological alteration. However, this effect is not uniform to all models, and the underlying ionic mechanisms for AP prolongation vary between models and species (Pye and Cobbe 1992; Hart 1994; Boyden and Jeck 1995).

### 4.7.7 Diabetes Mellitus and Metabolic Syndrome

Diabetes mellitus (DM) increases the risk for SCD roughly twofold (Bergner and Goldberger 2010). DM is a strong risk factor for coronary artery disease which by itself conveys an increased risk for ventricular arrhythmias. Proarrhythmic electrophysiological changes associated with DM include a prolonged QTc interval (>440 ms in about 25 % of diabetics), which has been related to increased mortality in type 1 diabetics in one study (Veglio et al. 2000). QTc prolongation may be a result of increased endogenous catecholamines in response to transient hypoglycemia (Robinson et al. 2003). Recent evidence suggests a higher incidence in QT prolongation and dispersion in patients with metabolic syndrome even in the absence of overt diabetes mellitus (Isik et al. 2012). However, current clinical evidence linking DM to increased ventricular arrhythmogeneity remains sparse. A large meta-analysis reported a 40 % increased risk for developing AF in diabetic patients (Robinson et al. 2003).

### 4.7.8 Renal Dysfunction

In patients with chronic kidney disease, worsening of renal function is linked to increased QT duration, QT dispersion, and minor arrhythmias (Stewart et al. 2005). LV hypertrophy and LV diastolic dysfunction are common findings in patients with advanced renal dysfunction and may contribute to the increased arrhythmogeneity. In the presence of dilative cardiomyopathy, renal dysfunction (GFR < 60 ml/min/1.72 $m^2$) is associated with increased incidence of ventricular arrhythmias (Takahashi et al. 2009). However, with worsening renal function, the presumed effect of arrhythmias on morbidity and mortality is outweighed by the concomitant increase in noncardiac mortality so that patients with advanced renal dysfunction generally profit less from primary prophylaxis for SCD using ICDs (Goldenberg et al. 2008). Renal dysfunction has evolved as a risk factor for AF in recent clinical studies (Piccini et al. 2013) and also in experimental conditions (Fukunaga et al. 2012); however, the underlying pathomechanisms are currently unclear. In end-stage renal failure patients, arrhythmias often occur during or shortly after hemodialysis, especially in patients with concomitant structural heart disease, and are mostly related to acute electrolyte imbalance (Zipes et al. 2006).

## 4.8 Summary and Perspectives

Arrhythmias are common in clinical practice and are not always symptomatic. AF and ventricular arrhythmias often occur as a manifestation of structural heart disease and are associated with increased morbidity and mortality. Genetic predisposition, acquired comorbidities, and neurohumoral activation are modulators of arrhythmogeneity. Especially in patients with structural heart disease, pharmacological therapy of arrhythmias is limited due to the proarrhythmic potential of

current specific antiarrhythmic drugs (Vaughan-Williams class I and III). The degree of LV dysfunction currently determines the need for an ICD for primary prophylaxis of SCD. Risk scores derived from selective gene profiling and comprehensive evaluation of relevant clinical comorbidities could allow for identification of a number of patients at risk for SCD that currently do not fulfill the criteria for an ICD. New therapeutic approaches for the treatment of AF include the relatively atrial-selective multichannel blocker vernakalant, inhibition of the late $Na^+$ current (ranolazine), and early catheter-based ablation of AF in selected patients. Future antiarrhythmic strategies that are currently experimentally tested include blockers of intracellular $Ca^{2+}$ leak and gene therapy.

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# Pulmonary Hypertension

5

Horst Olschewski and Andrea Olschewski

**Abstract**

Pulmonary hypertension (PH) is a group of devastating diseases, caused by functional and structural changes in the pulmonary vasculature, leading to increased pulmonary vascular resistance, which cause breathlessness, right ventricular failure, and premature death. PH is defined as an increase of mean pulmonary arterial pressure ≥25 mmHg at rest as assessed by right heart catheterization. Pulmonary hypertension has a multifactorial pathobiology. Apart from vasoconstriction and *in situ* thrombosis, remodeling of all layers of the pulmonary vessel wall represents the hallmark of this disease, accompanied by endothelial dysfunction, activation of fibroblasts and smooth muscle cells, cross talk between cells within the vascular wall, and recruitment of circulating progenitor cells. Potent vasoconstrictors such as endothelin-1 and the serotonin pathway are known to be upregulated. In addition, interplay between the BMP/TGF-β and the angiopoietin/vascular endothelial growth factor signaling pathways were recently demonstrated in genetic and functional genomic studies. Moreover, coagulation and infectious processes have an impact on the process of lung vascular remodeling. As soon as hypoxia comes into play, hypoxia-inducible factor-dependent oxygen sensing and signaling is of central importance, further

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contributing to the above mentioned pathways. Pulmonary hypertension has been classified into five groups that have unique characteristics in terms of pathologic mechanisms and treatment options. The first group is called pulmonary arterial hypertension (PAH) and is the only form with approved drugs. The other forms have been called non-PAH PH. In some of these diseases, e.g., PH is associated with left heart disease, chronic lung disease, and chronic thromboembolic pulmonary hypertension (CTEPH). Many efforts have been made to diagnose patients at an earlier stage. There is an urgent need for the development of screening techniques for PH among the general population. It might be advantageous to treat such patients before PH is manifest.

**Keywords**
Pulmonary vascular remodeling • Right heart hypertrophy • Growth factors • BMP signaling • Inflammation • Endothelial dysfunction • Classification of pulmonary hypertension • Targeted PAH drug therapy • Algorithm

## 5.1 Introduction

Pulmonary hypertension describes a group of devastating diseases, caused by functional and structural changes in the pulmonary vasculature, leading to increased pulmonary vascular resistance, which causes breathlessness and premature death. The different categories share similarities in pathogenetic mechanisms, clinical presentation, and therapeutic options.

## 5.2 Special Features of the Pulmonary Circulation

The pulmonary circulation is unique compared with systemic vascular beds. The most significant difference in the regulation between all systemic organs and the lung is that hypoxemia elicits vasoconstriction of small resistance arteries in the pulmonary circulation (Bradford and Dean 1894). This physiological response that diverts mixed venous blood away from hypoxic alveoli, thus optimizing the matching of perfusion and ventilation and preventing arterial hypoxemia, is called hypoxic pulmonary vasoconstriction (Von Euler and Liljestrand 1946; Olschewski 2011). In contrast, in the systemic circulation, low oxygen tension leads to vasodilatation that increases oxygen delivery to the tissues. The other significant difference concerns blood pressure regulation. In the systemic circulation, arterial pressure is the variable with the most extensive regulation system. The feedback control system, the so-called arterial baroreflex located in the brain stem, and the various associated changes in heart, vessel, and endocrine functions are well understood. In contrast, the pressure in the pulmonary circulation is not regulated by a central nervous control mechanism, and the vessels are very much in a relaxed state. The regulation of

the vascular tone, the molecular mechanisms of hypoxia signaling, and how changes in environmental oxygen tension are translated into signals recognizable by the cell are just beginning to be understood.

In addition, there is also a significant anatomical difference between the pulmonary and systemic circulation. In the systemic circulation, the arterioles have a thick layer of smooth muscle cells, whereas no such cells in the pulmonary vasculature exist. Instead, the large, muscular arteries merge into small, partially muscular vessels that have a very low perfusion resistance and directly feed the pulmonary capillaries.

## 5.3 Pulmonary Hypertension

Pulmonary hypertension has a multifactorial pathobiology. Apart from vasoconstriction and *in situ* thrombosis, remodeling of all layers of the pulmonary vessel wall represents the hallmark of this disease, accompanied by endothelial dysfunction, activation of fibroblasts and smooth muscle cells, cross talk between cells within the vascular wall, and recruitment of circulating progenitor cells (Morrell et al. 2009; Hassoun et al. 2009). Potent vasoconstrictors such as endothelin (ET)-1 and the serotonin pathway are known to be upregulated. In addition, interplay between the BMP/TGF-β and the angiopoietin/vascular endothelial growth factor (VEGF) signaling pathways was recently demonstrated in genetic and functional genomic studies. Moreover, coagulation and infectious processes have an impact on the process of lung vascular remodeling. As soon as hypoxia comes into play, hypoxia-inducible factor (HIF)-dependent oxygen sensing and signaling is of central importance, further contributing to the above mentioned pathways.

Pulmonary hypertension is classified as pulmonary arterial hypertension (PAH) or pulmonary hypertension due to a variety of causes including left heart diseases, lung diseases, or chronic thromboembolic pulmonary hypertension as described in detail later in this chapter (Simonneau et al. 2009).

### 5.3.1 Pathophysiology of Pulmonary Arterial Hypertension

#### 5.3.1.1 Pulmonary Arterial Remodeling

The histological picture shows characteristic structural changes in the pulmonary arteries. The remodeling of the vessel wall results in (a) intimal fibrosis, (b) hypertrophy of the media, and (c) so-called *de novo* muscularization: the smooth muscles of the media grow distally, initially in a longitudinal direction, providing a complete muscular layer to smaller pulmonary arterial vessels (Gaine and Rubin 1998). The smooth muscle cells secrete extracellular matrix proteins, in particular glycoproteins and elastin. Concomitantly, changes in the adventitia and the intima occur. There is a proliferation of fibroblasts in the adventitia and possibly migration of these cells into the vessel wall. The origin of these cells could be one of the

constitutive cell types of the vascular wall, cells migrating there from the adventitia, or cells from the blood. Indeed, in neointimal formation in coronary arteries after stent implantation, the new cells stem from the blood, originating from mononuclear cells or stem cells (Tuder et al. 2001).

In the intima, more changes occur. The glycocalyx layer of the endothelial cells seems to be altered, possibly associated with a reduction in heparan sulfate, which, by itself, could trigger smooth muscle proliferation. Moreover, it seems that the mediator profile of the endothelial cells shifts from anticoagulatory to predominantly prothrombotic. A recent concept proposes that as an early event of the disease, the normal endothelial cells are destroyed and exchanged by apoptosis resistant cells forming a new endothelium with changed properties. This concept is very appealing and would explain why a loss of VEGF, a maintenance factor for the endothelial cells, has detrimental effects for pulmonary hypertension (Sakao et al. 2007; Abe et al. 2010).

The internal elastic lamina, which is important for preventing intimal fibrosis, is fragmented in pulmonary hypertension. This may be caused by upregulation of the endogenous vascular elastase (EVE) (Rabinovitch 1999; Rabinovitch 2001) and the associated changes in tenascin C and upregulation of several other pathways including tyrosine kinases that promote proliferation and inhibit apoptosis. Tenascin C has been reported to be colocalized with epidermal growth factor (EGF) in PAH lesions suggesting a direct role in disease progression (Asahara et al. 1997), since EGF facilitates proliferation and migration of SMCs. The so-called plexogenic arteriopathy or lesions are characterized by the formation of multiple, convoluted endoluminal channels in small, relatively thin-walled branches of the pulmonary arteries that appear histologically similar to glomeruli in the kidneys. It has been postulated, that endothelial cells acquire a proproliferative, apoptotic-resistant phenotype that, in the case of the plexiform lesion, contributes to the loss of the endothelial cell monolayer (Sakao et al. 2007; Abe et al. 2010). Plexiform lesions do not only occur in the idiopathic form of PAH but also in severe congenital heart defects and pulmonary hypertension associated with liver cirrhosis.

#### 5.3.1.2 Inflammation

Inflammation plays a significant role in various types of human pulmonary hypertension, such as idiopathic PAH and PAH associated with connective tissue diseases or HIV infection (Hassoun et al. 2009). The role for inflammation in PAH is based on the finding of inflammatory cells, including macrophages and T and B lymphocytes, and dendritic cells around the plexiform lesions of PAH (Nicolls et al. 2005). Cytokine- and chemokine-dependent mechanisms leading to inflammatory cell recruitment in human PAH are also prominent in PAH. Fractalkine (CX3CL1) was reported to be upregulated in circulating CD4+ and CD8+ T lymphocytes from PAH patients as compared with control subjects (Balabanian et al. 2002). These patients also have elevated soluble CX3CL1 plasma concentrations and increased CX3CL1 mRNA expression in their lung tissue samples. Perros et al. (2007) demonstrated that pulmonary arterial smooth muscle cells (PASMCs) from PAH patients have

increased CX3CR1 expression. In addition, in cultured rat PASMCs, CX3CL1 induces proliferation of these cells. Therefore, fractalkine might act as a growth factor for PASMCs.

#### 5.3.1.3 BMP Signaling

Bone morphogenic proteins (BMPs) are the largest group of cytokines within the transforming growth factor (TGF)-β superfamily (Miyazono et al. 2001). BMPs are now known to regulate growth, differentiation, and apoptosis in a diverse number of cell lines (Miyazono et al. 2005). BMPs act via a restricted set of receptor-mediated Smads (R-Smads), Smads-1, -5, and -8. In the lung, BMP-receptor 2 is highly expressed on the vascular endothelium of the PAs and at a lower level in PASMCs and fibroblasts (Atkinson et al. 2002). Mutations in the BMPR2 gene have been found in approximately 70 % of families with PAH (Machado et al. 2005; Machado et al. 2006). In addition, up to 25 % of patients with apparently sporadic IPAH harbor mutations (Thomson et al. 2000). The expression of BMPR2 is markedly reduced in the pulmonary vasculature of patients with mutations in the BMPR2 gene (Atkinson et al. 2002).

#### 5.3.1.4 Growth Factors

Several growth factors, including platelet-derived growth factor (PDGF) (Humbert et al. 1998; Schermuly et al. 2005), epidermal growth factor (EGF) (Merklinger et al. 2005), and vascular endothelial growth factor (VEGF) (Cool et al. 1997), have been shown to induce increased proliferation and migration of PA vascular cells. They act as potent mitogens and chemoattractants for SMCs, fibroblasts, and endothelial cells and cause resistance to apoptosis.

Several findings suggest a central role for VEGF in PAH: Cool et al. demonstrated intense expression of the VEGF receptor KDR in the ECs of plexiform lesions in severe PAH (Cool et al. 1997). In addition, expression of C-Src kinase, a protein that mediates VEGF-induced production of prostacyclin and nitric oxide in ECs, is decreased in PAH (Tuder et al. 2001). Furthermore, platelet-derived growth factor (PDGF) induces the proliferation and migration of SMCs and fibroblasts and has been proposed as a key mediator in the progression of PH (Humbert et al. 1998). As a result, novel therapeutic agents, such as tyrosine kinase inhibitors, have been tested in experimental models of PH (Schermuly et al. 2005) and more recently in clinical trials. The rationale for use of these agents is the increased expression of PDGF and PDGF-receptors in PAs from native lungs of patients with severe IPAH who underwent lung transplantation (Perros et al. 2007). *In vitro*, the PDGF-BB-induced proliferation and migration of PA-SMCs is inhibited by imatinib (Perros et al. 2007). Serotonin (5-HT) is a well-recognized vasoconstrictor. In addition to its vasoactive effects, 5-HAT exerts mitogenic and co-mitogenic effects on PASMCs. Animal studies provided direct evidence for the key role of 5-HT transporters in PA remodeling. Mice with targeted 5-HTT gene disruption developed less severe hypoxic PH than wild-type control subjects (Eddahibi et al. 2000) and selective 5-HTT inhibitors attenuate hypoxia- and monocrotaline-induced animal model of PH. Finally, angiopoietin-1 was reported to regulate pathologic SMC hyperplasia in

PAH. Ang-1 is overexpressed in most forms of nonfamilial PAH (Perros et al. 2007; Guignabert et al. 2005). In PAH, Ang-1 causes activation of the TIE2 receptor by tyrosine autophosphorylation in the pulmonary vascular endothelium (Perros et al. 2007; Jones 1996). Enhanced TIE2 levels and a fourfold increase in TIE2 phosphorylation are found in human PAH lung tissue, compared with control subjects (Perros et al. 2007; MacLean et al. 2000).

#### 5.3.1.5 Endothelial Dysfunction

Endothelial dysfunction in PAH is reflected by reduced production of the vasodilators/growth inhibitors NO and $PGI_2$ and increased production of the vasoconstrictor/co-mitogens, e.g., endothelin-1 and thromboxane $A_2$. Patients with idiopathic PAH have increased plasma levels of the endogenous inhibitor of eNOS (Pullamsetti et al. 2005). In addition, a deficiency of $PGI_2$ and $PGI_2$ synthase and an excess of thromboxane are found in PAH (Christman et al. 1992).

#### 5.3.1.6 Potassium and Calcium Channels

In PASMCs from IPAH patients, the amplitude of whole-cell potassium current (IK(V)) and mRNA/protein expression levels of Kv channel subunits (e.g., Kv1.2 and Kv1.5) are both significantly decreased in comparison with cells from controls or patients with secondary PH (Yuan et al. 1998). The downregulated voltage-gated potassium channels and decreased IK(V) are associated with a more depolarized resting membrane potential in IPAH PASMCs, and the resting cytosolic calcium concentration is much higher than in PASMCs from controls. The magnitude of capacitative calcium entry (CCE), evoked by passive store depletion with CPA, is significantly greater in PASMCs from IPAH patients than in cells from secondary PH patients. Enhanced CCE, possibly via upregulation of TRPC channels, may represent a critical mechanism involved in the development of severe PAH (Fig. 5.1) (Yu et al. 2004).

## 5.4 The Clinical Picture

### 5.4.1 Clinical Classification of Pulmonary Hypertension

Based on the 4th World Conference on Pulmonary Hypertension in Dana Point, 2009, the updated European Guidelines on the diagnosis and treatment of pulmonary hypertension were jointly developed by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) (Galie et al. 2009a). These guidelines were adopted by most national guidelines, although the recommended therapies are not available in every country. Most of these therapies are very expensive.

Starting from the 2nd PH World Conference in Evian, 1998, pulmonary hypertension has been classified into five groups that have unique characteristics in terms of pathologic mechanisms and treatment options (see Table 5.1). The first group is called pulmonary arterial hypertension (PAH) and is the only form with approved drugs. The other forms have been called non-PAH PH (Hoeper et al. 2009) and can be treated by specific measures; however, there are no targeted drugs for non-PAH PH. In some of these diseases, e.g., PH associated with left heart disease, chronic lung disease, and

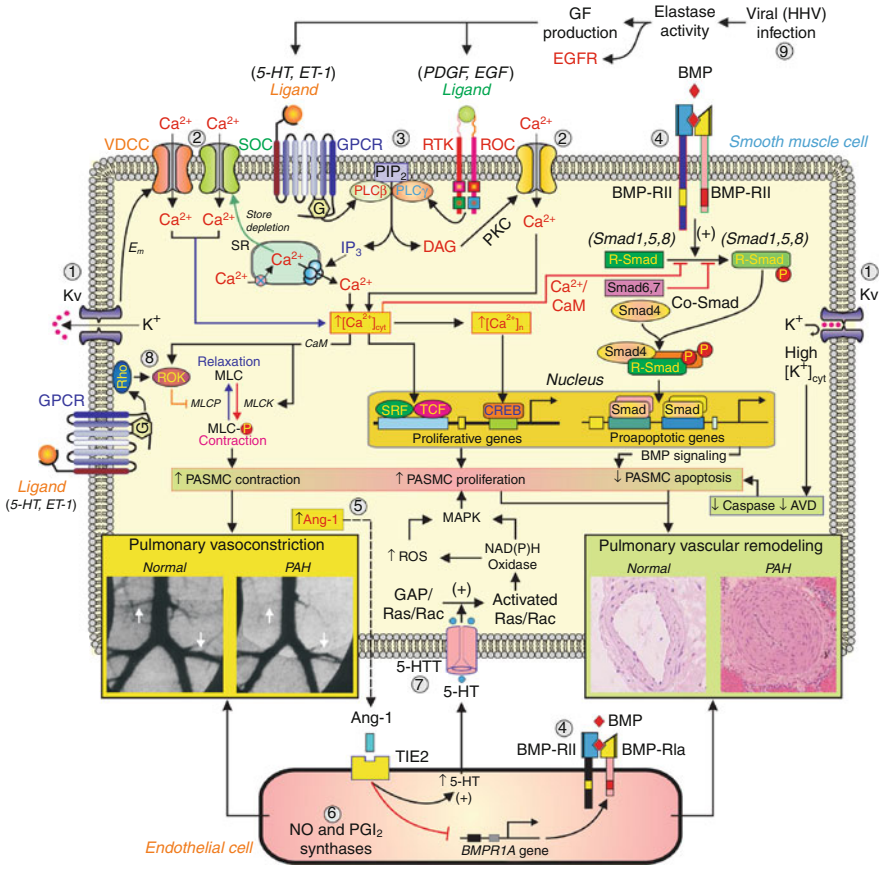


**Fig. 5.1** Schematic diagram depicting potential mechanisms involved in the development of PAH. *AVD* apoptotic volume decrease, *CaM* calmodulin, *DAG* diacylglycerol, *Em* membrane potential, *EGF* epidermal growth factor, *GPCR* G protein-coupled receptor, *HHV* human herpes virus, $IP_3$ inositol 1,4,5-trisphosphate, *MLC* myosin light chain, *MLCK* myosin light chain kinase, *PDGF* platelet-derived growth factor, *PKC* protein kinase C, *PLC* phospholipase C, *ROS* reactive oxygen species, *RTK* receptor tyrosine kinase, *SR* sarcoplasmic reticulum (From Morrell et al. 2009)

chronic thromboembolic pulmonary hypertension (CTEPH), PAH medication may cause severe side effects from pulmonary congestion and gas exchange disturbances.

### 5.4.2 Diagnostics

Many cases of PAH are diagnosed in a late stage of disease where the pulmonary vascular resistance has increased tenfold and more due to massive remodeling of the small pulmonary arteries. There is an urgent need for more awareness for the disease and better noninvasive diagnostics for PH screening. The other challenge is frequent misclassification of PH. Often the diagnosis of PAH is made without considering non-PAH PH.

**Table 5.1** Updated clinical classification of pulmonary hypertension (Dana Point 2009)

| |
|---|
| 1. Pulmonary arterial hypertension (PAH) |
| 1.1. Idiopathic PAH |
| 1.2. Heritable PAH |
| 1.2.1. BMPR2 mutations |
| 1.2.2. ALK1, endoglin mutations (with and without hereditary hemorrhagic telangiectasia) |
| 1.2.3. Unknown mutations |
| 1.3. Drugs or toxins 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 |
| 1.4.6. Chronic hemolytic anemia |
| 1.5. Persistent pulmonary hypertension of the newborn |
| 1.6. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) |
| 2. Pulmonary hypertension due to left heart disease |
| 2.1. Systolic dysfunction |
| 2.2. Diastolic dysfunction |
| 2.3. Valvular disease |
| 3. Pulmonary hypertension due to lung diseases and/or hypoxia |
| 3.1. Chronic obstructive pulmonary disease |
| 3.2. Interstitial lung disease |
| 3.3. Other pulmonary diseases with mixed restrictive/obstructive pattern |
| 3.4. Sleep-disordered breathing |
| 3.5. Alveolar hypoventilation syndrome |
| 3.6. Chronic exposure to high altitude |
| 3.7. Developmental abnormalities |
| 4. Chronic thromboembolic pulmonary hypertension (CTEPH) |
| 5. Pulmonary hypertension with unclear or multifactorial mechanisms |
| 5.1. Hematological disorders: myeloproliferative disorders, splenectomy |
| 5.2. Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis |
| 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders |
| 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on hemodialysis (BMPR-2, bone morphogenetic protein receptor type-2; ALK-1, activin receptor-like kinase 1 gene) |

### 5.4.3 Definitions

Pulmonary hypertension (PH) is defined as an increase of mean pulmonary arterial pressure (PAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). This value has been used in most of the randomized controlled trials and registries to select patients with PAH. However, the normal mean PAP at rest is 14.0 ± 3.3 mmHg, with an upper limit of normal of about 20 mmHg (Kovacs et al. 2009). The significance of mean PAP values between 21 and 24 mmHg is unclear. These patients

develop higher PAP values during exercise than controls. However, there is currently no generally accepted definition of exercise-induced PH.

A pulmonary arterial wedge pressure (PAWP) >15 mmHg speaks in favor of increased pulmonary capillary pressure due to left ventricular or valve disease and is associated with a risk of pulmonary edema after start of PAH therapy.

There is no generally accepted definition for right heart insufficiency or decompensation. A German guideline has suggested a definition based on hemodynamic parameters that depend on a decreased cardiac output and/or an increased filling pressure of the right ventricle (Hoeper et al. 2011).

### 5.4.4 Right Heart Catheterization and Vasoreactivity

RHC is required to confirm the diagnosis of PAH, to assess the severity of the hemodynamic impairment, and to test the responsiveness of the pulmonary circulation. About 10 % of patients with idiopathic PAH have a positive pharmacologic testing, i.e., a strong acute vasodilative response to inhaled NO or other strong vasodilator substances. These patients can very effectively be treated with inexpensive calcium channel blockers which are given at very high doses. For the definition of a strong response, see Galie et al. (2009b).

### 5.4.5 Clinical, Echocardiographic, and Hemodynamic Parameters

Some of the hemodynamic variables obtained by RHC at rest represent important prognostic factors. These parameters indicate impaired right ventricular function. They are associated to low cardiac output or increased right ventricular filling pressure. Interestingly, in PAH patients, PAP itself is not indicative of prognosis. This is due to the fact that PAP is linearly related to cardiac output, and in the failing heart, both parameters may decrease.

Physical capacity as assessed by WHO functional class and 6-min walk test as well as brain natriuretic peptide (BNP) or its stable cleavage product nt-pro BNP are prognostic parameters together with quality-of-life measures like the Minnesota Living With Heart Failure questionnaire (Cenedese et al. 2006). Patients typically report to the specialist center for pulmonary hypertension every 3–6 months where all these measures are taken and therapeutic decisions are based on the results and the patient's expectations.

### 5.4.6 Therapy of Non-PAH PH

Left heart disease is the most common cause of pulmonary hypertension. There are two different factors elevating the pulmonary arterial pressure. One is the increased filling pressure of the left ventricle which mostly corresponds to the outflow

pressure of the lung. The filling pressure may rise to 20 mmHg and more in severe left heart disease. The second factor is the increase in pulmonary vascular resistance (PVR) which increases the transpulmonary pressure gradient. This gradient between the inflow and the outflow pressure is typically around 7 mmHg, but with an elevated PVR, it may rise to 12 mmHg and more. The PAP increase itself may cause right ventricular failure. In contrast to PAH, in left heart disease, PAP itself is an important prognostic parameter. Despite this, PAH therapy is not recommended in these patients because it may cause lung edema and gas exchange disturbances. A large randomized controlled study investigating the effects of sildenafil, one of the PAH drugs, is ongoing, while several studies with endothelin receptor antagonists have been negative. A study employing the prostanoid epoprostenol demonstrated excess mortality as compared to control (Califf et al. 1997).

Chronic lung diseases are quite common causes of pulmonary hypertension and cor pulmonale. Among these diseases, chronic obstructive pulmonary disease (COPD) and lung fibrosis have the highest prevalence but also chronic hypoventilation syndromes like kyphoscoliosis or muscle diseases may be complicated by cor pulmonale. The underlying mechanisms are alveolar hypoxia (hypoxic pulmonary vasoconstriction with remodeling of pulmonary arteries) and pulmonary inflammation. Smoke may specifically induce pulmonary arterial remodeling via iNOS activation (Seimetz et al. 2011). Therapy is directed to the underlying disease. The most important specific therapy is long-term oxygen therapy. PAH therapies are not approved and bear the risk of severe gas exchange disturbances (Blanco et al. 2010).

Chronic thromboembolic pulmonary hypertension (CTEPH) is as commonly diagnosed as idiopathic PAH; however, the estimated number of unrecorded cases is probably higher. There are some established risk factors for CTEPH like thrombophilic disorders (32 %) and splenectomy (3.5 %); however, in most of the patients, no specific risk factor is found. About 75 % of CTEPH patients are aware that they had had a thromboembolic event (Pepke-Zaba et al. 2011). Probably, the resting patients have suffered from silent recurrent thromboembolism. The backbone of therapy is lifelong anticoagulation and pulmonary endarterectomy. This demanding operation is performed in few specialized centers worldwide where is shows excellent results (Mayer et al. 2011). If PEA is not possible, PAH therapy may be indicated (Condliffe et al. 2009). However, currently there is no approval for such medications for CTEPH except for inhaled iloprost in Australia.

Sarcoidosis may cause pulmonary hypertension in association with lung fibrosis (common), with left heart involvement or due to isolated involvement of the pulmonary vessels (rare). Therapy is directed to the underlying disease and involves corticosteroids and eventually other immunosuppressants. There is limited experience with PAH medication.

End-stage renal disease is associated with pulmonary hypertension. This is often caused by left heart involvement but sometimes by PAH-like remodeling of the pulmonary arteries. These patients may be treated like PAH patients, although there is limited experience and no data from randomized controlled studies. The same is true for sarcoidosis of the pulmonary arteries without lung fibrosis and for sickle cell disease and schistosomiasis associated PH without left heart insufficiency.

### 5.4.7 Therapy of PAH

The first targeted PAH therapy, continuous intravenous infusion of epoprostenol, was applied long-term intravenously to an IPAH patient in the UK in 1984 (Higenbottam et al. 1984). Epoprostenol is the synthetic analog of prostaglandin $I_2$ ($PGI_2$). It was first approved for IPAH in the USA in the year 1995. In recent years, a number of oral and inhaled therapies have been approved for PAH. A meta-analysis performed on all the pivotal published trials indicated that targeted PAH therapy decreased overall mortality by 43 % (Galie et al. 2009c). It is therefore considered unethical to randomize patients to placebo without at least one approved PAH therapy in place.

### 5.4.8 Targeted PAH Drug Therapy

#### 5.4.8.1 Calcium Channel Blockers

High-dose calcium channel blockers (CCB) are recommended only for acute hemodynamic responders. In the right patient, this therapy has favorable effects on physical capacity and quality of life. These patients can typically perform more than normal exercise without exertion and live a nearly normal life. Side effects are mostly minor and include leg edema (common) and gingival hyperplasia (rare).

#### 5.4.8.2 Endothelin Receptor Antagonists

Endothelin receptor antagonists may block both the ETA and ETB receptor (bosentan, macitentan) or specifically the ETA receptor (ambrisentan, sitaxsentan). Bosentan and ambrisentan have been approved in Europe, in the USA, and many other countries worldwide, while macitentan has recently been submitted for approval and sitaxsentan has been removed from the market due to idiosyncratic hepatic failure (very rare). These substances may cause edema formation, particularly in the elderly, and bosentan may induce transaminase elevation in about 10 % of patients. Other side effects are rare and mostly mild; however, teratogenic effects have been demonstrated in animal models. Bosentan induces some cytocrome isoenzymes and blocks hepatic bile carriers. Therefore, drug-drug interactions must be considered.

#### 5.4.8.3 PDE5 Inhibitors

Phosphodiesterase type 5 (PDE5) inhibitors cause a cGMP elevation specifically in those vessels where PDE5 is present. PDE5 is abundant in the genitals and in the respiratory tract. In the pulmonary arteries, PDE5 inhibitors cause strong acute vasodilatation without rebound phenomenon and without tachyphylaxia. All available PDE5 inhibitors (sildenafil, tadalafil, vardenafil) have similar pharmacological and clinical effects but only sildenafil and tadalafil have been approved for PAH. The typical side effects are dyspepsia and headache.

#### 5.4.8.4 IP Agonists

Prostanoids are synthetic analogs of prostaglandin $I_2$ ($PGI_2$) and activate the IP receptor on the target cells. This causes cAMP elevation and a strong vasodilatation. Some of these have been approved both in Europe and in the USA. Epoprostenol has been approved for continuous intravenous infusion, treprostinil for continuous subcutaneous infusion (or intravenous if sc. is not tolerated), and iloprost as inhalation which is applied six or nine times daily. Inhaled treprostinil with four times daily application has only been approved in the USA. Intravenous iloprost has only been approved in New Zealand. Oral beraprost is approved in Japan and some other far eastern countries. A new class of non-prostanoid IP agonists has been developed, and selexipag, the first drug of this new class, is being tested in a phase III clinical trial.

All IP agonists may cause headache, flushing, jaw pain, and diarrhea, side effects that are dose-dependent. Rarely foot pain and ascites or other fluid retention may cause severe problems. All prostanoids need uptitration over weeks and months in order to maintain their efficacy. However, inhaled iloprost and treprostinil necessitate much less uptitration than continuous infusions. This may be explained either by the intermittent application or by the application via the airways.

#### 5.4.8.5 Combination Therapy

Combination therapy is recommended when monotherapy does not lead to satisfactory clinical results (sequential therapy). Dual therapy and triple therapy are very common in patients who have been treated for more than 2 years. Currently, there is no evidence that initial combination therapy is superior to the sequential therapy approach; however, the only study that investigates this issue (AMBITION) is still recruiting patients.

#### 5.4.8.6 Transplantation

If medical therapy does not result in satisfactory results, patients may qualify as candidates for lung transplantation. Heart transplantation is not necessary because the right ventricle improves quite dramatically when its afterload is reduced. Since targeted PAH medication became available, the number of lung transplantations for PAH has dramatically dropped. In the waiting time for lung transplantation atrial septostomy may be indicated (bridging to transplant). In this risky procedure, a perforation of the intra-atrial septum is performed by means of a catheter procedure and a balloon that is inflated in the septum to 8–12 mm diameter. The procedure improves the blood filling of the left ventricle but decreases arterial oxygenation because deoxygenated blood shunts from the right to the left atrium and does not pass the lung capillaries.

#### 5.4.8.7 Treatment Algorithm

An evidence-based treatment algorithm for patients with PAH is provided in Fig. 5.2 (Galie et al. 2009a). These recommendations do not apply to other forms of PH; however, there is a number of general measures like diuretics that also would apply for non-PAH PH. Anticoagulation is recommended for idiopathic and heritable

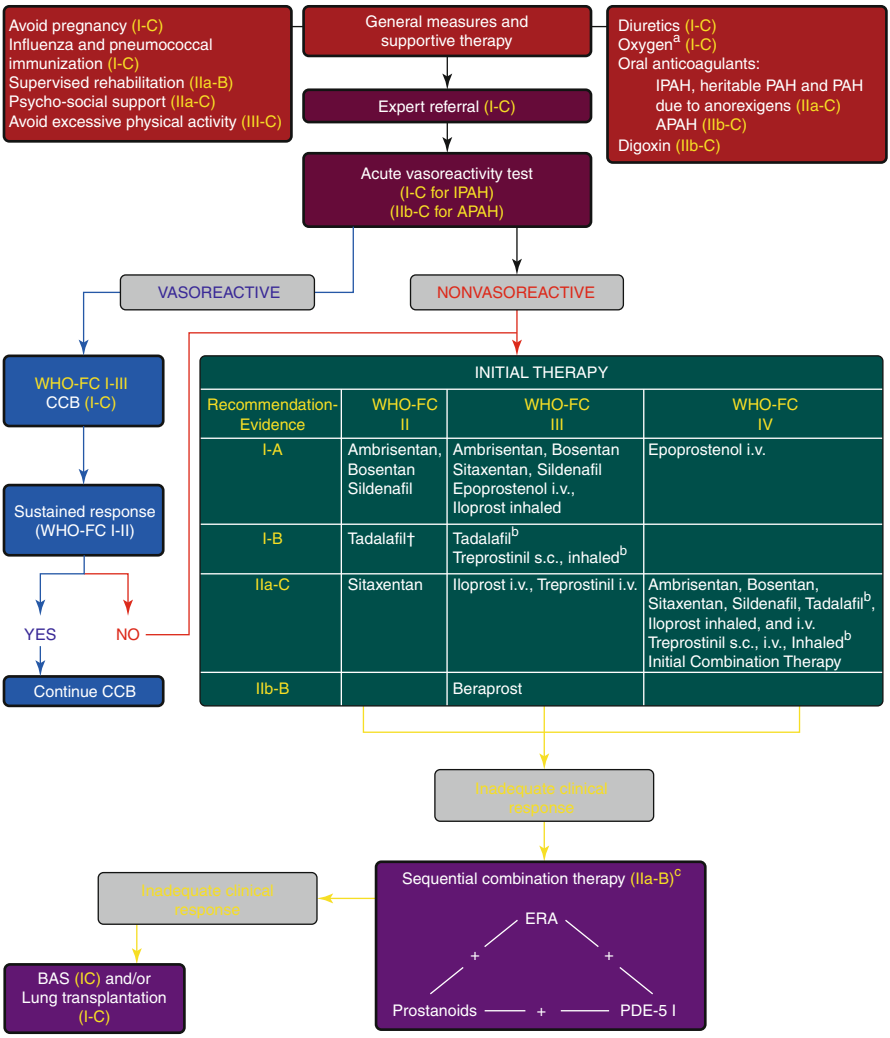


**Fig. 5.2** Evidence-based treatment algorithm for pulmonary arterial hypertension patients (for group 1 patients only). [a]To maintain arterial blood $O_2$ pressure ≥8 kPa (60 mmHg). [b]Under regulatory review in the European Union. [c]IIa-C for WHO-FC II. *APAH* associated pulmonary arterial hypertension, *BAS* balloon atrial septostomy, *CCB* calcium channel blocker, *ERA* endothelin receptor antagonist, *IPAH* idiopathic pulmonary arterial hypertension, *PDE5 I* phosphodiesterase type-5 inhibitor, *WHO-FC* World Health Organization functional class (From Galie et al. 2009a)

PAH and is mandatory for CTEPH. In the other forms, an individual decision is made. Physical training may improve physical capacity and may be safe (Grunig et al. 2011). However, supporting data were generated at only one highly specialized center and may not be transferable to other centers.

#### 5.4.8.8 New Developments

##### 5.4.8.8.1 New drugs

Several new therapy approaches for PAH have been developed. Pivotal studies are ongoing using a new endothelin receptor antagonist (macitentan), a non-prostanoid IP receptor agonist (selexipag) and two oral prostanoids (beraprost and treprostinil). A tyrosine kinase inhibitor (imatinib) which is approved for chronic myeloid leukemia and GIST tumors showed remarkable efficacy in selected PAH patients on both hemodynamics and clinical outcome (Ghofrani et al. 2010) but also an increased risk for subdural hematoma which is currently a major concern for further development.

A completely new targeted PAH drug is riociguat. This is a stimulator of the soluble guanylate cyclase (sGC) that induces sGC activity by itself and in combination with NO. This drug is being tested for PAH, CTEPH, and left heart disease with pulmonary hypertension in large randomized controlled studies.

## 5.5 Early Diagnosis

Many efforts have been made to diagnose patients at an earlier stage. Doppler echocardiography has been the preferred technical method; however, results are largely investigator dependent and not always correct. Methods based on magnetic resonance imaging and CT may be more advantageous, however, not available for large-scale investigations. Stress-Doppler echocardiography may be effective among patients at risk for PAH. This has been shown in relatives of IPAH patients (Grunig et al. 2009) and in scleroderma patients (Kovacs et al. 2010) but may also apply for patients with other forms of collagen vascular disease and other risk factors like liver disease, HIV infection, and left-to-right congenital heart defects. There is an urgent need for the development of screening techniques for PAH among the general population.

## 5.6 Early Therapy

There are patients with a risk for PAH who develop gradual elevation of pulmonary arterial pressure. It may be indicated to treat such patients before they meet the formal criteria for PAH. Once these patients meet the criteria of PAH (PAP$\geq$25 mmHg), the prognosis is very poor, despite optimized targeted PAH drugs. It might be advantageous to treat such patients before PAH is manifest (Kovacs et al. 2012).

## 5.7 Summary and Perspectives

Pulmonary vascular diseases have emerged as a leading field of research since diagnostics and therapy of pulmonary hypertension (PH) have made tremendous progress over the past 15 years. Over the past years, various therapeutic strategies

were developed, which include different type prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors. Approved drugs are available only for pulmonary arterial hypertension (PAH). The other forms have been called non-PAH PH and can be treated by specific measures; however, there are no targeted drugs for non-PAH PH. In some of these diseases, e.g., PH associated with left heart disease, chronic lung disease, and chronic thromboembolic pulmonary hypertension, PAH medication may cause severe side effects from pulmonary congestion and gas exchange disturbances. Further progress in early diagnosis and drug development, especially for the non-PAH PH, is urgently needed to achieve long-term survival with good quality of life.

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# Peripheral Arterial Disease

# 6

Yoko Sotoda and Ichiro Wakabayashi

**Abstract**

Peripheral arterial disease (PAD) is characterized by an impaired blood supply to the lower extremities, and the prevalence of PAD increases with age. Patients with PAD show intermittent claudication and ischemic ulcers, depending on the degree of ischemia in the lower extremities, and in addition, are often complicated with cardiovascular disease represented by coronary artery disease. Accordingly, the rate of mortality due to cardiovascular disease and the total mortality rate are known to be higher in patients with PAD compared with individuals without PAD.

The traditional risk factors of PAD are ageing, smoking, diabetes mellitus, dyslipidemia, and hypertension. In particular, ageing, smoking, and diabetes strongly affect the onset of PAD. Race/ethnicity, an elevation of blood inflammatory markers, chronic kidney disease, and obesity (metabolic syndrome) are also known as nontraditional risk factors for PAD.

Smoking strongly influences both the onset and progression of PAD. There is a dose-response relationship between smoking and the incidence of PAD, and the prevalence of PAD was reportedly 3–4 times higher in heavy smokers than in nonsmokers. Smoking-induced vascular endothelial cell injury, dyslipidemia, and increased blood coagulability facilitate atherosclerosis and increase the vascular tone. These detrimental effects of smoking are, in part, explained by the increase in reactive oxygen species caused by smoking.

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Diabetes mellitus is also a major independent risk factor for PAD, and PAD is classified as a diabetic macroangiopathy. The relative risk of diabetic vs. nondiabetic patients for PAD has been shown to be 2.0–3.0. PAD patients with diabetes are characterized by the presence of distal vascular lesions such as infra-femoral, and especially infra-popliteal and posterior tibial artery lesions. The risk of limb amputation in PAD patients with diabetes is greatly increased by the complication of "diabetic foot," which is classified as a diabetic microangiopathy that is caused by increased vascular permeability and a decreased neurogenic vasodilatory response. In patients with diabetes, hyperglycemia and insulin resistance cause endothelial damage which leads to the formation of the initial lesion occurring before atheroma formation. The pathogenesis of PAD in patients with diabetes is explained by disorders of vascular endothelial cells, vascular smooth muscle cells and platelets caused by activation of the diacylglycerol (DAG)-protein kinase C (PKC) pathway, the overproduction of advanced glycation end products (AGE), and activation of the polyol metabolism pathway.

The ACC/AHA guidelines for the management of PAD and the TASC I and II recommended aggressive lifestyle change, including smoking cessation, and medication therapy for diabetes, hypertension, and dyslipidemia to modify the risk of PAD, which aim to prevent the onset of PAD, improve the symptoms of intermittent claudication, and avoid lower limb amputation. Furthermore, PAD is an independent risk factor for cardiovascular disease, and thus, careful risk modification against PAD is thought to decrease the morbidity and mortality of cardiovascular disease.

**Keywords**
Ageing • Atherosclerosis • Diabetes mellitus • Gene-environmental interaction • Inflammation • Peripheral arterial disease • Smoking

## 6.1 Introduction

The incidence of atherosclerotic diseases has recently been increasing because of the increase in the elderly population and alterations in diet. A recent publication by the WHO has reported that the most frequent cause of death was atherothrombosis, which is a polyvascular disease caused by inflammation, which includes plural diseases such as coronary arterial disease, stroke and peripheral arterial disease (PAD), and strongly influences the quality of life and life expectancy of affected individuals.

PAD is regarded to be part of atherothrombosis and is defined as atherosclerotic, aneurysmal, and thromboembolic peripheral arterial diseases in general arteries, excluding the coronary artery, but including the abdominal aorta, renal artery, mesenteric artery, and limb arteries by the American College of Cardiology/American Heart Association (ACC/AHA). The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) defined PAD as atherosclerotic disease in the lower extremities. Thus, PAD is, in general, considered to have the same meaning as arteriosclerosis obliterans in the lower extremity arteries. Similar to other atherosclerotic diseases, the frequency of PAD increases with age. Smoking and diabetes mellitus are other risk factors strongly affecting the onset and progression of

PAD, and correction of these risk factors is particularly important for the prevention of PAD. The exact mechanisms responsible for the direct and indirect effects of smoking and diabetes on the onset of PAD remain unknown. However, part of the mechanism(s) has been clarified by recent studies based on previous epidemiological findings and using molecular biological experiments. In this chapter, the proposed pathophysiological mechanisms for PAD in relation to its major risk factors are introduced, and possible methods for preventing PAD in the future are considered.

## 6.2 Epidemiology of PAD

### 6.2.1 Definition and Classification of PAD

PAD is defined as a disease manifesting ischemia of the extremities and visceral organs due to morphological, as well as functional, degeneration of peripheral arteries. PAD in the narrow sense is usually used to describe ischemia of the lower extremities due to atherosclerosis, and thus, this definition is also used in this chapter. PAD is classified by the degree of ischemia into the following types:
*Classification of PAD*

1. Asymptomatic PAD
2. Symptomatic PAD

   Intermittent claudication (IC)
   Critical limb ischemia (CLI)
   Acute limb ischemia (ALI)

Asymptomatic PAD is diagnosed when the ABI (ankle-brachial systolic pressure index: the ankle pressure divided by the highest brachial pressure) is 0.9 or below. Mild, moderate, and severe types of PAD are defined as ABI as $0.7 \leq \text{ABI} \leq 0.9$, $0.5 \leq \text{ABI} < 0.7$, and $\text{ABI} < 0.5$, respectively (Shammas 2007). The typical symptoms of IC are discomfort and pain in the calf that are induced by exercise and disappear after rest for some minutes. CLI is characterized by pain at rest and ulcers in the lower extremity and is sometimes complicated with gangrene. In patients with CLI, the frequency of lower limb amputation is as high as 10–40, 40–70, and 80–95 % at 1, 5, and 10 years, respectively, after the onset of CLI. The frequencies of complication with diabetes and chronic renal insufficiency have been reported to be as high as 70.4 and 27.8 %, respectively, in patients with CLI (Shammas 2007).

ALI is characterized by the acute disappearance of arterial pulsation and acute appearance of resting pain in the lower extremity and is caused by the rupture of a local plaque and embolism originating from the central thrombus.

### 6.2.2 Prevalence of PAD

#### 6.2.2.1 Prevalence of Asymptomatic PAD

The ABI, a noninvasive measurement, is often used to diagnose PAD. The possibility of significant narrowing in the lower extremity artery is high when the ABI is

0.9 or lower, and the sensitivity and specificity of this criterion are 95 and 100 %, respectively (Norgren et al. 2007). In the Edinburgh Artery Study, complete occlusion of the lower extremity main arteries was reported to be observed in one-third of the cases with an ABI of 0.9 or lower (Fowkes et al. 1991). Thus, the ABI is thought to be a useful measure for diagnosing PAD. According to the National Health and Nutrition Examination Survey from 1999 to 2000, the prevalence of PAD was 4.3 % in patients aged 40 years or older and was 14.5 % in those aged 70 years or older, showing a great age-dependent increase in the prevalence of PAD in the elderly (Selvin and Erlinger 2004).

#### 6.2.2.2 Prevalence of Symptomatic PAD

In epidemiological surveys, PAD is usually diagnosed by the existence of IC in the questionnaire. Because this is a subjective method of assessing the presence of PAD, there is a possibility that the prevalence and incidence of PAD were underestimated in previous studies. The prevalence of IC was reportedly 2.5 % at 50–59 years, 8.3 % at 60–69 years, and 18.8 % at 70 years or older, thus increasing with age (Criqui 2001). In the Framingham study, the biennial incidence rate of PAD in all-age subjects was 7.1 and 3.6 per 1,000 males and females, respectively, and tended to be higher in the older group aged 65–74 years than in the younger group aged 54 years or younger (Kannel and McGee 1985). Thus, both the prevalence and incidence of PAD tend to increase with age (Fig. 6.1).

### 6.2.3 The Relationship of PAD with Cardio- and Cerebrovascular Diseases

The pathogenesis of PAD, as well as that of cardio- and cerebrovascular diseases, is usually based on atherosclerosis. In the PARTNERS (the PAD Awareness, Risk, and Treatment: New Resources for Survival) study (Hirsch et al. 2001), the prevalence of PAD was 29 % (1,865/6,417 persons), and 16 % of the subjects had both PAD and cardiovascular diseases (atherosclerotic coronary, cerebral, or abdominal aortic aneurysmal disease). Thus, about 55 % of subjects with PAD also had cardiovascular diseases. In particular, the coincidence of coronary artery disease in PAD patients was high: 53.6 % of PAD cases had angina pectoris and 45.1 % of PAD cases had a history of myocardial infarction. The coincidences of transient ischemic attack and cerebral infarction in PAD cases were 17.7 and 18.8 %, respectively, and were lower than the coincidence of coronary artery disease. Thus, PAD is strongly associated with coronary artery disease. There were inverse associations of the ABI with cardiovascular mortality and all-cause mortality in the Cardiovascular Health Study (CHS) (Newman et al. 1993; Resnick et al. 2004). Therefore, PAD shows a strong association with cardiovascular disease, in particular, coronary artery disease, and the primary and secondary prevention of PAD may contribute to decreasing the mortality due to cardiovascular disease.

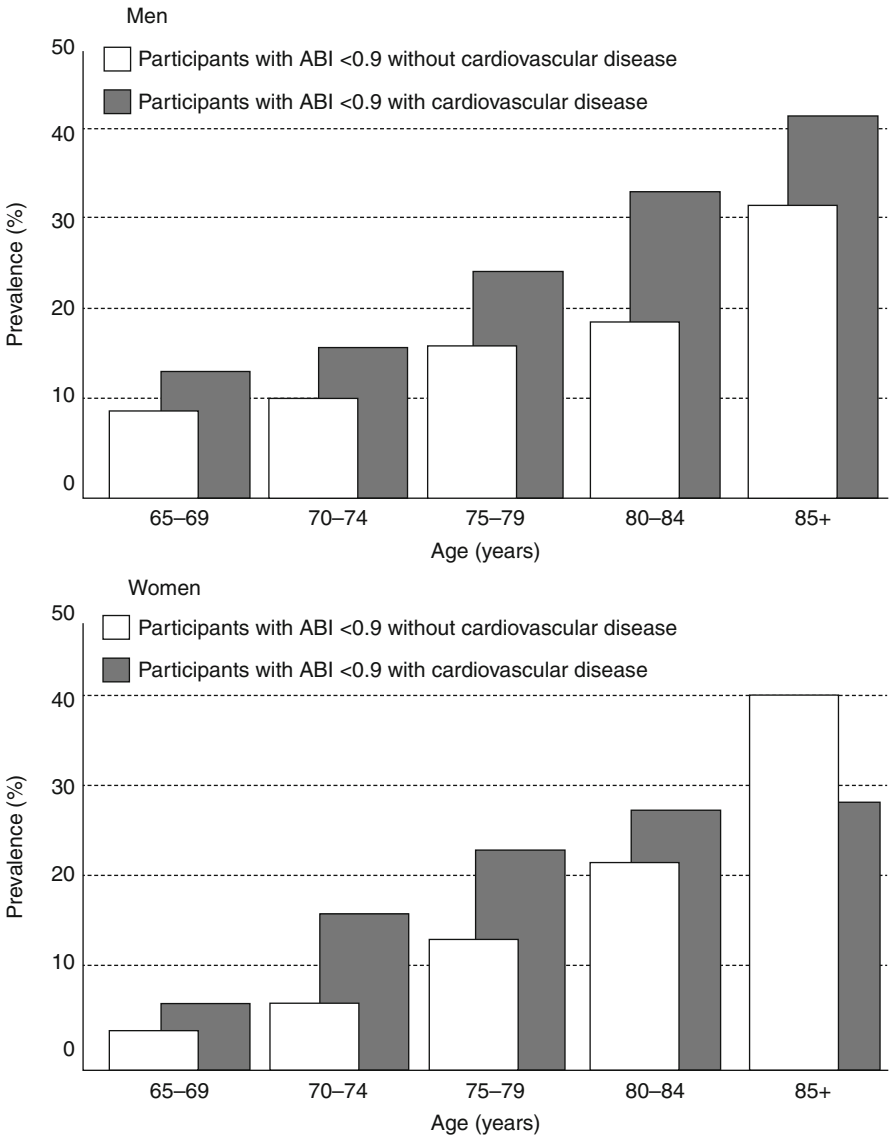


**Fig. 6.1** The relationship between age and the prevalence of an abnormally low ankle-brachial systolic pressure index (ABI: less than 0.9) in males and females with and without cardiovascular disease (Newman et al. 1993)

## 6.3 Risk Factors of PAD

The risk factors for PAD have been classified largely into traditional and nontraditional risk factors (Table 6.1). Pathophysiological mechanisms of the initiation of atherosclerosis associated with major risk factors for PAD are summarized in

**Table 6.1** Risk factors of peripheral arterial disease

| |
|---|
| Traditional risk factors |
| Advanced age |
| Smoking |
| Diabetes mellitus |
| Hyperlipidemia |
| Hypertension |
| Nontraditional risk factors |
| Race/ethnicity |
| Elevated levels of inflammatory markers (C-reactive protein, fibrinogen, leukocytes, interleukin-6) |
| Chronic kidney disease |
| Genetics |
| Hypercoagulable states |
| Homocysteine |
| Abdominal obesity |

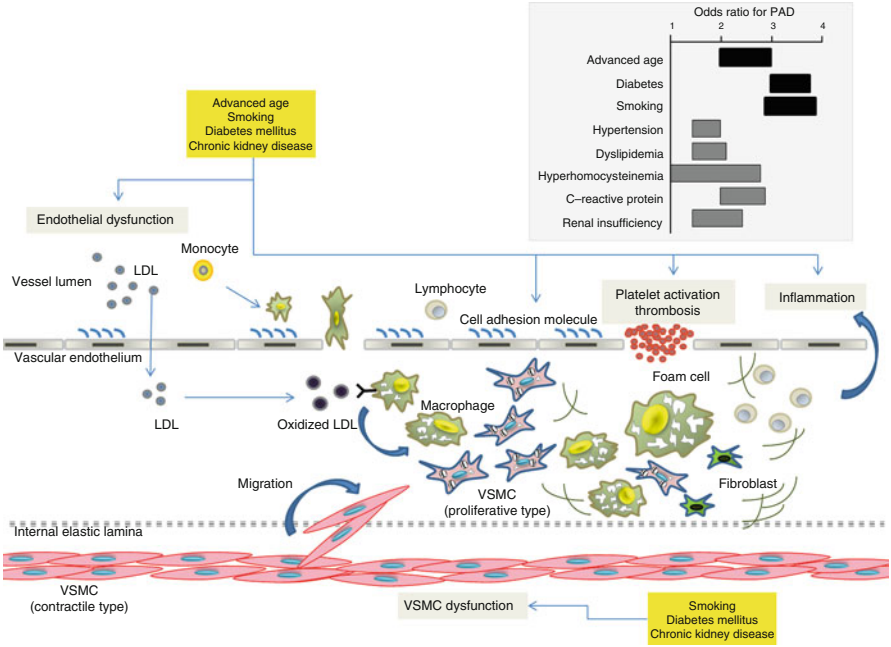


**Fig. 6.2** Pathophysiological mechanisms of the initiation of atherosclerosis associated with major risk factors for peripheral arterial disease (*PAD*). The *inset figure* displays the odds ratios with their 95 % confidence interval for PAD in subjects with vs. without each risk factor (Norgren et al. 2007). *LDL* low-density lipoprotein cholesterol, *VSMC* vascular smooth muscle cell

Fig. 6.2. In addition, the subcellular mechanisms underlying the dysfunctions of platelets, vascular endothelial cells, and vascular smooth muscle cells induced by risk factors for PAD are illustrated in Fig. 6.3.

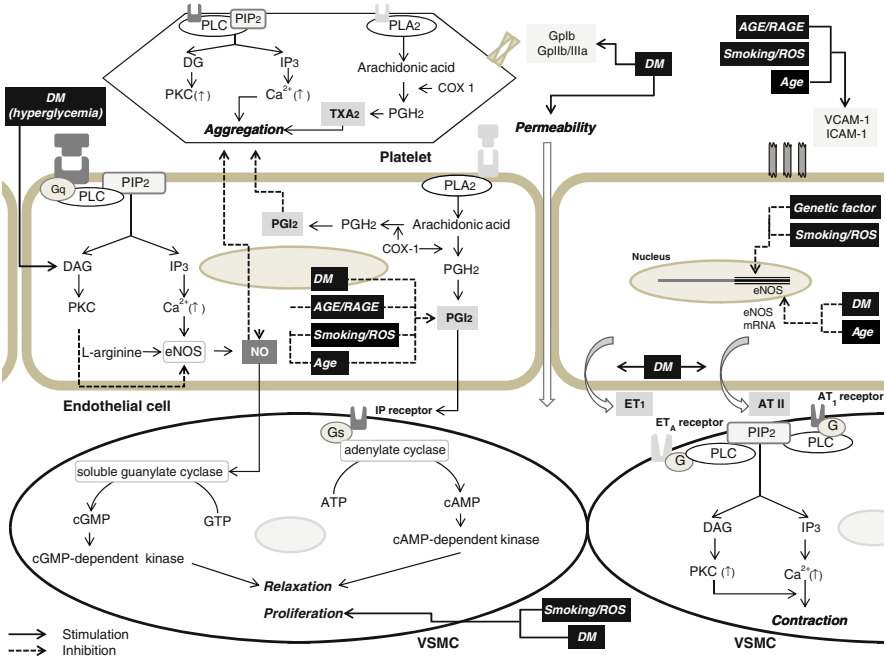


**Fig. 6.3** The subcellular mechanisms underlying the dysfunctions of platelets, vascular endothelial cells, and vascular smooth muscle cells induced by risk factors for peripheral arterial disease. *AGE* advanced glycation end products, *AT1 receptor* angiotensin type 1 receptor, *AT II* angiotensin II, *COX-1* cyclooxygenase-1, *DAG* diacylglycerol, *DM* diabetes mellitus, *ET1* endothelin-1, *ET-A receptor* endothelin-A receptor, *eNOS* endothelial nitric oxide synthase, *GpIb* glycoprotein Ib, *GpIIb/IIIa* glycoprotein IIb/IIIa, *Gq* Gq-protein, *Gs* Gs-protein, $IP_3$ inositol 1,4,5-trisphosphate, *NO* nitric oxide, $PGH_2$ prostaglandin $H_2$, $PGI_2$ prostaglandin $I_2$, $PIP_2$ phosphatidylinositol 4,5 bisphosphate, $PLA_2$ phospholipase $A_2$, *PLC* phospholipase C, *PKC* Protein kinase C, *RAGE* receptor of AGE, $TXA_2$ thromboxane $A_2$, *VCAM-1* vascular cell adhesion molecule 1, *VSMC* vascular smooth muscle cell

## 6.3.1 Advanced Age

As mentioned above, many previous epidemiological studies have shown that the prevalence of PAD increases with age (Fig. 6.1). Ageing is involved in a variety of diseases via biological mechanisms such as cell injury, DNA damage, and alterations in inflammatory cytokine production. The senescence of cells is defined as irreversible termination of somatic cell proliferation, caused by the shortening of telomeres, which is recognized as DNA injury and activates the DNA-injury-responsive pathways, resulting in the disappearance of cell proliferation capability (Hayflick and Moorhead 1961; Collado et al. 2007).

Dysfunction of the vascular endothelium due to ageing is also involved in the pathogenesis of atherosclerotic disease. Vascular endothelial cells play obligatory roles in regulating the arterial tone and arterial smooth muscle cell proliferation by producing a

variety of factors affecting vascular smooth muscle contraction and proliferation. Nitric oxide (NO) and prostacyclin are representative vasorelaxing products of endothelial cells. In endothelial cells, the stimulation of plasmalemmal receptors by agonists, e.g., acetylcholine, ADP released from platelets, and thrombin, induces an elevation of the cytosolic $Ca^{2+}$ level, which activates endothelial nitric oxide synthase (eNOS). Consequently, NO is synthesized through the hydration of the guanidine residue of L-arginine. NO activates guanylate cyclase and increases the intracellular cGMP concentration, which causes vascular smooth muscle relaxation and inhibition of platelet aggregation. Prostacyclin released from the vascular endothelium in response to agonists, e.g., bradykinin and thrombin, which bind to their receptors coupled with Gs-protein, activates adenylate cyclase and increases intracellular cAMP, which also causes vascular smooth muscle relaxation and inhibits platelet aggregation.

Cell senescence causes vascular endothelial dysfunction, which attenuates the production of both NO and prostacyclin, resulting in an increase in arterial tone and augmentation of platelet aggregation. Senescence is also known to be involved in the progression of atherosclerosis by increasing the expression of transcription factors involved in inducing inflammatory response, which augment the production of adhesion factors, such as VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1), as well as inflammatory cytokines, e.g., MCP-1 (monocyte chemotactic protein-1) (Minamino and Komuro 2007). The detailed mechanism of initiation of atherosclerosis by inflammation-inducing transcription factors remains unknown. However, a decrease in the ABI has been reported to be associated with increases in the plasma VCAM-1 and ICAM-1 concentrations (Brevetti et al. 2006). Inflammatory cytokines have been shown to facilitate the remodeling of smooth muscle cells from the contractile type to the proliferative type and to induce the differentiation of smooth muscle cells into osteochondrocytes, resulting in calcification of the arterial wall (Owens et al. 2004).

### 6.3.2 Race

Racial differences in the prevalence of PAD have recently been reported, and race is regarded to be an important risk factor. In most of the previous studies, the prevalence of PAD was reportedly higher in African Americans and black Americans than in non-Hispanic whites. According to a review by Bennett et al. (2009) on racial differences in PAD, the prevalence of PAD in African Americans was 7.2–22.8 %, which was higher than the prevalence in non-Hispanic whites (2.7–13.2 %) and Hispanics (1.7–13.7 %). These differences are thought to be attributable to the higher prevalence of diabetes, hypertension, and obesity and the higher smoking rates in African Americans and black Americans than in Hispanics and non-Hispanic whites, all of which are risk factors for PAD.

Based on the Multi-Ethnic Study of Atherosclerosis (MESA), the odds ratio for PAD in African Americans vs. non-Hispanic white was reported to be 2.28. However, when adjusted for nontraditional risk factors, such as CRP, fibrinogen, lipoprotein(a), and homocysteine levels, as well as the presence of metabolic syndrome and chronic kidney disease, the odds ratio of African American vs. other

races was decreased to 1.47, suggesting that these risk factors are responsible for the majority of the racial difference (Allison et al. 2006). Therefore, while a racial difference exists in the prevalence of PAD, it may be largely explained by the differences in the prevalence of diabetes and other risk factors for PAD.

### 6.3.3 Genes

About 70 % of the population burden of PAD is reportedly attributable to conventional atherosclerotic risk factors, such as old age, hypertension, cholesterol levels, smoking status, fibrinogen level, and diabetes (Meijer et al. 2000). In addition, previous family studies using ABI for the detection of PAD have suggested that genetic factors contribute to 21–48 % of the susceptibility to PAD (Carmelli et al. 2000; Murabito et al. 2006). Recently, a variety of genes have been shown to be associated with PAD. Gene polymorphisms contributing to PAD are classified into three categories, including proatherosclerotic genes (e.g., connexin 37$^{\alpha}$, apolipoprotein E and B, IL-6 promoter, E-selectin, ICAM-1, MCP-1, matrix metalloproteinase-1 and -3, eNOS, angiotensin-converting enzyme D, and CDKN2b and CDKN2a), proatherothrombotic genes (e.g., factor II, P2Y12, fibrinogen, and methylenetetrahydrofolate reductase), and novel function-unknown genes (e.g., *SLC2A10*$^{\alpha}$*, PAOD1, LSq-1 and CHRNA3*) (Katwal and Dokun 2011). The risk of PAD has been shown to be significantly increased in the presence of both the ACE DD genotype and traditional atherosclerotic risk factors, such as smoking, dyslipidemia, and hypertension in patients with type 2 diabetes, while no significant association was found between the DD genotype and PAD risk in a crude analysis (Tseng et al. 2012). Thus, a gene-environment interaction is suggested to contribute to the pathogenesis of PAD, and further studies are needed to clarify the complex interactions between genotype variability and the conventional risk factors for cardiovascular diseases including PAD. Moreover, specific microRNAs (miRs) have recently been suggested to be involved in the pathological processes of PAD (Zhou et al. 2012). For example, the serum levels of miR-130 and miR-27b, which are involved in the regulation of angiogenesis, have been shown to be increased in patients with PAD (Li et al. 2011). The expression of miR-21, which is related to hypoxia inducible factor 1-α and tropomyosin, was reportedly increased in smooth muscle cells isolated from the femoral artery of patients with PAD (Wang et al. 2011b). Further studies are also needed to investigate the relationships between alterations in miRs and classical risk factors for PAD, and to clarify the significance of miR in the pathogenesis of PAD.

### 6.3.4 Gender

The prevalence of PAD has been demonstrated to be higher in males than in females, and thus, male gender has been thought to be a risk factor for PAD. However, a recent population-based study has reported no apparent gender-related difference in the prevalence of PAD (8.2–19.8 % [mean 13.4 %] in males vs. 5.5–23.2 % [mean

15.6 %] in females) (Vavra and Kibbe 2009). In patients younger than 70 years, the prevalence of PAD was 11.5 % in females vs. 17.1 % in males, while in those aged 85 years or older, the prevalence was 39.0 % in females vs. 27.0 % in males, suggesting a higher prevalence in old females than in old males (Higgins and Higgins 2003).

The decrease in sex hormones, represented by estrogen, strongly influences the susceptibility of females to PAD. There has been accumulated knowledge on the cardioprotective actions of estrogen, including the augmentation of endothelium-dependent vasorelaxation induced by the NO produced via activation of the estrogen receptor (ER). In addition, estrogen is known to regulate eNOS expression, endothelial cell proliferation, and endothelial cell senescence. Estrogen also influences lipid metabolism: estrogen decreases LDL cholesterol, increases HDL cholesterol, and inhibits LDL oxidation by an antioxidant action, resulting in a suppression and retardation of the progression of atherosclerosis (Hayashi et al. 2000, 2006).

An association between a low blood testosterone level and risk of cardiovascular disease in males suggests that testosterone also has a cardioprotective action, which is, at least in part, explained by the testosterone-induced increase in the production of NO in vascular endothelial cells (Yu et al. 2010). Thus, both estrogen and testosterone have NO-increasing actions. Further studies are needed to clarify the other possible vascular actions of testosterone. The age-related difference in the prevalence of PAD is thought to reflect the postmenopausal decrease in the cardioprotective actions of sexual hormones.

### 6.3.5 Smoking

Smoking is an independent risk factor for cardiovascular disease. Smoking, as well as diabetes, is strongly associated with the onset of PAD and exacerbation of the symptoms of PAD (Bartholomew and Olin 2006).

#### 6.3.5.1 Epidemiology

In the Edinburgh Artery Study, the incidence of PAD during 5-year follow-up was 5.1 %, and the rate of smokers, including current smokers and recent ex-smokers, in patients with PAD was 53.1 %, which was significantly higher than the rate of smokers in the non-PAD group (30.7 %) (Price et al. 1999). The incidence of PAD was 2.6 % in nonsmokers (pack years = 0), 4.5 % in moderate smokers (0 < pack years ≤ 25), and 9.8 % in heavy smokers (pack years > 25), suggesting a dose-response relationship between the amount of smoking and the risk of PAD. The risk for PAD was significantly higher in persons exposed to secondhand smoke than in those not exposed (odds ratio: 1.87 [95 % confidence interval (CI), 1.30–2.68]), and dose-response relationships were found between the amount and duration of secondhand smoke and the risk of PAD (He et al. 2008). Thus, passive smoking, as well as active smoking, increases the risk of PAD.

In a cross-sectional study on the relationship between PAD and the time after cessation of smoking, the odds ratio for PAD in ex-smokers at 11–20 years after cessation of smoking vs. current smokers was 0.41 (95 % CI: 0.19–0.86), while the odds

ratio for PAD in current smokers vs. nonsmokers was 4.3 (95 % CI: 2.13–8.66). Thus, the risk of PAD is thought to decrease in ex-smokers a long time (more than 10 years) after quitting smoking (Lee et al. 2011).

#### 6.3.5.2 Pathophysiology

Smoking harmfully influences blood vessels by causing injuries to the arterial endothelium, inducing inflammatory response, causing blood lipid disorders, having unfavorable effects on hereditary predisposition, and inducing an abnormal blood coagulation-fibrinolysis balance. These effects of smoking are mediated by nicotine, polycyclic aromatic hydrocarbons, carbon monoxide, and reactive oxygen species (ROS) (Ambrose and Barua 2004). In particular, the decrease in the bioavailability of NO due to increased ROS is thought to be deeply involved in the vascular injury caused by smoking. Tobacco smoke contains nicotine, carbon monoxide, cyanic gas (hydrogen cyanide: HCN), superoxide, hydroxyradicals, and hydrogen peroxide, and the concentrations of ROS are also increased by smoking, which activates the endogenous ROS-producing system such as uncoupled eNOS, the xanthine oxidase system, and the mitochondrial electron transport system. Oxidative stress due to ROS induces vascular endothelial injury and reduces the bioavailability of NO, resulting in a decrease in endothelium-dependent vasorelaxation, an increase in inflammatory cytokine release, augmentation of platelet aggregation and enhancement of vascular smooth muscle cell proliferation (Cai and Harrison 2000).

In experiments using human umbilical vein endothelial cells and bovine aortic endothelial cells, exposure of the cells to the serum derived from smokers and the cigarette smoke extract reportedly decreased the expression and activity of eNOS and subsequent production of NO (Ambrose and Barua 2004; Zhang et al. 2006). As a mechanism for these effects, smoking caused an attenuation of NO production by decreasing the arginine uptake due to inhibition of the expression of type 1 cationic amino acid transporter (CAT1), an arginine transporter (Zhang et al. 2006).

Smoking also decreased the blood HDL cholesterol levels and increased the blood triglyceride and LDL cholesterol levels. In addition, the increase in ROS induced by smoking has been shown to increase the amount of oxidized LDL cholesterol through attenuation of paraoxonase activity (Ambrose and Barua 2004; Burke and Fitzgerald 2003).

Smoking is known to cause elevations of the levels of blood fibrinogen, von Willebrand factor and fibrin D-dimer, and a decrease in tissue-type plasminogen activator, which are thought to be associated with the coagulation-fibrinolysis imbalance observed in smokers (Ambrose and Barua 2004). DNA damage due to increases in oxidative stress, adhesion molecules and inflammatory cytokines are also suggested to be involved in the onset and progression of PAD, as well as other atherosclerotic diseases in smokers (Ambrose and Barua 2004).

### 6.3.6 Alcohol

Moderate alcohol consumption is known to be inversely associated with the risk of cardiovascular disease, particularly coronary artery disease (Corrao et al. 2000).

Similarly, from previous prospective and cross-sectional studies using the ABI or the representative symptom of intermittent claudication for a diagnosis of PAD, moderate alcohol consumption has been shown to be associated with a lower risk of PAD (Jepson et al. 1995; Camargo et al. 1997; Djoussé et al. 2000; Vliegenthart et al. 2002). The inverse associations of wine consumption with the incidence and prevalence of PAD have been shown to be stronger than the associations of other alcohol beverages, such as beer and spirits (Jepson et al. 1995; Djoussé et al. 2000; Vliegenthart et al. 2002). In the Rotterdam study, an inverse relationship between moderate alcohol consumption and PAD was found in female and male nonsmokers, but not in male smokers (Vliegenthart et al. 2002). Therefore, the relationship between alcohol and PAD is strongly confounded by smoking, which is a major risk factor for PAD, and is much more prevalent among males than among females. The causality of the inverse relationship between alcohol consumption and PAD, as well as the mechanism responsible for the alcohol-induced reduction of the PAD risk, remains to be clarified. However, it is understandable that, similar to coronary artery disease, the antiatherogenic actions of alcohol itself and the polyphenol compounds contained in alcohol beverages contribute to the lower risk of PAD in drinkers, since there are common atherosclerotic risk factors for coronary artery disease and PAD, and the risk of coronary artery disease is greatly increased in patients with PAD, as mentioned above. In addition, moderate alcohol consumption has been reported to be associated with lower cardiovascular mortality in patients with PAD (Garcia-Diaz et al. 2011).

### 6.3.7 Physical Activity

The prevalence of PAD has been shown to be inversely related to previous physical activity in male smokers (Housley et al. 1993). Higher physical activity levels during daily life have been reported to be associated with less functional decline among people with PAD (Garg et al. 2009), and there was a relationship between the physical training volume and improvement in walking distance in patients with intermittent claudication (Nicolaï et al. 2010). Moreover, PAD patients with higher physical activity during daily life reportedly had reduced mortality rate and a lower incidence of cardiovascular events compared with patients with lower daily physical activity (Garg et al. 2006). Therefore, daily physical activity is a determinant for the improvement of the symptoms of PAD and prevention of complication with cardiovascular disease in PAD patients. Various mechanisms, including the improvement of endothelial functions such as increased NO bioavailability associated with reduced oxidative stress and an increased expression and activity of eNOS, have been proposed for the antiatherogenic effects of physical exercise (Seals et al. 2009). Habitual exercise is thought to reduce the oxidative stress levels due to the decrease in the expression and activity of NADPH oxidase and the increase in the activity of superoxide dismutase (Seals et al. 2009). Moreover, physical activity has been shown to increase the production and circulating numbers of endothelial progenitor cells via a partially NO-dependent, antiapoptotic effect (Laufs et al. 2004).

### 6.3.8 Diabetes Mellitus

#### 6.3.8.1 Epidemiology

Diabetes mellitus is a potent independent risk factor for atherosclerotic diseases such as coronary artery disease, stroke, and PAD and additively acts with other atherosclerotic risk factors (Bartholomew and Olin 2006). In the National Health and Nutrition on Examination Surveys (NHANES), 20.8 million people (7.0 % of the total population) were reported to suffer from diabetes in the United States, and 30 % of these were potential diabetes patients who had not yet received an official diagnosis (Deshpande et al. 2008). Worldwide, 120–140 million people are speculated to suffer from diabetes. The cardiovascular mortality has been shown to be two to four times higher in patients with diabetes than in nondiabetic people, and about two-thirds of the deaths of patients with diabetes were due to atherosclerotic diseases, such as coronary artery disease and stroke.

Diabetes is also an independent risk factor for PAD, and the relative risk of diabetic vs. nondiabetic patients for PAD has been shown to be 2.0–3.0 (Bartholomew and Olin 2006; Marso and Hiatt 2006). Diabetes and smoking are considered to be the two major risk factors for PAD. The prevalence of PAD in patients with diabetes, which depends on the age of patients and the method used to diagnose PAD, has been reported to be 3.0–38 %. In the Framingham study, the incidence of PAD in diabetics was 12.6/1,000 person-years in males and 8.4/1,000 person-years in females, while in nondiabetics, the incidence of PAD was 3.3/1,000 person-years in males and 1.1/1,000 person-years in females (Jude et al. 2010). There were positive associations of the duration and severity of diabetes with the prevalence of PAD, and these associations are especially prominent in males with a history of hypertension and in smokers (Jude et al. 2010).

PAD in patients with diabetes is characterized by high frequencies of vascular lesions in the femoral artery, popliteal artery and tibial artery (distal to the inguinal ligament, particularly at the infra-knee joint), bilateral and multiple lesions, and a danger of lower limb amputation due to ulcers and necrosis (CLI). More proximal (aorto-ilio femoral) lesions are more frequently detected in smokers and patients with hypertension than in nonsmokers and those without hypertension (Menzoian et al. 1989; Haltmayer et al. 2001). In patients with diabetes, the age of PAD onset is younger and its progression is more rapid than in nondiabetic people. The secondary patency after revascularization is lower in PAD patients with diabetes than in those without diabetes (Jude et al. 2001).

In patients with diabetes, advanced age, the duration of diabetes, severity of diabetes, presence of peripheral neuropathy, and history of hypertension are further risk factors for PAD (American Diabetes Association 2003; Jude et al. 2010). The odds ratio for PAD in patients who had had diabetes for 20 years or longer vs. those without diabetes was reportedly higher than the odds ratio in patients with diabetes for 10–19 years (odds ratio: 4.3 vs. 3.8) (Zander et al. 2002). When evaluating the severity of diabetes by the hemoglobin A1c (HbA1c) level, a 1 % increase in (HbA1c) has been shown to result in a 28 % increase in the risk of PAD

(Jude et al. 2010). In patients with diabetes, the systolic blood pressure has been strongly associated with the onset of PAD, and a 10 mmHg blood pressure elevation resulted in a 25 % increase in the PAD risk (Zander et al. 2002; Jude et al. 2010). Moreover, a high mortality rate due to cardiovascular diseases has been shown in diabetes patients complicated with PAD.

#### 6.3.8.2 Pathophysiology

Diabetes is a disease characterized by chronic hyperglycemia due to a deficiency of insulin action. A variety of complications due to metabolic disorder following hyperglycemia occur in patients with diabetes, and cardiovascular complications are particularly important, because they are responsible for 44 % of the deaths of patients with diabetes. The vascular complications in diabetes are largely classified into microangiopathy and macroangiopathy. Microangiopathy consists of vascular lesions at the arterioles and capillaries and is further classified into retinopathy, nephropathy, and neuropathy. Macroangiopathy consists of atherosclerotic lesions at elastic and muscular arteries and includes coronary artery disease, PAD, and stroke. The morphological changes, such as stenosis and occlusion, in patients with PAD complicated with diabetes are similar to those observed in other atherosclerotic diseases. Atherosclerosis is facilitated by dysfunctions of endothelial cells, smooth muscle cells, and platelets, resulting from dyslipidemia and insulin resistance due to diabetes.

PAD in patients with diabetes is characterized by distal vascular lesions, such as infra-femoral and especially infra-popliteal and posterior tibial artery lesions. “Diabetic foot,” a characteristic complication of diabetes, manifests as ulcers, phlegmon, and paronychia of the foot and toe, and amputation is needed for patients with the progressed stage of diabetic foot. Diabetic neuropathy is involved in the pathogenesis of diabetic foot.

##### 6.3.8.2.1 Endothelial Cell Dysfunction

Elastic and muscular types of arteries have three layers: the intima, media, and adventitia. The intimal layer consists of a monolayer of endothelial cells supported by connective tissues. Endothelial cells regulate the vasotone, vascular permeability, neovascularization, platelet aggregability, hemostatic balance, monocyte attachment, and vascular smooth muscle cell proliferation. The mechanisms explained below for diabetes-induced endothelial dysfunctions and subsequent vascular disorders are summarized in Fig. 6.4.

In patients with diabetes, hyperglycemia and insulin resistance cause endothelial damage, which is an initial lesion occurring before atheroma formation (Beckman et al. 2002). Known mechanisms responsible for the hyperglycemia-induced impairment of endothelial function include the activation of the diacylglycerol (DAG)-protein kinase C (PKC) pathway, overproduction of advanced glycation end products (AGEs), and activation of the polyol metabolism pathway (Akbari and LoGerfo 1999). Hyperglycemia has been shown to activate PKC through the *de novo* synthesis of DAG in diabetic patients (Shahab 2006). PKC inhibits the phosphoinositide 3 (PI3)-kinase-AKT pathway via insulin receptor substrate (IRS)-1, resulting in

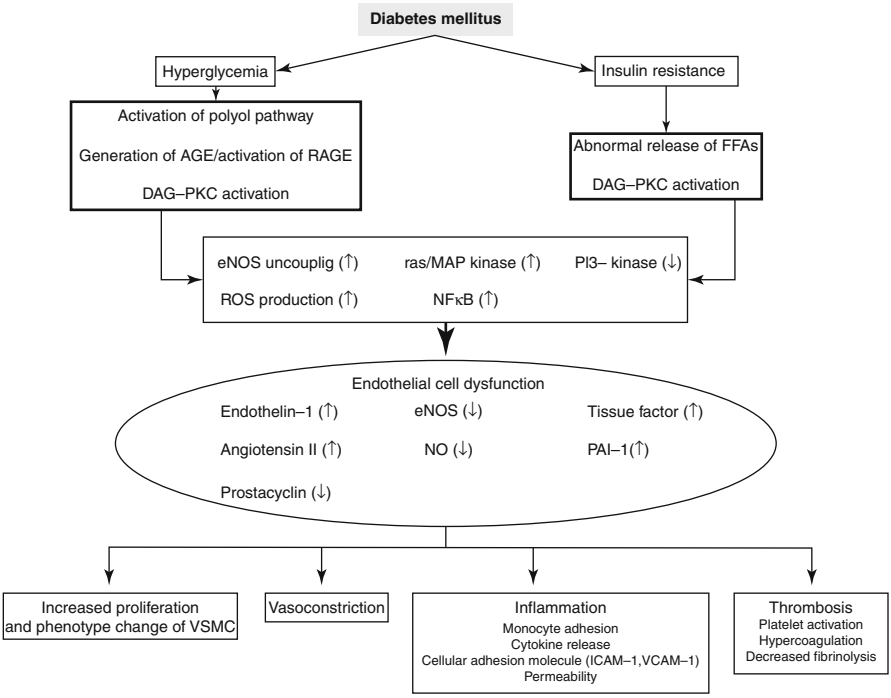


**Fig. 6.4** The mechanisms underlying the diabetes-induced vascular endothelial cell dysfunctions and subsequent disorders related to atherosclerosis. *AGE* advanced glycation end products, *DAG* diacylglycerol, *eNOS* endothelial nitric oxide synthase, *FFA* free fatty acid, *ICAM-1* intercellular adhesion molecule 1, *NFκB* nuclear factor kappa B, *NO* nitric oxide, *PAI-1* plasminogen activator inhibitor type 1, *PI3-kinase* phosphatidylinositol 3-kinase, *PKC* protein kinase C, *RAGE* receptor of AGE, *Ras/MAP kinase* Ras/mitogen-activated protein kinase, *ROS* reactive oxygen species, *VCAM-1* vascular cell adhesion molecule 1, *VSMC* vascular smooth muscle cell

decreases in eNOS activity and subsequent NO production (Beckman et al. 2002). This mechanism also causes an increase in endothelin (ET)-1 expression, thereby inducing vasoconstriction and smooth muscle proliferation via the ET-A receptors (Jude et al. 2010). The activation of PKC also induces an increase in vascular permeability and decrease in eNOS activity by producing oxidative stress as a result of the activation of NAD(P)H oxidase (Inoguchi et al. 2003; Rask-Madsen and King 2005; Liu et al. 2007).

Under hyperglycemic conditions, reducing sugars, e.g., glucose, nonenzymatically bind to the amino acid in proteins to form Schiff bases and Amadori compounds. Subsequently, AGEs are formed after repeated dehydration and condensation reactions. AGEs are formed in circulating blood and accumulate in tissues, where they are involved in various types of organ damages. In capillary endothelial cells, AGEs are deposited at the basement membrane and increases its permeability. AGEs are known to increase oxidative stress, which inhibits the bioavailability of NO derived from the endothelium. Moreover, AGEs have been shown to act on

RAGE (receptor for AGE), resulting in the activation of nuclear factor κB (NFκB) through the Ras/MAP kinase pathway, and thereby inducing the expression of ICAM-1 and VCAM-1 and enhancing monocyte attachment (Beckman et al. 2002; Marso and Hiatt 2006).

Under chronic hyperglycemic conditions, the polyol pathway, which converts glucose to sorbitol by aldose reductase and further converts sorbitol to fructose by sorbitol dehydrogenase, is activated. During the former conversion, NADPH is utilized, causing an increase in oxidative stress, eNOS uncoupling, and a decrease in NO production (Beckman et al. 2002). Because the former conversion is more rapid than the latter conversion, and because sorbitol does not readily penetrate through the plasma membrane, the sorbitol accumulates in the cell and increases the intracellular osmotic pressure, resulting in relative decreases in other factors, such as myo-inositol and taurine, which compensate for the osmotic pressure increase. Consequently, oxidative stress is increased due to the decrease in taurine, an antioxidative substance, and the $Na^+/K^+$ ATPase activity is decreased due to the reduction of myo-inositol, resulting in cellular dysfunction.

In addition to hyperglycemia, insulin resistance/hyper-insulin status, which is strongly associated with the pathogenesis of metabolic syndrome, causes endothelial dysfunction (Beckman et al. 2002). Hyper-insulin status has been shown to inhibit endothelium-dependent vasodilation by increasing oxidative stress (Arcaro et al. 2002). Relative insulin deficiency due to chronic hyperglycemia enhances the release of free fatty acids (FFA) from fatty tissues and increases FFA synthesis in the liver, resulting in triglycerides-rich lipoprotein, such as atherogenic remnant lipoprotein. Furthermore, the glycation of lipoprotein due to hyperglycemia induces secondary dyslipidemia. The activation of PKC and inhibition of PI3-kinase by the increased FFA are thought to be involved in the impairment of endothelial cells.

The production of angiotensin II in vascular endothelial cells has been shown to be augmented in diabetes, and AT1-receptor stimulation by angiotensin II causes an increase in oxidative stress, resulting in endothelial dysfunction and smooth muscle proliferation (Prasad et al. 2000; Beckman et al. 2002). Therefore, the oxidative stress increased by hyperglycemia and insulin resistance is deeply involved in the endothelial dysfunction in patients with diabetes, and avoidance of damage to the vascular endothelium is crucial for the prevention of PAD in diabetics.

In patients with diabetes and those with PAD, the blood histamine concentration has been reported to be higher than that in the age-adjusted control subjects (Gill et al. 1989). The histamine contents in leukocytes and platelets were also higher in patients with PAD than in the control (Gill et al. 1988, 1989). The histamine $H_1$ receptor-mediated increase in vascular endothelial permeability is thought to induce LDL accumulation in the intimal layer (Rozenberg et al. 2010). Moreover, histamine has been shown to upregulate the mRNA expression of atherogenic inflammatory modulators, such as NFκB, inflammatory cytokines, and matrix metalloproteinases (Wang et al. 2011a). The expression of early growth response factor 1 (Egr-1), a key regulator of atherogenesis, is also reportedly increased by histamine through activation of PKC-δ (Hao et al. 2008).

#### 6.3.8.2.2 Vascular Smooth Muscle Cell Dysfunction

There are two phenotypes, the contractile type and proliferative type, of vascular smooth muscle cells, and phenotype changes are induced by the extracellular environment. Under normal conditions, arterial smooth muscle cells of the contractile type, which contain a large amount of myosin filaments, regulate the vascular tone. Smooth muscle cells with the proliferative type increase in the neointima of atheromatous lesions.

In patients with diabetes, increases in the vascular smooth muscle cell contractility, migration, and proliferation are involved in the onset and progression of PAD. The blood levels of endothelin-1 and angiotensin II are increased in patients with diabetes. Endothelin-1 induces vasoconstriction by activating ET-A receptors in vascular smooth muscle cells and induces their hypertrophy and proliferation by activating the renin-angiotensin system. Similarly, angiotensin II induces smooth muscle cell contraction and proliferation through activation of AT-1 receptors (Beckman et al. 2002).

Vascular smooth muscle cells play an important role in plaque stabilization in the process of atheroma formation, which is initiated by the attachment of monocytes to the subendothelial layer and their phagocytosis of oxidized LDL. Foam cells consist of monocytes with excessive uptake of oxidized LDL, and accumulated foam cells become a fatty streak. The proliferation and migration from the media to the intima of vascular smooth muscle cells are induced, and a fibrin cap is formed at the surface of the fatty streak by collagen secreted from the cells, resulting in an increased local thickness of the vascular wall and further narrowing and occlusion of blood vessels. The fibrin cap stabilizes the plaques by covering the atheromatous lesions.

In patients with diabetes, the vascular smooth muscle cell functions, as well as the endothelial cell functions, are disturbed by the activation of the DAG-PKC pathway (Hall et al. 2000), RAGE and NFκB (Beckman et al. 2002; Marso and Hiatt 2006; Jude et al. 2010). The number of intimal smooth muscle cells in advanced atherosclerotic lesions has been reported to be lower in diabetics than in nondiabetics, and this decrease in smooth muscle cells is explained by their increased apoptosis. In addition, in the smooth muscle cells of diabetics, the *de novo* synthesis of collagen is decreased, and the expression of matrix metalloproteases, which break down collagen, is increased. Thus, reduction of intimal smooth muscle cells and decrease in collagen result in fragility of the plaque and subsequent plaque rupture. Thrombus formation with plaque rupture causes acute vascular occlusion. The above vascular smooth muscle cell dysfunctions are involved in the progression of atherosclerosis and acute ischemia of the lower extremities associated with diabetes.

#### 6.3.8.2.3 Platelet Dysfunction

Platelets are involved in thrombus formation and hemostasis. The glucose uptake into platelets is insulin-independent, and thus, the intra-platelet glucose concentration reflects the blood glucose level. Consequently, the DAG-PKC pathway is activated, NO production is attenuated, and oxidative stress is increased in the platelets of patients with diabetes. Disorder of the intra-platelet $Ca^{2+}$ homeostasis causes deformities of platelets and abnormalities in their aggregation and thromboxane $A_2$

production in diabetics. In addition, the expression of plasmalemmal glycoprotein Ib and glycoprotein IIb/IIIa is augmented in the platelets of diabetic patients, and therefore, the collagen binding via von Willebrand factor and subsequent fibrinogen binding are increased. Furthermore, the production of prostacyclin and NO in endothelial cells is attenuated in diabetics, and this also contributes to the increase in aggregability of the platelets in diabetic patients. The above abnormalities in platelets are involved in thrombus formation and acute ischemia at loci of plaque rupture in diabetics (Beckman et al. 2002; Marso and Hiatt 2006).

#### 6.3.8.2.4 Abnormal Coagulability

The suppression of blood fibrinolysis due to activation of plasminogen activator inhibitor type 1 (PAI-1), augmentation of the expression of tissue factor and factor VII, and attenuation of the expression of anticoagulants, such as antithrombin III and protein C, have been demonstrated in patients with diabetes. These abnormalities in the coagulation-fibrinolysis balance cause a hyper-coagulation state, which is involved in the progression of atherosclerosis in patients with diabetes (Beckman et al. 2002).

#### 6.3.8.2.5 Diabetic Foot

As mentioned above, the vascular disorders associated with diabetes are classified into macroangiopathies and microangiopathies. While PAD is classified as a diabetic macroangiopathy, microangiopathies, disorders in arterioles and capillaries, are also involved in the pathogenesis of diabetic foot. Diabetic foot is a complication of diabetes showing skin lesions including dryness of the foot skin, an increase in keratinization, complication with trichophytosis, paronychia, phlegmon, and ulcers. The terminal stage of diabetic foot is gangrene of the foot, for which lower limb amputation is needed as a therapy. Diabetic foot is observed in 15 % of patients with diabetes, and the risk for limb amputation was reportedly 40 times higher in PAD patients with diabetes than in PAD patients without diabetes (Akbari and LoGerfo 1999). Diabetic foot ulcers, in which foot ischemia due to PAD is deeply involved, have been reported to be a cause of 85 % of cases of lower limb amputation in patients with diabetes (Boulton 2008; Moxey et al. 2011). In fact, the prevalence of PAD was reportedly about 50 % in patients with diabetic foot ulcers (Hinchliffe et al. 2012). Moreover, an intervention trial using revascularization therapy against diabetic foot ulcers in patients with PAD resulted in a significant reduction in the frequency of lower limb amputation (Hinchliffe et al. 2012). Therefore, both micro- and macrovascular diseases are thought to contribute to the pathogenesis of diabetic foot ulcers.

Although the detailed pathophysiological mechanism of diabetic foot is unknown, microvascular dysfunction, peripheral nerve abnormalities, and infections are thought to be involved in the mechanism. The microvascular dysfunction in diabetic patients is caused by an increase in the vascular permeability of arterioles and capillaries and by the attenuation of the autoregulation function of blood flow (Akbari and LoGerfo 1999). An increased thickness of the capillary basement membrane is induced by activation of the polyol pathway, PKC activity abnormalities, increased oxidative stress, and activation of the AGE-RAGE system due to hyperglycemia

(Akbari and LoGerfo 1999). Consequently, the vascular permeability is increased, while neither stenosis nor occlusion is induced, and the blood flow is not changed or may be increased. Vulnerability to infections occurs in diabetic patients due to the impairment of leukocyte migration and a hyperemic response resulting from the thickened basement membrane of blood vessels (Jörneskog et al. 1995).

The decrease in the neurogenic vasodilatory response due to nerve dysfunction is also involved in the onset and progression of diabetic foot. Peripheral nerve disorders have been shown to be found in 50–60 % of patients with diabetes (Dyck et al. 1993) and in 80 % of diabetic patients with foot ulcers (Caputo et al. 1994). Diabetic neuropathy is thought to be caused by chronic hypoxia resulting from metabolic disorders and circulatory abnormalities in the peripheral nerve. Activation of the polyol pathway increases the intracellular osmolarity by elevating the sorbitol concentration in neuronal cells, which is compensated by a decrease in the intracellular myo-inositol content, resulting in functional disorder and damage to neurons due to abnormalities in phosphoinositide metabolism and $Na^+/K^+$ ATPase activity, resulting in a decrease in the nerve transmission velocity (Greene et al. 1987; Pfeifer and Schumer 1995). In the skin, an axon reflex is induced through nociceptive C fibers in response to pain stimulation and triggers the release of substance P and calcitonin gene-related peptide, which act directly on blood vessels to induce vasorelaxation and increase the vascular permeability (Aronin et al. 1987). Similar vascular responses are induced by histamine released from mast cells in response to substance P and calcitonin gene-related peptide. In diabetics, a dysfunction in the C fibers causes a decrease in the axon reflex, followed by attenuation of the neurogenic vasodilatory response (Akbari and LoGerfo 1999).

In summary, diabetic foot is thought to be due to functional microvascular impairment, an increased vulnerability to infection, and attenuation of the neurogenic vasodilatory response in arterioles and capillaries.

### 6.3.9 Chronic Kidney Disease (CKD)

CKD is a known risk factor for cardiovascular disease, which strongly influences the mortality of patients with CKD. The mortality due to cardiovascular disease has been shown to be 10–30 times higher in dialysis patients than in the general population (Sarnak et al. 2003). The rate of nontraumatic lower limb amputation was reportedly ten times higher in diabetic subjects with end-stage renal disease (ESRD) than in those without ESRD, and most of the cases of lower limb amputation were due to PAD (Eggers et al. 1999). Thus, ESRD was suggested to be associated with PAD. Recent epidemiological studies using the symptom of intermittent claudication or ABI for the diagnosis of PAD have demonstrated that the existence of CKD is significantly associated with the risk of PAD, as well as the risks of other atherosclerotic diseases (O'Hare 2005; Shlipak et al. 2002). In the National Health and Nutrition Examination Survey, the crude odds ratio for PAD in subjects with renal insufficiency vs. subjects with normal renal function was 9.7 (CI: 5.6–16.7), and the odds ratio after adjustment for potential

confounders, such as age, gender, race, comorbid conditions (including diabetes, coronary artery disease, stroke, and hypertension), BMI, total cholesterol, blood pressure, and smoking history was 2.5 (CI: 1.2–5.1), which remained significant (O'Hare et al. 2004). Therefore, CKD may be an independent risk factor for PAD, although patients with renal insufficiency are more prone to have other cardiovascular risk factors, such as diabetes and hypertension, than those with normal renal function.

Although CKD is thought to be a risk factor for PAD based on the previous epidemiological findings, it remains to be clarified how CKD is involved in the pathogenesis of PAD. Renal insufficiency has been shown to be associated with the risk of atherosclerotic disease through various mechanisms, including the development of metabolic disorders, chronic inflammation, and a hypercoagulation status. Secondary hyperparathyroidism, a metabolic disorder in patients with renal failure, is characterized by high phosphate and low calcium levels in the blood due to a decrease in vitamin D activity, and this causes general ectopic calcification (Cunningham et al. 2011). Calcification also occurs in atherosclerotic lesions in the vascular endothelium and media and causes an increase in arterial stiffness, which contributes to atherosclerotic progression by increasing the cardiac afterload and elevating the pulse pressure. Patients with CKD, especially patients with ESRD, have been reported to show high homocysteine and lipoprotein(a) levels in the blood (DeLoach and Mohler 2007), which are risk factors of atherosclerosis. Chronic inflammation is prone to be induced by uremia, malnutrition, and hypoalbuminemia, as well as dyslipidemia complicated with CKD (Schiffrin et al. 2007). Malnutrition and hypoalbuminemia cause decrease in antioxidant capacity. The blood levels of inflammatory mediators, such as C-reactive protein, fibrinogen, IL-6, TNF-α, factor VIIc, factor VIIIc, D-dimer, E-selectin, VCAM-1, and ICAM-1, have been shown to be elevated in 30–50 % of patients with CKD (Schiffrin et al. 2007). Thus, the chronic inflammatory response is thought to be involved in the complication of cardiovascular disease in patients with CKD through the increase in oxidative stress and vascular endothelial damage. Further investigations are needed to clarify whether other specific mechanism(s) exists to explain the causal relationship between CKD and PAD.

### 6.3.10 Inflammatory Markers

Inflammation is known to be involved in the pathophysiology of atherosclerotic progression at various stages of cardiovascular disease, in particular, coronary artery disease. There have also been recent epidemiological studies on the association between PAD and inflammation, as described below.

In the National Health and Nutrition Examination Survey (1999–2002), the odds ratio for PAD was shown to be higher in the highest quartile of each inflammatory marker, such as CRP, fibrinogen, and the leukocyte count, than in the lowest quartile (Selvin and Erlinger 2004; Wildman et al. 2005). In a

prospective study with a 60-month following-up of 144 healthy males, the blood CRP level at baseline was shown to be significantly higher in symptomatic PAD patients showing intermittent claudication or in patients receiving angioplasty therapy compared with subjects without PAD (mean CRP (mg/L): 1.34 [with PAD] vs. 0.99 [without PAD]), and the relative risk (RR) for PAD tended to be higher with an increase in the quartile of CRP (RR: 1.0 [1st quartile], 1.3 [2nd quartile], 2.0 [3rd quartile] vs. 2.1 [4th quartile], $p = 0.02$) (Ridker et al. 1998). The blood concentrations of proinflammatory molecules, such as IL-1 receptor antagonist, fibrinogen, CRP, and cellular adhesion molecules (VCAM-1, ICAM-1, E-selectin, and P-selectin), have been shown to be higher in patients with PAD than in those without PAD (McDermott et al. 2005; Silvestro et al. 2005; Brevetti et al. 2006). The above findings suggest the involvement of inflammatory responses in the pathogenesis of PAD, as well as in the pathogenesis of coronary artery disease.

### 6.3.11 Homocysteinemia

Homocysteinemia is an independent risk factor for cardiovascular disease and is known to induce atherosclerosis by affecting various types of cells, including vascular endothelial cells and smooth muscle cells. A recent random effect meta-analysis using 14 studies performed from 1989 to 2007 showed that the blood homocysteine levels (normally 3–15 μmol/L) were higher by 4.31 (95 % CI: 1.71–6.91) μmol/L in patients with PAD than in the control subjects without PAD (Khandanpour et al. 2009b). Homocysteinemia causes endothelial injury by decreasing the number of endothelial cells due to cell death and attenuated proliferation capacity (Tsai et al. 1994) and through decreases in endothelium-derived NO production and NO bioavailability due to increased ROS production (Steed and Tyagi 2011). Homocysteine also causes an attenuation of the relaxation mediated by endothelium-derived hyperpolarizing factor (EDHF), which is suggested to result from decreases in the activity of $Ca^{2+}$-activated potassium channels ($K_{Ca}$), especially the small-conductance $K_{Ca}$ channel (SK) and intermediate-conductance $K_{Ca}$ channel (IK), due to increased ROS production and tyrosine nitration (Lang et al. 2000; Cheng et al. 2011). Moreover, homocysteine has been shown to induce vascular smooth muscle cell proliferation and inflammatory responses. Increased expression levels of the RAGEs, VCAM-1, tissue factor, and MMP-9 through an increase in NFκB expression has been demonstrated in the vascular tissues of patients with homocysteinemia (Hofmann et al. 2001; Steed and Tyagi 2011). A randomized controlled trial investigating the effects of homocysteine-lowering therapy has shown an elevation of the ABI and prolongation of the pain-free walking distance following the administration of folic acid in patients with PAD (Carrero et al. 2005; Khandanpour et al. 2009a). The levels of inflammatory mediators have been reported to be decreased by supplementation with folic acid (Zhou et al. 2011). However, further studies are needed to confirm the effectiveness of homocysteine-lowering intervention therapy for the reduction of cardiovascular risk.

**Table 6.2** Grading of recommendations defined by the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC)

| Grade | Recommendations |
|---|---|
| A | Based on the criterion of at least one randomized, controlled clinical trials as part of the body of literature of overall good quality and consistency addressing the specific recommendation |
| B | Based on well-conducted clinical studies but no good quality randomized clinical trials on the topic of recommendation |
| C | Based on evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities (i.e., no applicable studies of good quality) |

Recommendations and selected statements are rated according to guidance issued by the Agency for Healthcare Research and Quality. Note that the grade of recommendation is based on the level of available evidence and does not necessarily relate to the clinical importance

**Table 6.3** Grading of recommendations defined by American College of Cardiology (ACC)/American Heart Association (AHA)

| Class | Recommendations |
|---|---|
| Class I | Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective |
| Class II | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment |
| Class IIa | Weight of evidence/opinion is in favor of usefulness/efficacy |
| Class IIb | Usefulness/efficacy is less well established by evidence/opinion |
| Class III | Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful |

## 6.4 Secondary Prevention of PAD

PAD is an independent risk factor for various cardiovascular events. Therefore, modification of the risk factors for PAD not only prevents the progression of PAD but also contributes to lowering of the cardiovascular disease mortality. Evidence-based risk modification of PAD, introduced in the ACC/AHA guidelines for the management of PAD and the TASC I and II, includes aggressive lifestyle changes and aims to improve the functional disorder and QOL of patients by medical therapy and to decrease the morbidity and mortality due to cardiovascular disease. The criteria for grades and classes of recommendations defined by the TASC and ACC/AHA guidelines are summarized in Tables 6.2 and 6.3, respectively.

### 6.4.1 Lipid-Lowering Agents

TASC II recommends management of blood lipid levels by drugs represented by statin (hydroxymethylglutaryl coenzyme-A reductase inhibitor) as follows:

1. The blood LDL cholesterol level in symptomatic PAD patients should be lower than 100 mg/dL (Grade A).
2. The blood LDL cholesterol level in PAD patients with a history of other cardiovascular diseases (e.g., coronary artery disease) should be lower than 70 mg/dL (Grade B).

3. Dietary modification should be an initial intervention for management of blood lipid levels (evidence level B).
4. The blood LDL cholesterol in asymptomatic PAD patients without a history of other cardiovascular diseases should be lower than 100 mg/dL (Grade C).

The above (1) and (2) are also recommended in the ACC/AHA guidelines as class I and class IIa. Although it remains to be clarified how lipid-lowering agents improve the risk of PAD at present, management of the blood lipid levels is important for risk modification of PAD and has been reported to improve the walking distance, repair the arterial structure and function, and prevent cardiovascular events and death in PAD patients. However, in a survey of 34,157 patients with PAD, lipid-lowering agents were reportedly administered to only 45 % of the patients (Flu et al. 2010). Therefore, an increase in the intervention rate is expected to retard the progression of PAD and lower the cardiovascular disease-related mortality.

### 6.4.2 Antihypertensive Drugs

Hypertension is a risk factor for PAD, and the TASC II recommends the management of blood pressure as follows:

1. The blood pressure in patients with a history of atherosclerotic diseases including symptomatic PAD should be lower than 140/90 mmHg. In addition, when the patients also suffer from diabetes or renal insufficiency, the blood pressure should be lower than 130/80 mmHg (Grade A).
2. In order to prevent cardiovascular events, angiotensin-converting enzyme (ACE) inhibitors are recommended as antihypertensive drugs for the initial treatment for patients with symptomatic PAD (Grade B).
3. β-adrenergic blocking drugs are not contrarily indicated for patients with PAD (Grade A).

In the ACC/AHA guidelines, the above (1) and (3) are recommended as class I, and the above (2) is recommended as class IIa. ACE inhibitors are recommended for asymptomatic PAD patients as class IIb in the ACC/AHA guidelines. In a survey of the intervention rate for the secondary prevention, only 46 % of PAD patients with hypertension were reportedly receiving antihypertensive therapy (Flu et al. 2010).

### 6.4.3 Antiplatelet Drugs

Aspirin/acetylsalicylic acid (ASA) is a well-known drug used for secondary prevention. The TASC II recommends antiplatelet therapy for patients with PAD as follows:

1. Irrespective of the history of other cardiovascular diseases, the long-time administration of antiplatelet drugs to all symptomatic patients is recommended for reducing the cardiovascular morbidity and mortality (Grade A).
2. The administration of aspirin/ASA is effective for PAD patients with other cardiovascular diseases such as coronary artery disease and stroke (Grade A).

3. Aspirin/ASA administration can be considered for PAD patients without other cardiovascular diseases such as coronary artery disease and stroke (Grade C).
4. Irrespective of a history of other cardiovascular diseases, the administration of clopidogrel to symptomatic PAD patients is effective to reduce cardiovascular events (Grade B).
5. The administration of cilostazol for 3–6 months as a first-line pharmacotherapy for PAD patients with intermittent claudication is effective for improving the treadmill exercise performance, as well as the quality of life (Grade A).
6. Naftidrofuryl is useful as a drug for the treatment of intermittent claudication in PAD patients (Grade A).

The above (1), (2), (4), and (5) are recommended as class I in the ACC/AHA guidelines.

According to the intervention search of secondary prevention measures, 63 % of PAD patients were receiving antiplatelet therapy for the purpose of reduction of cardiovascular events, and cardiovascular morbidity and mortality are improved by continuous administration of antiplatelet drugs (Flu et al. 2010).

### 6.4.4 Therapy for Diabetes

Hyperglycemia and insulin resistance are important independent risk factors for the onset of PAD, and the risk of PAD onset has been shown to be increased three to four times by complication with diabetes. Previous epidemiological studies have demonstrated that the onset of diabetic microangiopathy can be prevented by aggressive blood glucose lowering (Gaede et al. 2003). On the other hand, there has been no confirmed evidence of the effectiveness of blood glucose lowering to prevent the onset of diabetic macroangiopathies including PAD. In the TASC II and ACC/AHA guidelines, therapies for diabetes in patients with PAD are recommended only as follows:

1. Blood glucose-lowering therapy for PAD patients with diabetes is recommended to achieve HbA1c levels of <7.0 % (Grade C in the TASC II and Class IIa in the ACC/AHA guidelines) or HbAlc levels of as close to 6.0 % as possible (Grade C in the TASC II).

In fact, 81 % of PAD patients with diabetes were receiving intervention using blood glucose-lowering agents (Flu et al. 2010). In the United Kingdom Prospective Diabetes Study (UKPDS), which was performed in order to survey the influence of blood glucose level management on the angiopathy of patients with diabetes, the risk of microvascular complications was reduced by oral blood glucose-lowering drugs or insulin injection, while these intervention therapies did not affect the incidence of macroangiopathy (Dormandy et al. 2005). In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial treating 11,140 patients with diabetes, the risk of major macrovascular complications, including fatal cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke, during a 5-year follow-up was shown to be decreased by 10 % in the group receiving aggressive blood glucose control (HbA1c<6.5 %) compared with the group receiving standard blood glucose control (HbA1c<7.3 %), while the risk of PAD was comparable between these groups (ADVANCE Collaborative Group 2008).

In addition to hyperglycemia, insulin resistance is known to be deeply involved in the pathophysiology of atherosclerotic disease in patients complicated with diabetes. Metformin, an antidiabetic drug, improves the insulin sensitivity and inhibits gluconeogenesis in the liver by activating AMP-activated protein kinase (AMPK) by increasing its phosphorylation. In the UKPDS, the incidence of macrovascular events in patients with diabetes was shown to be decreased by the administration of metformin, whereas the incidence was increased by combination therapy using metformin and sulfonylurea. Thus, the merit of metformin for macrovascular events has not yet been confirmed (Dormandy et al. 2005).

Thiazolidinediones (TZDs) cause the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), which results in the improvement of insulin sensitivity as a result of its inhibition of cytokine production and due to its augmentation of adiponectin production in adipocytes. By this anti-inflammatory action, TZDs are expected to inhibit the onset of atherosclerotic diseases. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive study), the incidence of major macrovascular events, including myocardial infarction, acute coronary syndrome, and stroke, was reported to be decreased by treatment with TZDs, while no beneficial effects of TZDs were obtained for the incidence of PAD (Dormandy et al. 2005).

Various mechanisms, e.g., activation of the DAG-PKC pathway, activation of the polyol pathway, and cell damage by AGEs/RAGE, are known to be involved in the pathogenesis of atherosclerotic disease complicated with diabetes. The clinical use of PKCβ inhibitors and AGE inhibitors developed for the prevention of diabetic angiopathy is expected to provide benefits for patients.

### 6.4.5 Smoking Cessation

Smoking, as well as diabetes, is an independent major risk factor for the onset and progression of PAD. The TASC II recommended that PAD patients should quit smoking as follows:

1. Smoking cessation should be strongly and repeatedly recommended for all PAD patients with a smoking habit (Grade B).
2. All PAD patients with a smoking habit should receive a program including a physician's advice, group counseling sessions, and nicotine replacement therapy to help them quit smoking (Grade A).
3. The success rate of smoking cessation is increased by the addition of an antidepressant treatment and nicotine replacement (Grade A).

As mentioned above, smoking is involved in both the onset and progression of PAD as a result of vascular endothelial cell injury due to increased oxidative stress, disorders of lipid metabolism and abnormalities in the blood coagulation-fibrinolysis balance. In addition, the blood levels of antioxidative vitamins, such as vitamins C and E, are lower in smokers than in nonsmokers, and these differences are associated with a reduction of dietary vitamin intake and consumption of vitamins by smokers. A prevention of vitamin deficiencies is therefore expected to result from the cessation of smoking.

Smoking cessation has been reported to improve the symptoms of intermittent claudication and to prevent the progression of ischemia-induced foot ulcers in patients with PAD, suggesting the importance of smoking cessation as part of the therapy for PAD. However, a smoking cessation program has been reported to be provided for only 39 % of patients with PAD. In the future, it will be necessary to establish evidence-based methods to successfully quit smoking and to spread public health education about smoking.

## 6.5 Summary and Perspectives

PAD is an atherothrombotic disease. Patients with PAD show an increased risk of cardiovascular disease, and early discovery and prevention of PAD are thought to contribute to a decrease in future cardiovascular death in patients complicated with PAD. There are many common risk factors for both PAD and other atherosclerotic diseases including coronary artery disease. In particular, ageing, smoking, and diabetes are strongly associated with PAD. However, the loci of frequent vascular lesion are known to be different in smokers and patients with diabetes, suggesting the existence of unknown specific pathophysiological mechanisms underlying the PAD caused by each of these risk factors. The identification of PAD-specific genes has recently been an attractive strategy to assess risk factors, but it remains to be clarified whether and how gene-environmental interactions are involved in the pathogenesis of PAD. The morbidity of PAD is predicted to further increase in the future due to the ageing of society and numerous lifestyle-related factors, and modification of the risk factors for PAD is necessary to prevent PAD and decrease mortality from cardiovascular disease.

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# Venous Thromboembolism: Deep Vein Thrombosis and Pulmonary Embolism

7

Thomas Gary and Marianne Brodmann

**Abstract**

Venous thromboembolism, namely, deep vein thrombosis and pulmonary embolism, are potentially life-threatening diseases requiring immediate exploration and anticoagulant therapy even when awaiting diagnostic procedures. Although awareness is increasing the all-cause mortality after 3 months associated with acute PE is up to 17 % as was shown in worldwide registries. To assure correct diagnosis of venous thromboembolism, clinical probability assessment usually with scoring systems like the Wells score is of importance. Recently novel oral anticoagulant drugs have been investigated as an alternative to the so far standard therapy with heparin treatment in the acute setting (or awaiting diagnostic results) followed by vitamin K antagonists. Those novel anticoagulant drugs are directed against thrombin or factor Xa and are currently under investigation for the treatment and prophylaxis of venous thromboembolism. However, in some patients, anticoagulant treatment might be impossible due to active bleeding or other absolute contraindications. In these patients, a transient interruption of the inferior vena cava with a vena cava filter device might be indicated to avoid life-threatening recurrence of pulmonary embolism.

This chapter will give the reader a brief overview of correct diagnosis, current treatment possibilities, and possible complications of venous thrombosis and pulmonary embolism.

**Keywords**

Venous thromboembolism • Deep vein thrombosis • Pulmonary embolism • Compression ultrasound • Anticoagulant therapy • Inferior vena cava filter • Chronic thromboembolic pulmonary hypertension

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## 7.1 Introduction

Pulmonary embolism (PE) is the third most common cause of death from cardiovascular disease after heart attack and stroke and originates from deep venous thrombosis (DVT). DVT is defined as blood clotting in the lower limb veins. In rare cases, venous thrombosis can occur in the upper extremity leading to upper extremity venous thrombosis. The entities DVT and PE are summarized as venous thromboembolism (VTE) and are nowadays interpreted as one disease. Treatment in VTE patients includes anticoagulation and compression therapy in case of DVT and anticoagulation and in rare cases fibrinolytic therapy or even embolectomy for PE patients. Patients with PE should therefore undergo risk stratification to establish whether they will benefit from the addition of such treatment.

## 7.2 Epidemiology

In the International Cooperative Pulmonary Embolism Registry (Goldhaber et al. 1999), all-cause mortality rate at 3 months associated with acute PE was 17 %. This registry enrolled more than 2,400 consecutive patients from 52 hospitals in seven countries in Europe and North America. PE was considered to be the cause of death in 45 % of patients. Important prognostic factors associated with death from PE were age older than 70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, systolic arterial hypotension, tachypnea, and right ventricular hypokinesis on echocardiography.

Slightly lower was the mortality rate in the Worcester pulmonary embolism study. In this study conducted in the Massachusetts metropolitan area, patients presenting with PE from the outpatient setting had an all-cause mortality rate of 11.1 % at 90 days (Spencer et al. 2010). However, some estimates of case fatality rate are lower. For example, in the Registry of Patients with Venous Thromboembolism (RIETE) 7 of 6,264 patients with PE, the cumulative overall mortality rate was 8.6 % at 3 months and the case fatality rate was 1.7 %. Although some studies report low rates of short-term mortality, long-term mortality associated with acute PE seems to be high (Laporte et al. 2008).

## 7.3 Diagnosis

### 7.3.1 Clinical Probability Assessment

Diagnosis of VTE is dependent on several, mainly noninvasive, diagnostic techniques that should be used sequentially. Massive PE should be diagnosed quickly; its clinical features include shock or hemodynamic instability. Clinical probability assessment aims to identify patients with a high or intermediate clinical probability who need anticoagulant treatment while awaiting the results of diagnostic tests. In patients with a low clinical probability, the diagnosis of VTE can be ruled out solely with a normal D-dimer test (Fig. 7.1). Clinical probability incorporates clinical

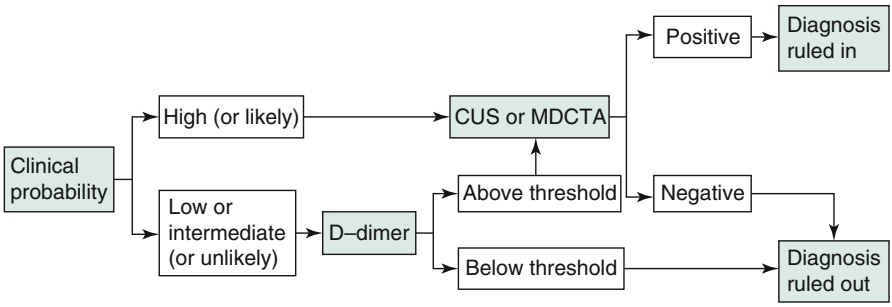


**Fig. 7.1** A diagnostic algorithm for clinically suspected pulmonary embolism

history (including personal and familial features) and symptoms, signs, and abnormalities of oxygen saturation, chest radiography, and electrocardiography. The probability can be assessed best by scoring systems.

For suspected PE, two scores are widely used: the Wells score (Wells et al. 2000) and the revised Geneva score (Le Gal et al. 2006) (Table 7.1).

The Wells score for DVT (Table 7.1) divides patients at low risk (score 0), from those with intermediate risk (score 1 and 2), and patients with high risk (score >3). As lined out in Table 20.1, this score consists of comorbidities with a high VTE risk (e.g., cancer) and clinical findings, such as swelling of the leg.

The Wells score for PE is now mostly used with a cutoff of four points (van Belle et al. 2006), which allows a dichotomous classification of likely or unlikely PE. According to a meta-analysis (Ceriani et al. 2010) of the performance of all available clinical prediction rules for suspected PE, these rules have similar accuracy, but are not totally equivalent. The choice among various prediction rules and classification schemes should be guided by the local prevalence of PE, the type of patients being assessed (outpatients or inpatients), and the type of D-dimer assay used. For example, the revised Geneva score should be used in populations with a prevalence of PE of more than 20 %, whereas the Wells score is the only validated score for patients admitted to hospital. The results of arterial blood gas oxygen saturation, electrocardiography (ECG), and chest radiography have low sensitivity and specificity for the diagnosis of PE and are incorporated in neither the Wells nor the revised Geneva score. Conversely, ECG might be useful to exclude PE (and, e.g., to suggest acute coronary syndrome), but chest radiography and arterial blood gas saturation should not be used routinely.

### 7.3.2 Compression Ultrasonography for Diagnosing Deep Vein Thrombosis

For suspected PE, diagnosis of proximal DVT in a symptomatic patient, or in an asymptomatic patient who has contraindications to CT angiography, is considered sufficient to rule in PE. Nowadays compression ultrasound (CUS) has replaced venography as the main imaging procedure for DVT diagnosis. Mainly complete CUS is used in clinical praxis. This approach leads to a DVT evaluation in the proximal deep veins

**Table 7.1** Scoring systems to assess probability of suspected VTE

| | Points |
|---|---|
| *Wells score for DVT* | |
| Cancer | +1 |
| Paralysis or recent plaster cast | +1 |
| Bed rest >3 days or surgery <4 weeks | +1 |
| Pain or palpation of deep veins | +1 |
| Swelling of entire leg | +1 |
| Diameter difference on affected calf >3 cm | +1 |
| Pitting edema (affected side only) | +1 |
| Dilated superficial veins (affected side) | +1 |
| Alternative diagnosis at least as probable as DVT | −2 |
| *Wells score for PE* | |
| Previous PE or DVT | +1.5 |
| Heart rate >100 beats per min | +1.5 |
| Recent surgery or immobilization | +1.5 |
| Clinical signs of DVT | +3 |
| Alternative diagnosis less likely than PE | +3 |
| Hemoptysis | +1 |
| Cancer | +1 |
| *Revised Geneva score for PE* | |
| Age >65 years | +1 |
| Previous DVT or PE | +3 |
| Surgery (under general anesthesia) or fracture (of the lower limbs) within 1 month | +2 |
| Active malignancy (solid or hematological malignancy, currently active or considered as cured since less than 1 year) | +2 |
| Unilateral leg pain | +3 |
| Hemoptysis | +2 |
| Heart rate 75–94 beats per min | +3 |
| Heart rate ≥95 beats per min | +5 |
| Pain on deep vein palpation in leg and unilateral edema | +4 |

and in the calf veins as well. Recent guidelines (Kearon et al. 2012) recommend against the treatment of isolated calf vein thrombosis in asymptomatic patients. However, to the authors' opinion, the apperception of pain might be different from patient to patient. So in case of doubt of the patient's apperception of DVT-related pain, anticoagulation should be initiated as would be in a patient with symptomatic distal DVT.

With CUS usually only DVT of the lower extremity can be evaluated without proper assessment of pelvic veins or the inferior vena cava (IVC). For these regions difficult to detect by CUS magnetic resonance (MR) venography is a useful tool for further exploration (see Sect. 22.3.4).

### 7.3.3 Multidetector CT Angiography for Diagnosing Pulmonary Embolism

CT angiography (Fig. 7.2) has largely replaced ventilation–perfusion (V/Q) lung scintigraphy as the main imaging modality in suspected PE. Single-detector CT angiography has a sensitivity of only about 70 % (Perrier et al. 2001) and needs

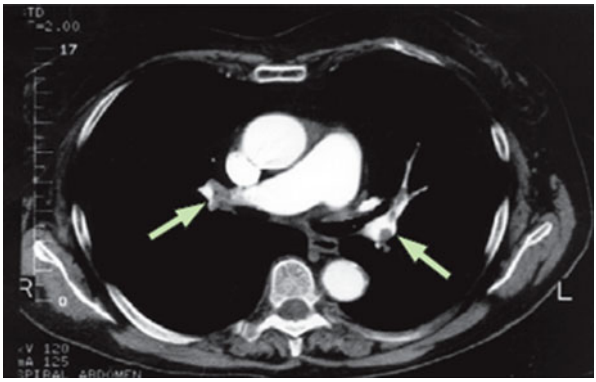

**Fig. 7.2** CT angiography showing several thrombi (*arrows*) in the main right pulmonary artery and in the left lobar and segmental arteries

combination imaging with CUS of the proximal veins of the leg if negative. Multidetector CT angiography is more sensitive than single-detector CT angiography (van Belle et al. 2006). This technological advance allows exclusion of PE without additional CUS of the leg (Righini et al. 2008).

### 7.3.4 Alternative Diagnostic Imaging Modalities for Suspected Deep Vein Thrombosis and Pulmonary Embolism

Gadolinium-enhanced magnetic resonance pulmonary angiography (MRA) could be used to diagnose PE because it is devoid of radiation. The accuracy of this technique combined with magnetic resonance venography (MRV) has been studied in the prospective, multicenter PIOPED III accuracy study (Stein et al. 2010). The proportion of technically inadequate images ranged from 11 to 52 % across the seven participating centers. Technically adequate MRA had a sensitivity of 78 % and a specificity of 99 %, whereas technically adequate MRA and MRV had a sensitivity of 92 % and a specificity of 96 %. However, 194 (52 %) of 370 patients had technically inadequate results, which substantially restricts its clinical use.

Conventional pulmonary angiography and venography remain the gold standards for diagnosis of PE and DVT, respectively. Because these exams are invasive, they should be restricted to patients in whom a clinically likely diagnosis cannot be confirmed by other means or in whom endovascular treatment of PE is being considered.

## 7.4 Treatment

### 7.4.1 Prognostic Stratification of Patients with Pulmonary Embolism

The initial treatment of DVT and PE consists of anticoagulation. However, DVT alone is not a life-threatening condition, but patients with PE should be stratified according to prognosis (Roy et al. 2005). The Pulmonary Embolism Severity Index (Aujesky et al. 2005) and its simplified version (Jimenez et al. 2010) allow such

**Table 7.2** Prognostic stratification of PE

| | Points |
|---|---|
| *Pulmonary Embolism Severity Index* | |
| Age >80 years | Age in years |
| Male sex | +10 |
| History of cancer | +30 |
| History of heart failure | +10 |
| History of chronic lung disease | +10 |
| Heart rate ≥110 beats per min | +20 |
| Systolic blood pressure <100 mmHg | +30 |
| Respiratory rate ≥30 breaths per min | +20 |
| Temperature <36 °C | +20 |
| Altered mental status | +60 |
| Arterial oxygen saturation <90 % | +20 |
| *Simplified Pulmonary Embolism Severity Index according to RIETE* | |
| Age >80 years | +1 |
| History of cancer | +1 |
| History of heart failure or chronic lung disease | +1 |
| Heart rate ≥110 beats per min | +1 |
| Systolic blood pressure <100 mmHg | +1 |
| Arterial oxygen saturation <90 % | +1 |

stratification on a clinical basis (Table 7.2). Several therapeutic implications exist for patients with PE: (1) high-risk patients (who represent about 5 % of all symptomatic patients, with about a 15 % short-term mortality) should be treated aggressively with thrombolytic drugs or surgical or catheter embolectomy (Kucher et al. 2006); (2) low-risk patients (most patients with PE) with a short-term mortality of about 1 % might benefit from early discharge or even outpatient treatment (Aujesky et al. 2011); and (3) intermediate-risk patients (who represent about 30 % of all symptomatic patients) should probably be admitted to hospital, with potential benefit of thrombolytic treatment. Low-risk and intermediate-risk categories are referred to as non-massive PE. Echocardiography or measurement of biomarkers, such as troponin or pro-brain natriuretic peptide, might refine prognostic stratification, but whether their addition to the risk stratification workup is cost-effective remains to be established.

### 7.4.2 Standard Treatment of VTE

Treatment of non-massive VTE has three phases: the initial phase, the early maintenance phase, and the long-term secondary prevention phase. Low-molecular-weight heparin and fondaparinux are the cornerstones of initial treatment for patients with VTE (Kearon et al. 2008). Heparins act by binding to the natural anticoagulant antithrombin, thereby substantially accelerating the inactivation of thrombin by antithrombin and of several other activated coagulation factors (including activated factor *X* [FXa]). Unfractionated heparin is usually administered as an initial bolus,

followed by a continuous intravenous infusion. Because of a large individual difference in the binding of heparins to plasma proteins, the doses should be adjusted to the results of blood tests, such as the activated partial thromboplastin time or the anti-FXa activity.

The main advantage of low-molecular-weight heparins is that they can be administered subcutaneously in fixed weight-adjusted doses without needing monitoring in most cases. The mechanism of action of these heparins is similar to that of unfractionated heparin, but with a more pronounced effect on FXa compared with thrombin. The clinical equivalence of low-molecular-weight heparin and unfractionated heparin for treating DVT has been confirmed in a meta-analysis (Gould et al. 1999). One study confirmed this conclusion for PE (Simonneau et al. 1997). Fondaparinux, a pentasaccharide, is almost identical to the smallest natural component of heparin that can still bind to antithrombin to specifically inhibit FXa. By contrast with unfractionated heparin and low-molecular-weight heparins, which are derived from the porcine intestinal tract, fondaparinux is a synthetic compound. This drug is noninferior to low-molecular-weight and unfractionated heparin in patients with DVT and PE (Buller et al. 2003), respectively.

Low-molecular-weight heparin and fondaparinux are mainly cleared by the kidney. Particular caution is advised when the calculated creatinine clearance is less than 30 mL/min. In such cases, anticoagulation options include dose reduction, increase of the interval between injections, monitoring of FXa activity, or use of unfractionated heparin. Administration of heparins or fondaparinux should overlap during at least 5 days with that of vitamin K antagonists. The parenteral drug can be stopped when the anticoagulant concentration induced by the vitamin K antagonist has reached an international normalized ratio of 2.0. Patients with cancer have been recommended to be treated for at least 3 months with low-molecular-weight heparin rather than with vitamin K antagonists (Kearon et al. 2008). These antagonists block a late step in the biosynthesis of four plasma coagulation factors (prothrombin or factor II and factors VII, IX, and X) by the liver. Because of the different half-lives of circulating factors, steady-state anticoagulation cannot be reached before 4–7 days. Vitamin K antagonists include substances with a short (acenocoumarol), intermediate (warfarin), or long (phenprocoumon) half-life. For this reason, and because of genetically induced metabolic variability, the variable vitamin K content of food, a narrow therapeutic index, and several interactions with other drugs, treatment with vitamin K antagonists needs close monitoring with the international normalized ratio; the targeted therapeutic level is 2.5 (range 2.0–3.0).

### 7.4.3 Treatment Duration After VTE

The duration of anticoagulation treatment should be dictated by the balance between the risk of recurrent VTE with and without treatment and the risk of treatment-induced hemorrhage. In the literature review that supports the treatment durations recommended by the 8th ACCP consensus guidelines, Kearon and

colleagues (2008) reported that a 3-month course of anticoagulant treatment was as effective as a course of 6–12 months and that VTE related to transient (reversible) risk factors (e.g., surgery, trauma) is associated with a reduced risk of recurrence.

The decision about the optimum duration of anticoagulation can be approached on an individual basis that recognizes clinical variables (Le Gal et al. 2009), D-dimer concentration 1 month after stopping of anticoagulant treatment, or presence of residual thrombi in the leg veins. These potential methods have not gained widespread attention. At present, all patients with PE should be treated for at least 3 months. In case of a transient or reversible risk factor, especially if this risk factor was the clear precipitant of VTE, anticoagulant treatment might then be stopped. In patients with no triggering risk factor (the so-called idiopathic or unprovoked events), anticoagulant treatment should be continued as long as the benefit–risk balance is favorable, whereas patients with VTE and cancer should receive anticoagulant treatment until the cancer is considered under control and possibly cured.

### 7.4.4 Advances in Anticoagulant Treatment

Several new oral anticoagulant drugs are under development (Mavrakanas and Bounameaux 2011). These direct (i.e., antithrombin-independent) inhibitors of FXa (e.g., rivaroxaban, apixaban) or thrombin (e.g., dabigatran) avoid most of the drawbacks of heparin and could replace vitamin K antagonists and heparins in many patients. These drugs are administered in fixed doses, do not need coagulation monitoring in the laboratory, and have very few drug–drug or drug–food interactions.

## 7.5 Prophylaxis

To avoid VTE, prophylaxis with anticoagulants is recommended in situation with an elevated VTE risk. Findings from rigorous clinical trials have shown the effectiveness and safety of pharmacological prevention with low, fixed doses of anticoagulant drugs. For patients undergoing orthopedic surgery – e.g., total hip or knee replacement – novel oral anticoagulant drugs have been approved for thromboprophylaxis and are available instead of warfarin, heparins, and fondaparinux.

Mechanical prophylactic measures, including graduated compression stockings and intermittent pneumatic compression devices, should be considered in at-risk patients who are not candidates for pharmacological thromboprophylaxis. Inferior vena cava (IVC) filters can also be used for the primary and secondary prevention of PE, but they will not halt the thrombotic process (see Sect. 22.5). In the USA, use of IVC filters seems to have substantially increased for primary prevention of venous thromboembolism (Stein et al. 2011).

Although prophylaxis for VTE is mandated for moderate-risk and high-risk patients at the time of hospital admission (Geerts et al. 2008), the decision to continue prophylaxis after discharge remains difficult. The risk of VTE during admission usually does not change by the time a patient is ready for discharge home. During admission to the hospital, nurses and therapists encourage patients to ambulate, and thus, immobilization is minimized. Patients often receive less physical therapy after discharge than during admission, which leads to a paradoxical increase in immobility and a presumed rise in risk of VTE. Early hospital discharge minimizes the hospital length of stay but blurs the traditional concept of inpatient versus ambulatory care.

A contemporary approach to the prevention of VTE focuses on the continuum of care from hospital to the community. Thus, extended prophylaxis up to 5 weeks is recommended after total hip arthroplasty (Geerts et al. 2008). Findings from a review (Spencer et al. 2007) of 1,897 patients with venous thromboembolism in the Worcester, Massachusetts, health-care system showed that 74 % of patients suffered VTE in the outpatient setting, not during a hospital admission. From these patients, 37 % had recently been admitted to hospital, and 23 % had undergone major surgery in 3 months before developing acute VTE. Of the episodes of VTE occurring within 3 months of a previous admission, 67 % occurred within the first month after discharge. The median length of admission was 4 days.

In the EXCLAIM Trial (Hull et al. 2010), extended duration prophylaxis for VTE was tested after hospital discharge in high-risk medical patients with heart failure, respiratory insufficiency, infection, or reduced mobility. Incidence of VTE was reduced in patients receiving extended prophylaxis after discharge with enoxaparin 40 mg/day. However, a substantial methodological issue with EXCLAIM was the change in enrolment eligibility halfway through the study (Kent and Lindenauer 2010); the inclusion criteria were made more restrictive than at the start of the study and required that patients be extremely immobile to participate in the trial. Overall, extended duration enoxaparin reduced the rate of VTE at 28 days from 4.0 % in the placebo group to 2.5 % in the enoxaparin group (absolute risk difference −1.53, 95 % CI −2.54 to −0.52). Major hemorrhage at 30 days was more frequent in patients receiving extended duration enoxaparin than in those receiving placebo.

The biggest difficulty in the specialty of in-hospital prophylaxis of VTE is underuse of prophylactic anticoagulant drugs. Failure to prevent VTE is a global problem. In ENDORSE, a cross-sectional study, 68,183 patients were enrolled from 358 hospitals in 32 countries across six continents. Of these patients, 52 % were at moderate to high risk of developing VTE. Although rates of prophylaxis were low, surgical patients more often received guideline-recommended prophylaxis than did medical patients (58 % vs. 40 %) (Cohen et al. 2008). Of the 9,257 US patients from 81 hospitals enrolled in ENDORSE, wide variation was noted in prophylaxis practices for VTE. The top quartile of hospitals implemented prophylaxis in 74 % of at-risk patients, whereas the bottom quartile implemented prophylaxis in only 40 %. Compared with the lowest quartile, more hospitals in the best performing quartile had residency training programs (43 % vs. 5 %) and had implemented individualized hospital-wide prophylaxis protocols for VTE (76 % vs. 40 %) (Anderson et al. 2010).

## 7.6 Inferior Vena Cava Filter

In VTE patients, anticoagulant treatment is the treatment of choice and should be initiated even when suspecting VTE. However, in case of contraindication to anticoagulant therapy, the insertion of an inferior vena cava (IVC) filter device could be one way to rule out further embolization of venous thrombotic masses. Various guidelines define absolute and relative indications for the insertion of IVC filters (Kearon et al. 2008; Baglin et al. 2006). Although IVC filters have been inserted for about 40 years now, only few prospective controlled trials were performed to evaluate safety and outcome of IVC filters so far (Decousus et al. 1998; PREPIC Study Group 2005; Johnson et al. 2010). In the PREPIC study, permanent filter devices were inserted in patients with proximal DVT. The outcome of these patients in regard to DVT progression and occurrence of PE was compared with patients randomized in a group without filter insertion. In this trial, the incidence of a recurrent DVT was significantly higher in filter patients compared with patients without IVC filter device. However, the incidence of PE was significantly lower in IVC filter patients. The increase in DVT recurrence is a drawback of permanent IVC filter devices. As a consequence of this higher incidence of DVT recurrence in permanent filter patients, retrievable filter models have been developed. Thus, the benefit of a filter, prevention of PE in the acute setting of DVT, is guaranteed, and the long-term complication of a filter, a higher recurrence rate of DVT, can be avoided. When therapeutic anticoagulation is possible again, the filter is retrievable up to several weeks after insertion depending on the filter model used.

## 7.7 Complication

### 7.7.1 Chronic Thromboembolic Pulmonary Hypertension

After mortality the most feared complication in PE patients is chronic thromboembolic pulmonary hypertension (CTEPH) (Piazza and Goldhaber 2011). CTEPH is defined as a mean pulmonary artery pressure greater than 25 mmHg that persists 6 months after the diagnosis of PE. The disorder occurs in 2–4 % of patients after acute PE and results in disabling dyspnea, both at rest and with exertion. Life expectancy is often shortened and patients frequently die of sudden cardiac death. Death is usually due to progressive pulmonary hypertension culminating in right ventricular failure.

## 7.8 Summary and Perspectives

Venous thrombosis is a life-threatening disease requiring correct diagnosis and immediate therapy. Anticoagulant treatment is one main column, as is compression therapy in case of deep vein thrombosis. Especially in the field of anticoagulant drugs, the former gold standard of heparin followed by vitamin K antagonist

therapy is now in radical change. Novel oral anticoagulants directed against coagulation factor II and Xa are now investigated for the treatment and prophylaxis of venous thromboembolism. As results of most phase III trials conducted in this filed are still pending the future will show whether standard therapy of venous thromboembolism will change in the following years.

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# Abdominal Aortic Aneurysm

8

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**Abstract**

Abdominal aortic aneurysm (AAA) is an increasingly common and life-threatening disease. The natural history of large and untreated AAAs is progressive expansion leading to rupture with a high mortality. Epidemiological studies point out risk factors including older age, male gender, positive family history, smoking, and associated atherosclerotic diseases. AAAs affect the population older than 50 years, with prevalence of 3–10 % for patients older than 50 years of age. Male gender is more frequently affected with a male to female ratio of 6. Positive family history of AAA is associated with doubled risk of AAA. Smoking is a major risk for aneurysm formation, expansion, and rupture. Nicotine increases AAA formation by stimulating adenosine monophosphate-activated protein kinase alpha2 (AMPKα-2) in vascular smooth muscle cells. Initial aortic diameter is the strongest predictor of AAA expansion and rupture. Pathological features of AAA are degradation of extracellular matrix proteins, elastin and collagen, apoptosis of smooth muscle cells, and infiltration of inflammatory cells including macrophages, neutrophils, lymphocytes, and mast cells. Various extracellular proteinases including matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9; cysteine proteases; and serine proteases which are secreted by macrophages, neutrophils, lymphocytes, and mast cells participate in the degradation of the extracellular matrix. The balance between proteases

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and antiprotease seems to be in favor of proteolysis in AAAs. Pathological processes include degradation of the extracellular matrix and impairment of biosynthesis of the extracellular matrix proteins. Although the specific etiology is unknown, aneurysms are probably initiated by aortic wall injury coupled with a series of epidemiological risk factors. Recruitment of leukocytes into the aortic media appears to be an early and pivotal event. The influx, migration, and effects of the inflammatory cells are controlled by an array of proinflammatory cytokines, chemokines, and growth factors, some of which may have dual and opposing functions depending on the specific context. AAA pathogenesis is the result of a complex interplay among distinct pathological processes, and each pathological process involves a network of signaling molecules and effector molecules of which levels of expression are differentially regulated. Various environmental and genetic stimuli may activate a final common pathway. c-Jun N-terminal kinase (JNK), one of the subfamilies of mitogen-activated protein kinases, is found to be a prime candidate for AAA. JNK inhibitor and inhibition of nuclear factor kappa B (NFκB), a critical transcription factor in cytokine signal transduction, not only prevent the development of experimental AAA but also regress the established AAA, indicating recovery of extracellular matrix synthesis. Recently, it is reported that inhibition of microRNA-29b abrogates aortic dilation in mice, suggesting that microRNA-29 may represent a novel molecular target to augment matrix synthesis and maintain vascular wall structural integrity. It is suggested that upregulation of microRNA-21 seems to be protective, as inhibiting its expression accelerates aneurysm expansion. There may be a common abnormality of cellular signaling that regulates the destructive processes. There are amount of processes that remain to be clarified in the pathophysiology of AAA.

**Keywords**
Older age • Male • Nicotine • Extracellular matrix proteases • Inflammation • MicroRNA

## 8.1 Introduction

An aortic aneurysm is a permanent focal dilatation of all three layers of an aortic wall that is associated with progressive aortic dilation and weakening of the vessel wall, ultimately leading to rupture. Approximately 80 % of all aortic aneurysms occur in the abdominal region, and nearly all (>80 %) abdominal aortic aneurysms (AAAs) involve the infrarenal aorta. Degenerative aneurysms account for more than 90 % of all infrarenal AAAs (Fillinger 2010). AAA is asymptomatic until it ruptures, and it is unrecognized until it is noticed as a pulsatile tumor in the abdomen. AAA is increasingly common and frequently fatal due to rupture. The rupture of an AAA may be associated with death rates as high as 90 % (Lloyd-Jones et al. 2009). AAA rupture can be prevented by open or endovascular repair of the aneurysm, with overall 30-day mortality of around 5 %. When an AAA is larger than 5.5 cm in diameter, the risk of rupture exceeds the risk for elective surgery. Although rupture risk

increases with increasing aortic diameter, rupture risk of AAAs smaller than 5.0 cm is still 0.5–5 %. Since surgical intervention does not offer a survival advantage for small AAA, "watchful waiting" is now the standard practice for small aneurysms until the risk of rupture reaches or exceeds the surgical risk.

## 8.2 Epidemiology

### 8.2.1 Definition

The Society for Vascular Surgery recommends that AAA is defined as a 50 % greater increase in infrarenal aortic diameter compared with the expected infrarenal aortic diameter based on age, sex, and other factors such as body size (Johnston et al. 1991). Although the definition varies somewhat by age and body surface area, generally, an AAA is considered to be present when the anteroposterior diameter of the aorta reaches to 3.0 cm (Lloyd-Jones et al. 2009).

### 8.2.2 Prevalence

AAAs affect the population older than 50 years. Ultrasound screening and autopsy series indicate that the prevalence of AAAs is 3–10 % for patients older than 50 years (Fillinger 2010). The prevalence of AAAs 2.9–4.9 cm in diameter ranges from 1.3 % in men 45–54 years of age to 12.5 % in men 75–84 years of age. For women, the prevalence ranges from 0 % in the youngest to 5.2 % in the oldest groups (Lloyd-Jones et al. 2009). The prevalence of AAA is up to six times more common in men than women and two to three times more frequent in white men than in black men.

Screening program for men older than 50 years of age shows that the incidence of new AAAs is 3.5/1,000 person-years. In men, AAAs begin to occur at about 50 years of age and reach a peak incidence near 80 years of age. In women, AAA onset is delayed, beginning around 60 years of age, with the incidence continuing to increase thereafter (Fillinger 2010).

AAAs arise over a period of years and most tend to gradually increase in size with time, and the risk of aortic rupture increases steadily with progressive aneurysm growth. Progression of AAAs towards rupture is not linear but usually presents point of acceleration which can remain stable at an early time. AAAs become enlarged with time at a mean rate that is initially slow and then increases exponentially. AAA expansion is not associated with age or sex. Large AAAs tend to expand more rapidly than small AAAs, and large AAAs are at substantially higher risk for rupture (Lloyd-Jones et al. 2009). To date, only initial aortic diameter has consistently been shown to predict a subsequent increase in aortic diameter. Average annual expansion rates are ~1–4 mm for aneurysms <4.0 cm in diameter, 4–5 mm for AAAs 4.0–6.0 cm in diameter, and as much as for those >6.0 cm in diameter (Lloyd-Jones et al. 2009).

The reported incidence of ruptured AAA ranges from 1 to 21/100,000 person-years. For patients older than 50 years, the incidence of AAA rupture is much

higher. A population-based study of ruptured AAAs noted an incidence of 76/100,000 person-years for men and 11/100,000 person-years for women older than 50 years, for a male to female ratio of 6.9 (Fillinger 2010). The median age at rupture is 76 years in men and 81 years in women. The median AAA size at rupture is 8 cm, but 4.5 % of the ruptured AAAs are smaller than 5 cm in diameter (Fillinger 2010). Rupture appears to occur at smaller diameters in women (5 cm) than men (6 cm). The absolute risk for eventual rupture is ~20 % for AAAs > 5.0 cm in diameter, ~40 % for AAAs > 6.0 cm in diameter, and >50 % for those >7.0 cm in diameter (Lloyd-Jones et al. 2009). The overall mortality associated with rupture is 90 %, and three-fourths of these deaths occur outside the hospital (Fillinger 2010).

### 8.2.3 Risk Factors

The prevalence of AAAs depends on the presence of risk factors associated with AAAs, including older age, male gender, positive family history, smoking, smoking history, hypertension, hypercholesterolemia, peripheral vascular occlusive disease, and coronary artery diseases. Independent risk factors for detecting an unknown 4-cm-diameter or larger AAA during ultrasound screening include smoking history (odds ratio (OR) 5.1), family history of AAA (OR 1.9), older age (per 7-year interval OR 1.7) as an increased risk, and associated diabetes mellitus (OR 0.5) and female gender (OR 0.2) as a decreased risk (Fillinger 2010).

## 8.3 Risk Factors for AAA Development

### 8.3.1 Family History

Fifteen to twenty-five percent of patients who underwent AAA repair have a first-degree relative with an AAA as compared with only 2–3 % of age-matched control patients. It is estimated that first-degree relatives of a patient with an AAA have a 12-fold increased risk for aneurysm development (Fillinger 2010). Brothers of a patient with an AAA have an 18-fold increased risk for the development of an AAA—highest in the 50- to 60-year-old range. In patients with familial aneurysms, they are on average 5–7 years younger and are more frequently women (Fillinger 2010). In a surgical series of patients undergoing AAA repair, women accounted for 35 % of the patient with a positive family history of AAAs but for 14 % of those without family history (Fillinger 2010). Population-based series show that a positive family history of AAA is associated with doubled risk of AAA compared to those without family history (Larsson et al. 2009).

### 8.3.2 Aging

Older age is an independent risk factor for AAA, and the risk increases by 40 % every 5 years after age of 65 years. Natural killer cells increase in number and have greater interleukin (IL)-4 production with aging (Plackett et al. 2004). It is supposed

that a relative paucity of elastin and collagen is present at the infrarenal abdominal aorta, and the additive depletion of elastin associated with aging together with the increasing production of IL-4 makes it especially vulnerable to repetitive high wall stress. Recent study shows that vascular aging and age-associated pathologies induce a significant upregulation of the microRNA-29 family in the human aorta. MicroRNA-29 targets several extracellular matrix proteins, which are known to play a key role in maintaining the integrity of the vascular wall. The increased expression of microRNA-29 family members is associated with a profound down-regulation of numerous extracellular matrix components in aortas in aged mice, and inhibition of microRNA-29 decreases the expression of matrix metalloproteinase (MMP)-9 in the aorta (Boon et al. 2011). These suggest that microRNA-29 family contributes to extracellular matrix loss, thereby, sensitizing the aorta for aneurysm formation (Boon et al. 2011).

### 8.3.3 Gender

Female gender appears to be protective in the development of AAA. In the elastase-perfused model, female rodents develop significantly smaller AAA and lower neutrophil and macrophage count in the aorta compared to male (Sinha et al. 2006). Estrogen decreases p38 mitogen-activated protein kinase (MAPK), a crucial upstream proinflammatory regulator of numerous cytokines, including tumor necrosis factor-alpha (TNF-α), IL-1, IL-4, and IL-8; decreases the activity of nuclear factor kappa B (NFκB), a key proinflammatory transcription factor; and decreases oxidant stress (Sinha et al. 2006).

### 8.3.4 Smoking

Smoking is a major risk factor for aneurysm formation, growth, and rupture. Smoking increases the relative risk of AAA 7.6-fold. Current smoker (>25 cigarettes/day) has 15-fold increased risk of AAA (Wong et al. 2007). Each year of smoking increases the relative risk of AAA by 4 % in all populations. Even for former smokers, the risk remained elevated, particularly for those who ceased smoking within 10 years (Wong et al. 2007). Smoking decreases the synthesis rates of collagens in the skin and levels of tissue inhibitor of metalloproteinase-1 (TIMP-1) in subcutaneous tissue in human, and the levels of matrix metalloproteinase-8 (MMP-8) are higher by 100 % in the subcutaneous tissue of the smokers. Cigarette smoke induces IL-4 expression from human aortic endothelial cells and MMP-1, MMP-9, and MMP-12 from human endothelial cells, macrophages, or epithelial cells. MMP-1, MMP-2, MMP-8, MMP-9, MMP-12 induce elastolysis and collagenolysis of the aortic wall.

Human AAA tissue samples showed an increased activity of adenosine monophosphate-activated protein kinase alpha2 (AMPKα-2) compared with aortic tissues from people without AAA (Wang et al. 2012). In regular smokers,

nicotine, which is a major component of cigarette smoke, is present in the blood at 90–100 nM over the first 6–8 h of each day (Benowitz 2003). Nicotine infusion for 6 weeks increased the incidence of AAA, maximal aortic diameters, and total aortic tissue weights in apolipoprotein E (apoE) knockout mice. However, genetic deletion of AMPKα-2 ablated nicotine-triggered AAA *in vivo*, indicating that deficiency of AMPKα-2 protects against nicotine-induced AAA formation in apoE-deficient mice (Wang et al. 2012). Infusion of nicotine increased the amount of malondialdehyde and 3-nitrotyrosine, markers of oxidative stress, in the aortic tissue of apoE-deficient mice, indicating that nicotine infusion increases reactive oxygen species (ROS) *in vivo* (Wang et al. 2012). Nicotine, at concentration relevant to those found in smokers, leads to increased levels of ROS and to AMPK activation in adipocytes (An et al. 2007). Nicotine infusion increased MMP-2 protein concentrations, MMP-2 mRNA levels, and MMP-2 activity in mice deficient in both apoE and AMPKα-1, but not in mice deficient in both apoE and AMPKα-2. Similar findings were seen in Ang II infusion model. These indicate that AMPKα-2 deficiency abolishes MMP-2 upregulation in AAA tissue (Wang et al. 2012). The exposure of human vascular smooth muscle cells (VSMCs) to low concentration of nicotine, equivalent to the blood concentrations present in habitual smokers, led to AMPK activation and increased MMP-2 mRNA, MMP-2 protein expression, and MMP-2 activity in the culture medium (Wang et al. 2012). Nicotine activates AMPKα-2 in VSMCs, and activation of AMPKα-2 results in phosphorylation of activator protein 2 alpha, a transcription factor that derives the expression of and smooth muscle cell release of MMP-2 and consequent AAA formation (Suganuma and Keaney 2012).

MicroRNA-21 expression in human diseased aortic tissue is 6.7-fold upregulated in nonsmokers with AAA and 12.8-fold upregulated in smokers with AAA, when compared with normal abdominal aortic tissue from a group of organ donor patients without AAA at the time of explantation (Maegdefessel et al. 2012a). In nicotine-supplemented animals, microRNA-21 expression was enhanced, increasing with AAA development, and was most prominent in the medial region of the diseased aorta (Maegdefessel et al. 2012a).

### 8.3.5 Hypertension

Hypertension (systolic blood pressure > 160 mmHg) is associated with AAA risk, but only in women (Forddahl et al. 2009). Mean elevated blood pressure (BP) is an independent risk factor for aneurysm rupture, but not a factor for AAA growth.

### 8.3.6 Obesity

Central obesity is independently associated with AAA. Waist circumference (OR 1.14) and waist-hip ratio (OR 1.22) are independently associated with AAA in screened men (Golledge et al. 2007).

### 8.3.7 Alcohol Consumption

High levels of alcohol intake (>30 g/day) are associated with increased risk of AAA (OR 1.65) (Wong et al. 2007). The mechanism between alcohol exposure and AAA is unclear, but long-term alcohol consumption results in increased MMP-2 activity and disruption of aortic elastic fibers in rat. It is shown that acetaldehyde, an immediate metabolic product of alcohol, has the ability to upregulate MMP-2 gene expression in cultured liver cells (Casini et al. 1994).

### 8.3.8 Low Flow in the Lower Extremities

Aneurysms frequently occur in the distal aorta. Compared with suprarenal aorta, the infrarenal environment in resting subjects is characterized by increased peripheral resistance, increased wall shear stress, and reduced flow. Major limb amputation, chronic spinal cord injury, and severe peripheral vascular occlusive disease are associated with increased AAA risk independent of other risk factors, including cigarette smoking. Resistive aortic hemodynamics such as those found in the infrarenal aorta under sedentary conditions promote aortic inflammation and production of reactive oxygen species (Dalman et al. 2006). There were significantly more AAAs, enlarged aortas, and small iliac arteries in spinal cord injury patients who had been unable to walk for 5 years, suggesting that the peripheral resistance is increased (Dalman et al. 2006). Therefore, patients with reduced activity levels are at higher risk of AAA disease.

### 8.3.9 Diabetes Treatment Drugs

Diabetes is independently associated with reduced AAA growth (Golledge et al. 2008). AMPKα-2 deficiency had a markedly protective effect for AAA formation. The activation of AMPK is the mechanism for the most widely used diabetes treatment drug, and AMPKα-2 is required for nicotine-induced AAA formation and expansion (Suganuma and Keaney 2012). This might help explain the clinical observation that diabetes is negatively associated with AAA formation (Golledge et al. 2008). Hyperglycemia suppresses AMPK activity (Choi et al. 2008); conversely, insulin treatment, which lowers blood glucose concentrations, promotes aortic diameter enlargement (Miyama et al. 2010).

## 8.4 Risk Factors for Aneurysm Expansion and Rupture

Initial aortic diameter is the strongest predictor of AAA expansion and rupture. Rapid increase of aortic diameter is a risk factor for rupture independent of the initial size. Age is not associated with AAA growth rate. There is no association between AAA expansion and gender. For a given diameter, the time to rupture is less in women than in men. In small aneurysm trial, the risk of rupture in women is

fourfold that of men. Continued smoking increases the expansion rate of AAA by 20–25 %. Active smoking is a risk factor for AAA rupture (OR 2.11) (Sinha et al. 2006). Nicotine is known to regulate microRNA-21 expression through NFκB-dependent modulation (Shin et al. 2011). Upregulation of microRNA-21 seems to be protective, as inhibiting its expression accelerates aneurysm expansion (Suganuma and Keaney 2012). Hypertension does not accelerate AAA expansion in human, but mean elevated blood BP (>110 mmHg) has been cited as an independent risk factor (OR 1.04) for aneurysm rupture in men and women. Positive family history is a risk factor for AAA rupture. A study of 313 pedigrees shows a fourfold higher rate of AAA rupture in familial cases than in sporadic cases (Verloes et al. 1995). Glucocorticoids inhibit vascular SMC proliferation and extracellular matrix protein synthesis. Steroids increase the rate of aneurysm expansion and may be a risk factor for rupture of AAA in humans (Lindholt et al. 1998). Although reasons are unclear, organ transplant patients may be at increased risk for AAA development and rupture. A total of 1,557 patients underwent heart, kidney, or liver transplantation and were screened for AAAs. Eighty-seven percent of cardiac transplant patients are screened and have a 5.8 % prevalence of AAAs. In addition, among these transplant patients with AAAs, the rate of aneurysm rupture is 22.5 %/year with a mean diameter of 6.3 cm (Englesbe et al. 2003).

From a biomechanical perspective, AAA rupture occurs when the forces within an AAA exceed the wall's "bursting strength." Peak wall stress is the greatest predictor of rupture (Fillinger 2010). In addition to the above, eccentric or saccular aneurysms present a greater risk for rupture than do more diffuse fusiform aneurysms (Fillinger 2010). Wall stress is substantially increased by an asymmetric bulge in AAA. Increased thrombus content within an AAA is associated with more rapid expansion and rupture (Swedenborg and Eriksson 2006). The aortic wall underlying the thrombus is thinner and shows more signs of proteolytic degradation. The intraluminal thrombus contains high amounts of MMP-9 with higher amounts in the luminal parts of the thrombus (Swedenborg and Eriksson 2006).

## 8.5 Pathology

Although AAAs are focal lesions, the entire vascular tree is abnormal in patients with AAAs. The mean diameter of all peripheral arteries is increased, and a reduction in the elastin/collagen ratio throughout the arterial vasculature is seen in patients with AAAs. Molecular changes found in the vasculature distant from AAA are similar to those present in the aneurysm wall. Atherosclerosis is primarily found within the intima and media of the vessel wall, whereas aneurysm disease typically affects the tunica media and adventitia of the aortic wall. Since not all patients with atherosclerosis develop AAAs, AAAs are likely to be a local representation of systemic disease rather than a consequence of atherosclerosis.

Pathophysiologically, AAA may roughly be divided into two related processes, extracellular matrix degeneration and inflammation. Histologically, AAAs are characterized by disruption and degradation of elastin and collagen in the media and

adventitia; smooth muscle cell (SMC) loss due to apoptosis leading to thinning of the medial wall; gross collagen disposition in the early stages; infiltration of a large number of polymorphonuclear neutrophils, lymphocytes, macrophages, and mast cells in the outer media and adventitia; and neovascularization. Neovessels are less mature and more prevalent at the sites of rupture. AAAs are filled to a varying extent with a mural thrombus and both aneurysm growth and rupture are associated with growth of the thrombus.

### 8.5.1 Extracellular Matrix Degradation

The elastic fibers are discontinuous and surrounded by large amounts of collagen, and 75–80 % reductions of adventitial elastin content are seen in small aneurysm wall as well as in large aneurysms. These suggest that adventitial elastin destruction is an early event in aneurysm formation (White and Mazzacco 1996). The experimental study using human iliac arteries shows that destruction of elastin results in a little dilatation of the vessel, whereas destruction of the collagen within the vessel wall results in rupture (Dobrin et al. 1984). Destruction of elastin and interstitial collagen initiates aortic dilatation and tortuosity with changes in aortic wall geometry increasing cyclic strain and wall tension over a period of years. Collagen synthesis increases during the early stages of aneurysm formation, suggesting a repair process. However, in the later stages of the disease, collagen turnover is increased and collagen destruction exceeds its synthesis. The adventitia, in which collagen is predominant, is responsible for the resistance of the aorta, and collagen degradation is the ultimate cause of rupture (Dobrin et al. 1984). Excess collagen degeneration is found in AAA and ruptured AAA. In addition to disappearance of elastic lamellae in the aneurysm wall, urinary elastin-derived peptides, product of elastin degradation, are significantly higher in patients with AAA than in control. There is no change in elastin synthesis in AAA compared with normal. Since elastin is synthesized early in life and has an extremely long half-life (~50 years), loss of elastin in adults certainly results from elastolysis rather than insufficient synthesis (Shimizu et al. 2006).

### 8.5.2 Proteases

Various extracellular proteinases participate in the process of the destruction of the aortic wall and are secreted by inflammatory cells including macrophages, neutrophils, lymphocytes, mast cells, and resident smooth muscle cells. Elastin and collagen fibers are degraded by protease enzymes mostly represented by MMPs that are locally activated either by other MMPs, mast cell-derived chymase, or plasmin generated by plasminogen activators. The critical role of MMP activity has been recognized. Targeted deletion of genes encoding for tissue inhibitor of metalloproteinase (TIMP) expression leads to the development of larger aneurysms. This suggests that aneurysm disease may result from a local or systemic imbalance between MMP and

TIMP production (Tedesco and Dalman 2010). The balance between proteases (MMPs) and antiproteases (TIMPs) seems to be in favor of proteolysis in AAAs. The relationship between MMP and TIMP production is almost certainly more nuanced in the human disease condition; tissue analysis has consistently demonstrated increased TIMP production in AAA surgical specimens (Tedesco and Dalman 2010). The elastolytic MMPs, particularly MMP-2 and MMP-9, are consistently elevated in human AAAs. High concentration of MMP-2 is found in small aneurysm aorta less than 5.5 cm, suggesting a role for MMP-2 during early aneurysm formation. Patients with intermediate-sized AAAs (5–7 cm) have higher serum levels of MMP-9 than those with smaller or larger ones do, suggesting a significant role for MMP-9 in disease progression (McMillan et al. 1997). MMP-8 and MMP-9 levels are significantly elevated in the rupture site biopsies compared with their paired other site biopsies of aneurysm wall (Wilson et al. 2006). MMP-8 is a type 1 collagenase, and type 1 collagen is predominant in the aneurysm wall. There are focal areas of weakened aortic wall, pointing to localized "hot spots" of MMP hyperactivity. Deletion of the genes for MMP-9 and/or MMP-2 completely protects mice from the development of AAA (Longo et al. 2002). The direct inhibitor of MMP-9, doxycycline, reduces AAA expansion in humans, and selectively suppresses MMP-8 and MMP-9 protein levels, and increases protein levels of the protease inhibitors TIMP-1 and cystatin C (Abdul-Hussien et al. 2009). Other proteases also contribute to the initiation and progression of AAAs. Upregulation of cysteine proteases is detected in the aneurysm wall. Cathepsins, cysteine proteases, express powerful elastolytic and collagenolytic activity. Expression of cystatin C, an inhibitor of cysteine protease, is reduced in human aneurysm tissue. Cystatin C knockout mouse models show increased activity of cathepsins, resulting in increased elastin degradation and subsequent dilatation in atherosclerotic aorta. Cysteine protease/protease-inhibitor balance is important in dysregulated arterial integrity and remodeling during aneurysm formation (Sukhova and Shi 2006). These indicate that pathological processes include degradation of the extracellular matrix and impairment of biosynthesis of the extracellular matrix.

### 8.5.3 Inflammation

In addition to proteolysis of elastin and collagen and loss of medial smooth muscle cellularity, chronic inflammation is a central pathophysiologic feature of aortic aneurysm disease. Human AAA tissues show extensive inflammatory infiltrates containing neutrophils, macrophages, lymphocytes, and mast cells in the outer media and adventitia. It remains unclear whether these cells simply respond to the pathologic process or incite it. An increasing aneurysm diameter is associated with a higher density of inflammatory cells and with an increasing number of mast cells in the adventitia. Degranulated mast cells are increased in the aneurysm wall.

#### 8.5.3.1 Neutrophils and Macrophages

Although the specific etiology is not known, aneurysms are probably initiated by aortic wall injury coupled with a series of epidemiological risk factors. The recruitment of

leukocytes into the aortic media appears to be an early and pivotal event, likely promoted by chemokines and elastin degradation peptides (White and Mazzacco 1996). Mononuclear phagocyte infiltration is associated with production of proinflammatory cytokines, prostaglandin derivatives, and reactive oxygen species as a part of innate inflammatory response. Macrophages are the principle source of MMPs, which can also be secreted by neutrophils, lymphocytes, and resident mesenchymal cells.

Neutrophils are present in the adventitia of AAA and are abundant within the intraluminal thrombus which is present in most AAA of a clinically relevant size. The mural thrombus may promote the progression and rupture of AAA by actively producing proteases. Experimental neutrophil depletion inhibits AAA development through a non-MMP-2/9-mediated mechanism associated with attenuated inflammatory cell recruitment (Eliason et al. 2005). Doxycycline treatment results in suppression of the inflammation, showing marked reduction of neutrophils and profound reduction of cytotoxic T cells in the human AAA wall (Lindeman et al. 2009).

#### 8.5.3.2 Mast Cells

Mast cells, which are observed predominantly in the adventitia of AAA tissue, serve as an important source of proinflammatory mediators and cytokines that can activate T lymphocytes and macrophages, whereas mast cells become activated on direct contact with T lymphocytes. There is a positive correlation between the mast cell number and AAA diameter (Tsuruda et al. 2008). Mast cells produce mast cell-restricted serine protease, chymase, and tryptase. There are significant correlations of serum chymase and tryptase levels with human AAA expansion rate. Human chymase can directly activate MMP-9 and induce synthesis of MMP-9 in macrophages by releasing tumor necrosis factor-alpha (TNF-α) (Sun et al. 2009). The tryptase serves as an activator for the pro-form of MMP-9. Mast cells express majority of cathepsin G, which is a powerful protease, and release MMP-9 on contact with activated T cells. Many mast cells are seen in the area which shows the most extensive neovascularization. Mast cell-derived chymase and cathepsin G convert angiotensin I to angiotensin II, which causes activation of MMP-2 in SMCs. Mast cell-derived chymase inhibits smooth muscle cell growth and collagen synthesis by viable SMCs. Mast cells release proinflammatory cytokines, IL-6 and interferon-gamma (IFN-γ), which may induce matrix-degrading protease expressions.

No AAA development is reported in mast cell-deficient mice model based on elastase infusion into the aorta. Inhibition of AAA formation in mast cell-deficient mice is found after induction of AAA with $CaCl_2$ (Tsuruda et al. 2008). Inhibition of chymase was demonstrated to prevent angiotensin II-induced AAA formation in apoE-deficient mice. Mice treated with tranilast, an inhibitor of mast cell degranulation, had fewer mast cells, T lymphocytes, and macrophages in their abdominal aortas and decreased capillary density parallel with attenuated aortic dilatation (Tsuruda et al. 2008).

#### 8.5.3.3 Lymphocytes

In addition to macrophages, neutrophils, and mast cells, human AAA tissues contain a large number of T cells, B lymphocytes, plasma cells, and dendrite cells and

large amounts of immunoglobulin protein. CD4+ T cells are predominant lymphocytes and 3–20-fold greater than CD8+ cells in the aneurysm tissue. One study reported that in the absence of CD4+ T cells, mice were resistant to aneurysm induction (Xiong et al. 2004). They showed that T cells and the T cell cytokine, IFN-γ, play in orchestrating matrix remodeling in AAA and that IFN-γ deficiency prevented aneurysm formation. On the other hand, in the aortic allograft mismatched model, the inflammation results in an intimal hyperplastic lesion without aneurysm formation in wild-type recipients, whereas allografts in IFN-γ receptor-deficient (GRKO) hosts developed severe AAA formation associated with markedly increased levels of MMP-9 and MMP-12 (Shimizu et al. 2004). Allografts in GRKO recipients treated with anti-IL-4 antibody to block the characteristic IL-4 or allografts in GRKO host congenitally deficient in IL-4 did not develop AAA and likely exhibit attenuated collagenolytic and elastolytic activities. This demonstrates that blockade of IFN-γ signaling pathways and subsequent IL-4-mediated events induced AAA formation associated with augmented elastolytic activity primarily due to increased MMP-12 expression. Some cytokines produced within aneurysm tissue, such as IL-6, IFN-γ, TNF-α, and transforming growth factor-beta (TGF-β), may have dual and opposing functions depending on the specific context (Curci and Thompson 2004). However, recent investigation assessing the relative expression of 79 cytokines in human AAA biopsies reveals that only three cytokines, IL-1beta (IL-1β), IL-8, and chemokine CC motif ligand 22 (CCL22), were consistently upregulated compared with two types of control biopsies (Golledge et al. 2010). In an attempt to minimize the concerns regarding controls, they used careful matching of cases (AAA) and controls (atherothrombosis), including matching of age, other risk factors, and medications as far as possible. They also used within-patient control (AAA body and AAA neck), allowing more appropriate identification of potential candidate cytokines. CCL22 preferentially attracts CD4+ cells, and its production from such cells is stimulated by IL-4 and is inhibited by IFN-γ.

Although acute rejection causes virtually complete medial smooth muscle cell death in all mismatched wild-type recipient aortic allografts, they do not develop aneurysms (Shimizu et al. 2004). Infrarenal aortic eversion endarterectomy which removes all of the intima and much of the media does not result in aneurysm formation (Inahara 1979). The tunica media ruptures at relatively low pressures. Pressure-diameter curves of whole-vessel canine infrarenal aorta and its adventitial layer after eversion endarterectomy show the same slopes of curves between them, indicating that structural integrity of the adventitia is sufficient to limit maximal aortic diameter (White and Mazzacco 1996). Since aortic intima and media can be removed without aneurysm formation, aneurysm disease must be a disorder of the adventitia (White and Mazzacco 1996). A onetime periadventitial delivery of pentagalloyl glucose, which binds specifically to arterial elastin, inhibits elastin degeneration, attenuates aneurysm expansion, and hinders AAA development in rats without interfering with pathologic mechanism typical of the model, namely, inflammation and high metalloproteinase activity (Isenburg et al. 2007).

### 8.5.4 Mitogen-Activated Protein Kinase Pathway (c-Jun N-Terminal Kinases)

The phosphorylation status of signaling molecules was assessed in human AAA samples, and it is found that c-Jun N-terminal kinase (JNK) was a prime candidate, because it was activated by stimuli implicated in AAA pathogenesis (Yoshimura et al. 2005). JNK is one of the subfamilies of mitogen-activated protein kinases (MAPKs) and is a proximal signaling molecule that regulates the proteolytic and synthetic functions of vascular SMCs, as well as proinflammatory cytokine production and proteolytic activity of macrophages (Yoshimura et al. 2005). Total and phosphorylated JNK are significantly increased in human AAA tissue. MMP-9 expression levels showed a highly positive correlation with levels of phosphorylated JNK. Most of the active JNK is localized in macrophages, which secrete proinflammatory cytokines and MMPs (Yoshimura et al. 2005). JNK downregulates TIMP-3, an endogenous inhibitor of MMPs, and gene expression of crucial extracellular matrix biosynthetic enzymes including lysyl hydroxylase (essential for the stability of collagen fibers), lysyl oxidase (responsible for the cross-linking and deposition of collagen and elastin fibers), and prolyl 4-hydroxylase (enzyme for collagen biosynthesis). Pharmacologic inhibition of JNK *in vivo* prevents aneurysm formation in response to abluminal application of $CaCl_2$ in mouse aorta (Yoshimura et al. 2005). JNK inhibition was also effective in treating established AAA induced by $CaCl_2$ treatment in mice and by continuous infusion of angiotensin II in apoE knockout mice (Yoshimura et al. 2005). JNK inhibition strongly reduces macrophage infiltration of the periaortic tissue, suggesting that chronic inhibition of JNK abrogates proinflammatory signaling in AAA. JNK inhibitor significantly suppressed MMP-9 and MMP-2 and prevented collagen degradation in human AAA wall in *ex vivo* culture, as well as restored the levels of expression of TIMP-3.

### 8.5.5 Transcription Factors (Nuclear Factor Kappa B and Ets)

There is marked activation of NFκB and ets, transcription factors, in human AAA tissue. NFκB- and ets-positive cells are increased in the outer aneurysm wall, and a part of the expression of NFκB and ets is detected in migrating macrophages (Miyake et al. 2007). NFκB directly controls the expression of MMP-1, MMP-2, MMP-3, and MMP-9 and inhibits the transcription of the elastin and collagen genes, leading to suppression of their synthesis. TNF-α increases the transcription activity of NFκB, suggesting that NFκB activity may play a role in the p38 MAPK-mediated regulation of MMP-9 (Cho et al. 2000). NFκB activation is required for maximal induction of MMP-9 transcription in some experimental systems and is a pivotal molecular mediator in aneurysm disease. Cigarette smoking, hypercholesterolemia, and oxidative stress promote NFκB activation. Ets is known to be a regulator of transcription of MMP-1, MMP-2, and MMP-9 and suppresses the induction of collagen type 1 genes in human fibroblasts. Chimeric decoy oligodeoxynucleotide (ODN)-based therapy inhibiting both NFκB- and ets-binding activity effectively

inhibits MMP-2 and MMP-9 expressions and activities and induces macrophage apoptosis (Miyake et al. 2007). Treatment with chimeric decoy with ODNs decreased the size of AAA and reduced recruitment of macrophages in elastase-induced rabbit model (Miyake et al. 2007). This regression is associated with an increase in elastin and collagen synthesis in the aneurysm wall (Sun et al. 2009). NFκB activation can be inhibited by pyrrolidine dithiocarbamate, an antioxidant inhibitor of NFκB, to reduce expression of NFκB-responsive gene products, leading to reduced AAA formation, decreased size of AAA, and decreased inflammation (Parodi et al. 2005).

JNK inhibitor and chimeric decoy ODN-based therapy for NFκB and ets not only prevent the development of experimental AAA but also regress the established AAA by inhibiting MMPs. Doxycycline is reported to inhibit JNK activity. NFκB synergistically regulates the expression of MMP-9 with activator protein-1 (AP-1), which is the major target of JNK pathway. Proinflammatory cytokines frequently activate both AP-1 and NFκB, and these transcription factors have been reported to synergistically activate downstream genes including MMP-9 (Aoki et al. 2008). However, NFκB and JNK pathways sometimes antagonize each other, showing the complexity of the inflammatory signaling network (Aoki et al. 2008).

### 8.5.6 MicroRNA

MicroRNAs are approximately 20-nucleotide, single-stranded RNA molecules that target messenger RNA (mRNA) and regulate gene expression at the posttranscriptional level, playing crucial roles in vascular integrity (Maegdefessel et al. 2012b). The increased expression of microRNA-29 family members is associated with a profound downregulation of numerous extracellular matrix components in aortas of aged mice. The microRNA-29 family (microRNA-29a, microRNA-29b, and microRNA-29c) promotes fibrosis through regulation of its downstream target genes. Of these, microRNA-29b levels are profoundly increased in biopsies of human thoracic aneurysms, and inhibition of microRNA-29b decreases the expression of MMP-9 in the aorta (Boon et al. 2011). Other study demonstrates that human patients with AAA display downregulated aneurysm tissue microRNA-29b and upregulated collagen mRNA levels compared with a group of control organ donor patients without AAA (Maegdefessel et al. 2012b). MicroRNA-29b is the only member of the microRNA-29 family found to be significantly regulated in patients with AAA. These were very similar to those obtained in experimental studies (Maegdefessel et al. 2012b). They showed in experimental study that overexpression of microRNA-29b led to augmented AAA expansion and significant increase of aortic rupture rate. *In vivo* administration of locked nucleic acid anti-microRNA-29b increased collagen expression, leading to a fibrotic response in the abdominal aortic wall and resulting in a significant reduction in AAA progression over time in an experimental study. It is suggested that downregulation of microRNA-29b is a physiologic response of the aortic wall to expansion. Increased collagen gene expression and augmented fibrosis substantially inhibited AAA expansion. MMP-2

and MMP-9 are direct targets of microRNA-29b, and an inhibition of gelatinase activity with anti-microRNA-29b is observed (Maegdefessel et al. 2012b).

MicroRNA-21 expression in human AAA tissue was 6.7-fold in nonsmokers and 12.8-fold in smokers compared with normal abdominal aortic tissue obtained from organ donors (Maegdefessel et al. 2012a). It is suggested that upregulation of microRNA-21 is a physiological response to aortic expansion. This protective response may be augmented when deleterious stimuli such as nicotine are present. Inhibition of microRNA-21 with locked nucleic acid (LNA) antagomir after elastase infusion greatly augmented AAA growth, whereas overexpression with pre-21 inhibits AAA expansion (Maegdefessel et al. 2012a). Mice that received both nicotine and anti-21 died due to rupture of massively enlarged AAAs, an extremely uncommon event in the elastase-infused aneurysm model (Maegdefessel et al. 2012a). In loss-of-function studies using anti-21, phosphatase and tensin homolog (Pten) expression was increased, resulting in augmented development and progression of AAA 28 days after initiation of Ang II infusion. Gain-of-function studies using pre-21 caused a decrease in Pten, limiting AAA expansion after 14 and 28 days compared with scrambled microRNA, empty vector, and anti-21 treatment (Maegdefessel et al. 2012a). The mortality rate due to aortic rupture throughout the 28-day follow-up period was increased in anti-21 injected mice. The pro-proliferative effects of downregulated Pten are diminished by treatment with anti-21, blocking microRNA-21 upregulation and leading to a marked acceleration of AAA development and even rupture in nicotine-supplemented animals (Maegdefessel et al. 2012a).

## 8.6 Summary

Epidemiological studies point out risk factors for AAA including older age, male gender, positive family history, smoking, and associated atherosclerotic diseases. AAAs affect the population older than 50 years, with prevalence of 3–10 % for patients older than 50 years of age. Nicotine increases AAA formation by stimulating AMPKα-2 in vascular smooth muscle cells. Pathophysiologically, AAA may roughly be divided into two related processes, extracellular matrix degradation and inflammation. Various extracellular proteinases including matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, cysteine proteases, and serine proteases participate in degradation of the extracellular matrix destruction. The balance between proteases and antiprotease seems to be in favor of proteolysis in AAAs. Various environmental and genetic stimuli may activate a final common pathway. c-Jun N-terminal kinase (JNK), one of the subfamilies of mitogen-activated protein kinases, has been found to be a prime candidate for AAA. JNK inhibitor and inhibition of NFκB, a critical transcription factor in cytokine signal transduction, not only prevent the development of experimental AAA but also regress the established AAA, indicating recovery of extracellular matrix synthesis. It is suggested that upregulation of microRNA-21 seems to be protective, as inhibiting its expression accelerates aneurysm expansion. The proposed pathophysiological mechanisms for

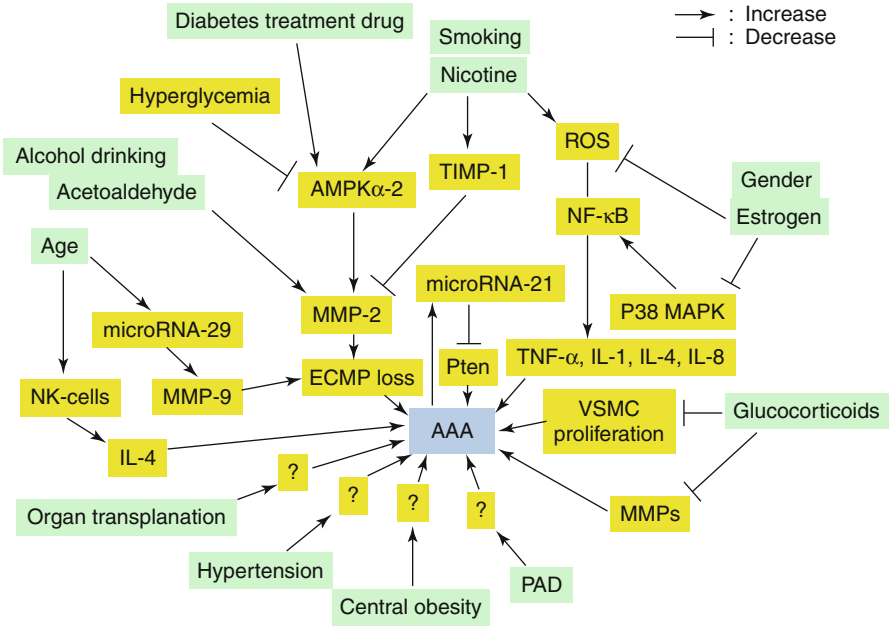


**Fig. 8.1** Proposed mechanisms for pathogenesis of abdominal aortic aneurysm

AAA introduced in this chapter are summarized in Fig. 8.1. Further studies are needed to clarify the detailed mechanisms to explain the relationships between AAA and its risk factors.

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