Updates in Hypertension and Cardiovascular Protection
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Maria Dorobantu · Giuseppe Mancia
Guido Grassi · Victor Voicu *Editors*

Hypertension and Heart Failure

Epidemiology, Mechanisms and Treatment

European Society of Hypertension

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Updates in Hypertension and Cardiovascular Protection

The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

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Hypertension and Heart Failure

Epidemiology, Mechanisms and Treatment

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Preface

Hypertension is the most prevalent risk factor for heart failure (HF) and large epidemiological studies show it to carry the highest population attributable risk for this disease compared to all other risk factors. A long known positive aspect, however, is that the blood pressure (BP) attributable risk of HF is modifiable by therapeutic interventions because randomized trials have shown that reducing an elevated BP by drug treatment is accompanied by a significant reduction in the risk of developing HF. Indeed, large meta-analyses show the benefit of BP reduction on new onset HF to be the most pronounced one among those associated with antihypertensive treatment, even more pronounced than the reduction of cerebrovascular events.

In this context, research on hypertension and HF continues to be lively, diversified and important. Efforts are constantly made to better understand the intimate mechanisms of progression from hypertension to HF. Furthermore, attention is continuously paid to new therapeutic options and strategies to prevent and treat HF in the hypertensive population. Diagnostic aspects are also intensively addressed, particularly in the area of early identification of HF in patients in whom antihypertensive drugs may sometimes confound the clinical picture. This results in a large amount of scientific data which need, however, to be prioritized and systematized in order to be friendly accessible to healthcare professionals.

Our idea of a book on hypertension and HF has been to divide the current status of knowledge in eight parts, covering 25 topics written by highly renowned experts. This has made possible to provide information on most, if not all, aspects of the hypertension-HF relationship, including those that are of an especially great current interest. Patients with HF and preserved ejection fraction (HFpEF), for example, are dealt with in depth because they more frequently have a history of or overt hypertension. At present HFpEF accounts for about 50% of HF cases, and its prevalence continues to rise relative to HF with reduced (HFrEF). In contrast to HFrEF, HFpEF presents also with many unique challenges such as diagnostic difficulties and lack of effective treatment.

Other important topics, however, are by no means overlooked. The genetic basis for HF is discussed because there is the hope that advancing knowledge in this area can provide key elements to the understanding of the underlying mechanisms that compromise the function of the heart leading to better diagnosis and personalized therapy. Several chapters are dedicated to the complex mechanisms of progression from hypertension to HF such as the neural, metabolic and renal abnormalities, as

well as the deficient natriuretic peptide response. This is currently regarded as a target for medications that can restore with special effectiveness the cardiovascular hemodynamics in both acute and chronic HF conditions (the neprylisin inhibitors). Other chapters deal in detail with the relationship between the prevalence or incidence of HF and the degree and type of blood pressure elevations in different demographic and clinical settings. Finally, much space is devoted to treatment aspects, including the BP at which to start antihypertensive drugs, the target values to aim at with treatment and the drugs or drug combinations to preferentially consider in different HF phenotypes.

We wish to further highlights few additional points. In the last decades a series of studies have indicated that the cardiovascular risk of hypertension, HF included, may not only depend on the magnitude of the elevation of average BP levels *per se* but also on the presence of associated conditions such as an increase of short (24 h) and long term (visit-to-visit) BP variability. One of the chapters of the book offers a practical approach on how to measure these parameters as well as on how to regard their clinical significance in the light of current evidence.

Part III of the book reports on the diagnosis of HF in hypertensive patients, with special attention to use of the tools (biomarkers, echocardiography or cardiac magnetic resonance) that can help to identify the transitional phase, i.e. when the heart starts deteriorating and becomes unable to support the workload associated with a high BP. Other chapters focus on the fact that once hypertension progresses to hypertensive cardiomyopathy, several complications may aggravate the natural history of the disease such as atrial fibrillation and other arrhythmias or episodes of flash pulmonary edema. The pathophysiology of these complications is discussed as well as the current recommendation for treatment. Last but not least the book also covers in all instances clinical prevention and treatment of heart failure, by non-pharmacological approaches as well as by invasive techniques such as carotid baroreceptor stimulation and renal nerves ablation.

Information is not restricted to the view proposed by guidelines, but it makes use of a much wider approach, including a discussion of promising technologies for which data from properly controlled trials are required before introduction in clinical routine.

In conclusion, we hope that this book will be found to represent a useful tool for a large number of healthcare professionals of different specialties, those who interact with hypertensive patients in various stages of their disease.

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Part I

Epidemiological Aspects

1 Epidemiological Aspects (Prevalence and Risk of Heart Failure Related to Blood Pressure)

Peter Wohlfahrt and Renata Cífková

1.1 Prevalence and Incidence of Heart Failure

1.1.1 Heart Failure Definition and Classification

According to the European Society of Cardiology guidelines, HF is defined as a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress [1]. Heart failure can present with preserved ejection fraction (HFpEF), midrange ejection fraction (HFmrEF), or reduced ejection fraction (HFrEF). These three entities differ in their epidemiological profiles, presentation, and mechanisms. Compared with HFrEF, patients with HFpEF are older and more commonly have hypertension and atrial fibrillation, while a history of myocardial infarction is less common. In several studies, HFpEF was more common in females than in males. This may be partially explained by sex distribution in the highest age groups (60% of the US population aged ≥75 years are women). A recent analysis has shown that among individuals of similar age and similar prevalence of other HF risk factors, women are not at higher risk of HFpEF

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than men but are at a lower risk for HFrEF [2]. Heart failure with midrange ejection fraction is an intermediate phenotype, with the prevalence of ischemic heart disease (IHD) similar to that of HFrEF, while other demographic characteristics, symptom profile, comorbidities, laboratory values, and short-term outcomes are closer to those with HFpEF [3].

1.1.2 Heart Failure Prevalence

Heart failure remains a rising global epidemic with an estimated current prevalence of 38 million worldwide. The prevalence of HF in developed countries is approximately 1–3% of the adult population, rising to ≥10% among people over 70 years of age (Fig. 1.1). In individuals aged 55 years, 1 in 3 will develop HF during their remaining life span [4]. In the community, approximately one half of HF patients have preserved ejection fraction, while isolated diastolic dysfunction is present in 44% of HF cases [5]. The incidence and prevalence of HFpEF increase more sharply with age as compared to HFrEF. In the Olmsted County (Minnesota, USA) population, a decrease of HFrEF prevalence and an increase in HFpEF rate were noted during a 15-year period [6]. Similar trends were observed over a three-decade period in the Framingham Heart Study [7], with a lower prevalence of asymptomatic left ventricular systolic dysfunction accompanied by a shift in the HF phenotype toward a preponderance of HFpEF (56% vs. 31% for HFpEF vs. HFrEF in the 2005–2014 decade, respectively) (Fig. 1.2). The prevalence of HFmrEF did not change over the 30-year period. Temporal trends in risk factors for HF, with a lower prevalence of IHD and rising hypertension rates among those with HF, explain 75% of the shift toward the greater prevalence of HFpEF.

1.1.3 Incidence of Heart Failure

The incidence of HF varies between 3 and 29 per 1000 person-years, reflecting differences in ascertainment and adjustment between studies. In the Atherosclerosis

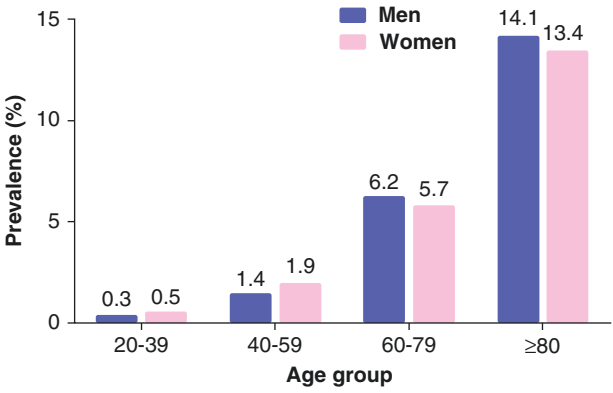

Fig. 1.1 Prevalence of heart failure by gender and age in the USA according to the National Health and Nutrition Examination Survey 2011–2014

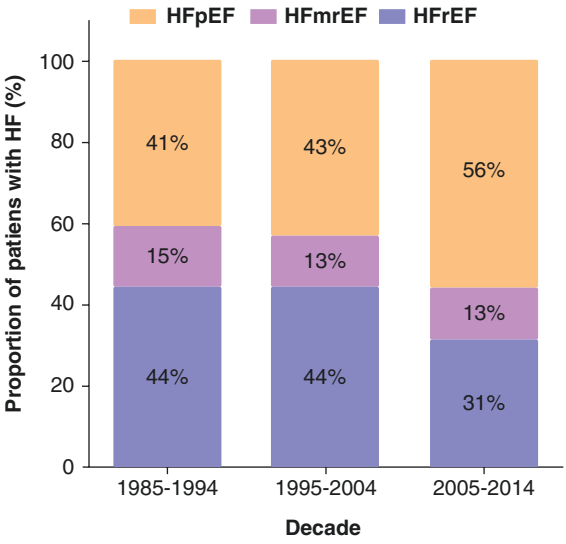

Fig. 1.2 Changes in the proportion of heart failure subtypes over three decades in the Framingham Heart Study. *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *HFmrEF* heart failure with midrange ejection fraction, *HFrEF* heart failure with reduced ejection fraction. Adapted from reference [7]

Risk in Communities (ARIC) study, the HF incidence rates varied by ethnicity, with the highest risk in African Americans, the intermediate risk in whites and Hispanics, and the lowest risk in Chinese Americans [8]. This ethnic disparity was related to differences in hypertension and diabetes prevalence.

1.1.4 Secular Trends in Heart Failure Epidemiology

Because most of the literature on HF epidemiology comes from North America and western European countries, estimation of HF trends in the global population is scarce and unreliable. A recent literature review on secular trends in HF epidemiology indicates that the incidence of HF in developed countries has been largely stable over time (with age-standardized rates even decreasing), while the HF epidemic in these countries is largely caused by improved HF survival and aging of the population [9]. In the USA, the absolute 5-year survival rate for HF increased by 9% between 1979 and 2000. Improvements in public health in high-income countries have shifted HF demographics toward the aging population with a high prevalence of chronic diseases. Elderly individuals live longer with HF, which leads to a great increase in hospitalizations with >1 million HF hospitalizations each year in both Europe and the USA. Assuming a stable prevalence of HF, the number of individuals with HF in the USA will increase by 46% over the next 20 years [10]. This increase will be largely related to aging of the population. The total direct medical costs of HF will increase from $21 billion in 2012 to $53 billion by 2030, with hospitalizations accounting for up to three quarters of these costs [10]. Except for the demographic changes, an expected 54% increase in diabetes prevalence by 2030 will further increase HF prevalence in the USA in the near future [11]. Similar trends are anticipated in other high-income countries.

1.1.5 Heart Failure Epidemiology in Middle- and Low-Income Countries

Much less is known about HF epidemiology and trends in middle- and low-income countries. Available data show several differences from high-income regions. In the PURE (Prospective Urban Rural Epidemiology) study, the cardiovascular risk factor burden was lowest in low-income countries, while the rates of major cardiovascular disease and death were substantially higher than in high-income countries [12]. Case fatality rates for HF increased with decreasing country income, being 2.6 times higher in middle-income and 3.7 times higher in low-income countries as compared to high-income countries. The International Congestive Heart Failure (INTER-CHF) study evaluating prospectively enrolled HF patients from low- and middle-income regions showed several demographic differences [13]. The mean age of HF patients in Africa and India was 53 and 56 years, respectively, while the mean age of HF patients from high-income regions was at least 10 years higher. Furthermore, the 20% prevalence of IHD in HF patients in Africa and 25% in South America is substantially lower than in other regions of the world. Similar findings were made in a systematic review of HF in low- and middle-income countries [14], in which the human development index integrating a country's life expectancy, education, and gross national income per capita positively correlated with age at admission for HF. Furthermore, IHD was the main reported cause of HF in all regions except Africa and the Americas, where hypertension was the predominant cause. According to the Global Burden of Disease Study, causes of HF differ by region, with a high incidence of preventable causes of HF such as hypertensive heart disease and rheumatic heart disease in low-income countries [15]. Thus, tailoring of policies to population-specific risks and underlying etiologies is required.

Although reliable estimates for middle- and low-income countries are lacking, evidence from the literature suggests that HF is the fastest-growing cardiovascular condition globally. The expected HF prevalence increase in middle- and low-income regions will be driven by population aging and increasing burden of hypertension and other cardiovascular risk factors. While the age-standardized prevalence of hypertension decreased by 2.6% in high-income countries from 2000 to 2010, there was a 7.7% increase in low- and middle-income countries [16]. Thus, global hypertension control is an important target to decrease the global epidemic of HF.

1.1.6 Mortality in Heart Failure

In developed countries, HF survival improved substantially during the early 1990s and early to mid-2000s, likely due to evidence-based medications [17, 18]. Lately, no significant change in mortality was observed in the community-based cohort from Olmsted County between years 2000 and 2010, with reported 20% age-adjusted mortality rates for incident HF at 1 year and 56% at 5 years [19]. This may be explained by the shift in the HF phenotype toward a preponderance of HFpEF

and the increasing comorbidity burden of HF. While the proportion of IHD decreased over the 10-year period in patients with HFrEF, there was a significant increase in the rates of hypertension, diabetes, and hyperlipidemia among subjects with HFpEF [19]. Moreover, more than half of deaths were due to non-cardiovascular causes, with respiratory, neoplasms, and mental or behavioral health being the most common. The proportion of non-cardiovascular deaths is higher in HFpEF than HFrEF. In the Framingham Heart Study, during the 1985–2014 period, prognosis of HFrEF improved, whereas that of HFmrEF and HFpEF remained unchanged [7]. This may be due to the absence of specific therapy influencing prognosis of patients with HFpEF.

In the INTER-CHF study, marked regional differences in HF mortality were noted in low- and middle-income countries, with the highest rates documented in Africa and India, intermediate in southern Asia, and lowest in China, South America, and the Middle East. A higher threshold for case definition, greater disease severity, and limited availability of evidence-based therapies might explain these differences.

1.2 Epidemiology of Hypertension and Heart Failure

Hypertension is the most prevalent risk factor for HF and carries the highest population attributable risk among all risk factors for HF. In the Framingham Heart Study cohort, hypertension antedated the development of HF in 91% of subjects, while in the Cardiovascular Health Study, the proportion was 82% [20]. After adjustment for age and other heart failure risk factors, hypertension increased the risk of HF twofold in men and threefold in women. Furthermore, hypertension accounts for 39% of cases of HF in men and 59% in women. The lifetime risk of HF for individuals with blood pressure >160/90 mmHg is double than for those with blood pressure <140/90 mmHg. An analysis of the Cardiovascular Health Study and Health ABC study in the elderly (mean age 73 years) not receiving antihypertensive therapy has shown that the risk of incident HF over 10-year follow-up increases with increasing systolic blood pressure, with subjects with blood pressure <120 mmHg having the lowest HF risk [21]. However, 38% of all incident HF events occurred in subjects with systolic blood pressure between 120 and 130 mmHg due to the highest proportion of subjects in this group (Fig. 1.3).

In the Multi-Ethnic Study of Atherosclerosis, late systolic hypertension, defined as the ratio of late (last one third of systole) to early (first two thirds of systole) pressure-time integrals (PTI) of the aortic pressure waveform, was an independent predictor of incident HF [22]. Late systolic hypertension was more predictive than the presence of hypertension. In another study [23], increased aortic pressure wave pulsatility and greater decrease in pulsatility on treatment were associated with functional improvement in patients with HFrEF receiving aggressive vasodilator titration. These differences were not identifiable using brachial cuff pressures. This suggests that central waveform analysis may provide additional prognostic information to traditional brachial blood pressure.

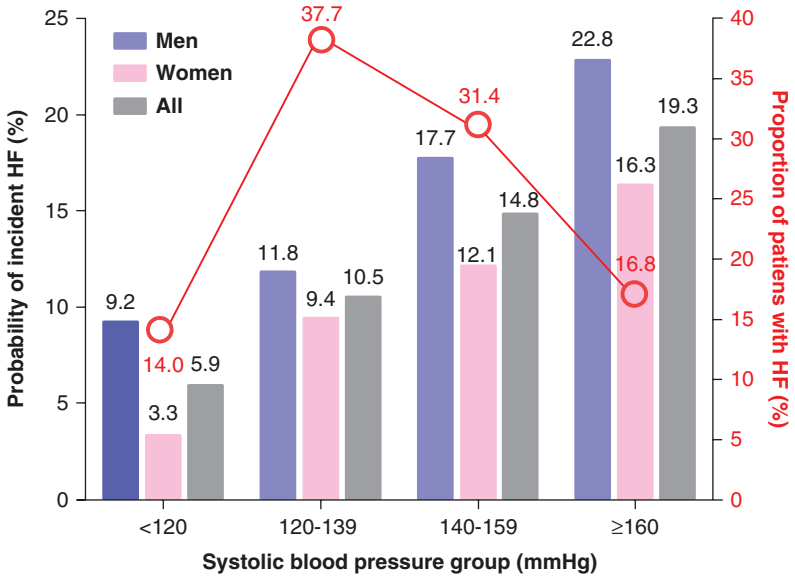

Fig. 1.3 Incident heart failure and proportion of patients developing heart failure over 10 years, by systolic blood pressure. Among elderly subjects not receiving antihypertensive therapy, the risk of incident HF over 10-year follow-up increases with increasing systolic blood pressure, with subjects with blood pressure <120 mmHg having the lowest HF risk. However, 38% of all incident HF events occurred in subjects with systolic blood pressure between 120 and 130 mmHg (red marks) due to the highest proportion of subjects in this group. Adapted from [21]

Table 1.1 Cardiovascular risk reduction by antihypertensive trials in subjects aged ≥60 years

Trial	*N*	Age	Stroke (%)	IHD (%)	HF (%)	All CVDs (%)
STOP-HTN	1627	70–84	47	13	51	40
SHEP	4736	≥60	33	27	55	32
Syst-Eur	4695	≥60	42	26	36	31
STONE	1632	60–79	57	6	68	60
Syst-China	2394	≥60	38	33	38	37
HYVET	3845	≥80	30	28	64	34
SPRINT	9361	68	11	17	38	25

IHD ischemic heart disease, *HF* heart failure, *CVD* cardiovascular disease, *HYVET* Hypertension in the Very Elderly Trial, *SHEP* Systolic Hypertension in the Elderly Program, *STONE* Shanghai Trial of Nifedipine in the Elderly, *STOP-HTN* Swedish Trial in Old Patients with Hypertension, *Syst-China* Systolic Hypertension in China, *Syst-Eur* Systolic Hypertension in Europe

Several interventional studies have highlighted the importance of hypertension control to decrease the HF risk, especially in elderly subjects. In subjects aged ≥60 years, antihypertensive therapy reduced the risk of HF by 36–68% and had a greater impact on HF prevention than on any other major cardiovascular outcome (Table 1.1). In the Systolic Blood Pressure Intervention Trial (SPRINT) among subjects at increased cardiovascular risk without diabetes or prior stroke and baseline systolic blood pressure >130/80 mmHg, target systolic blood pressure <120 mmHg was associated with a 46% HF risk reduction and an overall decrease in

cardiovascular death. Because the automated office measurement without medical staff being present used in the SPRINT study is 5–10 mmHg lower than conventional office measurement, the recent ACC/AHA/HFSA update on HF management recommends a goal blood pressure of <130/80 mmHg in subjects at high risk of HF [24].

Absence of hypertension, obesity, and diabetes substantially prolongs HF-free survival. Subjects free of these three risk factors at the age of 45 years have up to 85% lower risk of incident HF, greater than 10 years longer HF-free survival, and live up to 13 years longer than those with all three risk factors [25]. This suggests that primordial prevention of hypertension, diabetes, and obesity leads not only to the overall longer survival but also to a shortened period of chronic illness at the end of life.

1.3 Conclusion

Worldwide, heart failure is the most rapidly growing cardiovascular disease, which will lead to a substantial burden on global health-care system in the coming years. Sources of this epidemic differ between developed and developing countries. In high-income nations, improvements in public heath are shifting demographics toward an aging population. Furthermore, an expected increase in the prevalence of diabetes and obesity will increase heart failure prevalence in developed countries. While the proportion of heart failure with preserved ejection fraction is increasing in these countries, no therapy has been shown to affect the prognosis of this heart failure subtype. In developing countries, preventable causes of heart failure such as hypertensive heart disease are responsible for most of the heart failure cases. Affected patients are younger than those in the developed countries. The switch toward a Western lifestyle with an increase in age-standardized prevalence of hypertension and other cardiovascular risk factors is expected to drive the heart failure epidemic in developing countries. To combat this heart failure pandemic, improvement in the global control of heart failure risk factors will be required.

1.4 Future Directions

- Heart failure is the most rapidly growing cardiovascular disease with a substantial burden on the global health-care system in the near future.
- Hypertension is the most prevalent risk factor for heart failure with the highest population-attributable risk, particularly for heart failure with preserved ejection fraction.
- In high-income countries, the increase in heart failure prevalence is mostly related to aging of the population, whereas in low- and middle-income countries, there is also a contribution of increasing burden of hypertension.
- Treatment of hypertension substantially reduces the risk of developing heart failure, particularly in the elderly.
- Further research is warranted to identify measures for improving the prognosis of heart failure with preserved ejection fraction.

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Part II

Mechanisms of Heart Failure in Arterial Hypertension

Genetics of Hypertension and Heart Failure

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The high prevalence of hypertension (HTN) and its consequent significant adverse economic impact on the individual and population highlight the importance of understanding the causation of HTN and developing effective early primary prevention measures to interrupt and prevent the continuing and expensive cycle of managing HTN and its complications [1]. Heart failure (HF) is a leading cause of death worldwide [2] with HTN being one of its important risk factors. Both HTN and HF are complex multifactorial diseases involving multiple pathways affected by genetic predisposition, ageing process and environmental factors. HTN, cardiomyopathies and ischaemic heart diseases are among the biggest risk factors for causing HF, which are of two types—HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). In contrast to HFrEF, HFpEF which accounts for 50% of HF prevalence has many unique challenges including difficulty in diagnosis and lack of effective treatment [2]. For understanding and predicting HTN and HF, both individual life histories may be as important as population histories. Their genetic determinants can provide keys to the underlying mechanisms and lead to a better personalised diagnosis and therapy. In this chapter, we will describe the genetic

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underpinnings of HTN and HF—while both these conditions have different genetic predictors, the determinants of hypertension will have an impact on HF as part of the cardiovascular continuum [3]. The genetics of other causes of HF such as ischaemic heart disease is beyond the scope of this chapter.

2.1 Heritability of Hypertension and Heart Failure

Family studies have consistently demonstrated a genetic component influencing blood pressure (BP) as well as HF. The heritability of clinic systolic BP and diastolic BP is around 15–40% and 15–30%, respectively, whereas for ambulatory night-time systolic and diastolic BP, the heritabilities are 32–70% and 32–50% [4–10]. The sibling recurrent risk (λ_s) of HTN is around 1.2–1.5 [11]. In an analysis of the Framingham Heart Study, the occurrence of HF in at least one parent (occurring before 75 years of age) was a significant predictor of the HF phenotype in the offspring (hazard ratio 1.70 [95% confidence interval (CI) 1.11–2.60 [12]]). Even after accounting for echocardiographically determined left ventricular mass (LVM), the risk of HF was elevated, with a hazard ratio of 1.82 (95% CI 1.14–2.91). The familial risk of HF may be mediated by hereditary factors that predispose to myocardial abnormalities, such as left ventricular systolic dysfunction, dilatation and hypertrophy (e.g. abnormal increase in LVM). These left ventricular phenotypic abnormalities have been found to precede clinical HF. Twin studies demonstrated intra-class correlation coefficients of 0.69 and 0.32 for monozygotic and dizygotic twins, respectively [13], and heritabilities of 59% [14]. Data from the Framingham Heart Study estimated the heritability of LVM to be 0.24–0.32 [15]. Cardiovascular magnetic resonance (CMR) measured LV mass, and papillary muscle mass demonstrated substantially higher heritabilities of 84% compared to echocardiographic measures [16]. Recent studies have shown that pulse pressure and aortic stiffness, which are predictors of HF, are heritable traits, with the heritability of pulse pressure estimated at 37% [4, 17].

A sizeable proportion of the HF burden is attributable to CHD and MI. This is evidenced by the reduction from a one-in-five lifetime risk of HF in all men to one-in-nine in the absence of an antecedent MI [18]. However, the familial aggregation of HF is not explained solely by the presence or absence of CHD but by qualitative differences in disease burden. Heritability is high for hazardous coronary lesion locations, such as disease of the left main artery or proximal vessels and coronary calcification, whereas distal disease exhibits lower heritability [19, 20]. HFpEF is a highly heterogeneous disease, and genetic effects can be expected to be very limited as the disease is of late onset and associated with multiple environmental triggers [21, 22].

2.2 Hypertension and Heart Failure: Causation

While HTN is clearly defined by BP measurement, HF is an umbrella term for a compendium of patient symptoms and physical examination findings that are associated with impaired ventricular function, predominantly due to left ventricular systolic (contractile) dysfunction. HF and HTN are diseases with many aetiological roots and may in fact encompass several mechanistically distinct diseases. HTN in turn can cause HF. There is significant environmental contribution to both—but their effects on the phenotype may be either direct or indirect. For example, high salt intake can increase the risk of developing HTN and HF, and HTN is itself a major determinant of HF. From an evolutionary perspective, essential HTN is a disease of civilisation with its abundance of processed foods and long lifespan. The lifestyle characteristics of modern civilisation are ideal risk factors for the development of HTN, and this may be facilitated by the higher prevalence of genotypes that may have optimised fitness in an ancient environment [23–26]. It is recognised that HTN occurs earlier and with more severity in people of African ancestry compared to those of European ancestry (although clearly non-genetic factors may contribute) [27, 28]. The rates of HTN and sodium sensitivity are generally higher in individuals carrying the ancestral alleles of sodium-conserving genes, which show strong latitudinal clines with the ancestral sodium-conserving alleles more prevalent in African populations and less so in the northern regions [29–31]. The potential risk factors for HF include older age, HTN, CHD, obesity, diabetes and valvular disease. Even after accounting for these cardiovascular risk factors, however, a significant proportion of HF is not explained. Nonfamilial HF is typically a disease of the elderly and is the result not only of genetic factors that act to either protect or predispose individuals but also of environmental factors, such as smoking, diet and sedentary lifestyle.

2.3 Genetics of Hypertension and Heart Failure

The identification of rare mutations in genes causing monogenic syndromes comes from linkage analysis of pedigrees exhibiting a Mendelian pattern of inheritance. In contrast, the standard method for genetic dissection of complex trait is a genome-wide association study (GWAS) which is based on the common disease/common variant hypothesis. GWAS of BP and HTN have identified over 200 SNPs, and the list continues to grow as the sample size increases especially with emerging data from the UK Biobank. However, the percentage of the BP trait variance explained

by all the SNPs is less than 5% [32–36]. The complex aetiologies underlying HF, which means that HF is not a single diagnosis, have made HF GWAS studies more challenging. Thus GWAS of HF fall into two groups (all-cause genome-wide studies and genome-wide studies on a narrowly defined phenotype), and these have identified 14 SNPs so far [37–41]. The top GWAS signals for BP and HF are summarised in Fig. 2.1 and Table 2.1.

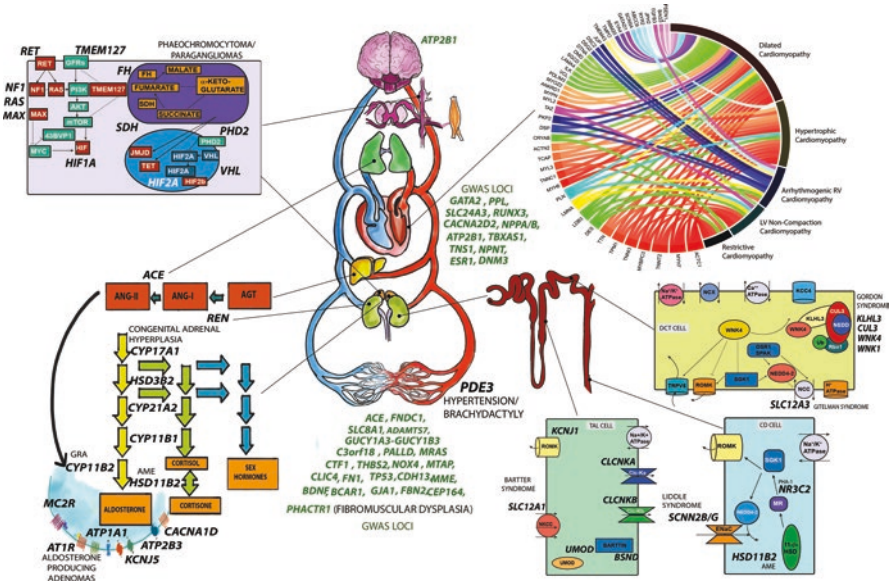

Fig. 2.1 Genetic pathways involved in blood pressure and heart failure. Genes containing known mutations that cause high or low blood pressure or cardiomyopathy in the context of the circulatory system. Plausible genes linked to GWAS loci are presented near the site of their likely phenotype effect

Table 2.1 GWAS signals for blood pressure, heart failure and heart failure-related traits

Locus	Phenotype	SNP	Nearest gene(s)
1p36.2	BP/HTN	rs880315	*CASZ1*
1p36.13	Dilated cardiomyopathy	rs10927875	*ZBTB17*
1p36.22	BP/HTN	rs17367504	*MTHFR*, *CLCN6*, *NPPA*, *NPPB*
		rs5068	
1p34.2	HF founder population	rs16830359	*SLC2A1*
1p21.2	Aortic root size	rs7543130	*PALMD*
1p13.2	BP/HTN	rs2932538	*SLC16A1*, *CAPZA1*, *ST7L*, *MOV10*
		rs17030613	
		rs10745332	
1q32.1		rs2169137	*MDM4*
1q41	HF founder population	rs12757165	*ESRRG*

Table 2.1 (continued)

Locus	Phenotype	SNP	Nearest gene(s)
1q42.2	BP/HTN	rs2004776	*AGT*
2p23.2		rs1275988	*KCNK3*
2q11.2		rs7599598	*FER1L5*
2q24.3		rs1446468	*FIGN*
		rs13002573	*FIGN*
		rs16849225	*FIGN*
		rs6749447	*STK39*
2q32.1		rs16823124	*PDE1A*
3p25.3		rs347591	*HRH1-ATG7*
3p24.1		rs13082711	*SLC4A*
		rs820430	
3p22.3	Heart failure	rs12638540	CMTM7
3p22.1	BP/HTN	rs9815354	*ULK4*
		rs3774372	
		rs1717027	
3p21.31		rs319690	*MAP4*
		rs7651237	
3p21.1		rs9810888	*CACNA1D*
3q26.1		rs16833934	*MIR1263*
3q26.2		rs419076	*MECOM*
4q12		rs871606	*CHIC2*
4q21.21		rs16998073	*FGF5*
		rs1458038	
4q24		rs13107325	*SLC39A8*
4q25		rs6825911	*ENPEP*, *PITX2*
4q32.1		rs13139571	*GUCY1A3-GUCY1B3*
5p13.3		rs1173771	*NPR3-C5orf23*
		rs7733331	
		rs1173766	
5q23.2	Aortic root size	rs17470137	*CCDC100*
5q33.3	BP/HTN	rs11953630	*EBF1*
6p22.2		rs1799945	*HFE*
		rs198823	
6p22.1	HF founder population	rs10947055	*TRIM38*
6p21.33	BP/HTN	rs805303	*BAG1*
		rs2021783	*CYP21A2*
	Dilated cardiomyopathy	rs9262636	*HGC22*
6p21.32	BP/HTN	rs2854275	*HLA-DQB1*
6p21.1		rs10948071	*CRIP3*
6p24.1		rs9349379	*PHACTR1*
6q22.31	LV internal dimension	rs89107	*SLC35F1*
		rs11153768	*PLN*
6q22.33	BP/HTN	rs13209747	*RSPO3*
6q25.1		rs17080102	*PLEKHG1*
7p15.2		rs17428471	*EVX1-HOXA*
7p12.3		rs2949837	*IGFBP3*
7q21.2		rs2282978	*CDK6*
7q22.3		rs17477177	*PIK3CG*
		rs12705390	
7q36.1		rs3918226	*NOS3*
8p23.1		rs4841569	*BLK-GATA4*
		rs2898290	
8q11.21	LV mass	rs4552930	*UBE2V2*

(continued)

Table 2.1 (continued)

Locus	Phenotype	SNP	Nearest gene(s)
8q24.12	BP/HTN	rs2071518	*NOV*
10p12.31		rs11014166	*CACNB2*
		rs1813353	
		rs4373814	
		rs12258967	
10q21.2		rs1530440	*c10orf107*
		rs4590817	
		rs12244842	
		rs7070797	
10q22.2		rs4746172	*VCL*
10q23.33		rs932764	*PLCE1*
10q24.32		rs1004467	*CYP17A1-NT5C2*
		rs11191548	
		rs12413409	
		rs4409766	
		rs3824755	
10q25.1	HF founder population	rs1320448	*COL17A1*
10q25.3	BP/HTN	rs2782980	*ADRB1*
		rs7076938	
		rs1801253	
10q26.11	Dilated cardiomyopathy	rs2234962	*BAG3*
10q26.12	IVS wall thickness	rs1571099	*PPAPDC1A*
11p15.5	BP/HTN	rs661348	*LSP1-TNNT3*
11p15.4		rs7129220	*ADM*
11p15.1		rs381815	*PLEKHA7*
		rs757081	*PIK3C2A*, *NUCB2*, *NCR3LG1*
11p15.2		rs2014408	*SOX6*
		rs4757391	
11q13.1		rs4601790	*EHBP1L1*
		rs3741378	*RELA*
11q22.1		rs633185	*FLJ32810-TMEM133*
11q24.3		rs11222084	*ADAMTS8*
12p12.2	Aortic root size	rs10770612	*PDE3A*
12q14.1	Heart failure	rs11172782	*LRIG3*
12q14.3	Aortic root size	rs4026608	*HMGA2*
12q13.13	BP/HTN	rs7297416	*HOXC4*
12q21.33		rs11105354	*ATP2B1*
		rs2681492	
		rs2681472	
		rs17249754	
12q22	Dilated cardiomyopathy	rs10859313	*CLLU1*
12q24.12	BP/HTN	rs3184504	*SH2B3*
		rs653178	
12q24.13		rs11066280	*RPL6-ALDH2*
12q24.21		rs35444	*TBX5-TBX3*
		rs2384550	
		rs10850411	
		rs1991391	
		rs11067763	*MED13L*
13q22.1	Ejection fraction	rs9530176	*KLF5*
15q12	HF founder population	rs17636733	*UBE3A*
15q21.1	BP/HTN	rs1036477	*FBN1*

Table 2.1 (continued)

Locus	Phenotype	SNP	Nearest gene(s)
15q22.2	Heart failure	rs10519210	*USP3*
15q24.1	BP/HTN	rs6495122	*CYP1A1-ULK3*
		rs1378942	
15q24.2		rs11072518	*COX5A*
		rs1133323	
15q26.1		rs2521501	*FURIN-FES*
16p12.3		rs13333226	*UMOD*
16q22.1		rs33063	*NFAT5*
17p13.3	Aortic root size	rs10852932	*SMG6*
		rs4523957	*SRR*
		rs413016	*TSR1*
17q21.31	BP/HTN	rs12946454	*PLCD3*
17q21.32		rs17608766	*GOSR2*
17q21.33		rs12940887	*ZNF652*
		rs16948048	
17q24.2	LV internal dimension	rs7213314	*WIPI1*
20p12.2	BP/HTN	rs1327235	*JAG1*
		rs1887320	
20q13.32		rs6015450	*GNAS-EDN3*
		rs6092743	*C20orf174*

2.4 Genetic Pathways of Hypertension and Heart Failure

2.4.1 Sodium and Intravascular Volume

Sodium homoeostatic pathways are the main pathways that account for the majority of the monogenic HTN and hypotension syndromes [42]. Sodium and intravascular volume are also crucial in the aetiology and manifestation of HF. Glucocorticoid-remediable aldosteronism or familial hyperaldosteronism type 1 (OMIM #103900) is an autosomal dominant syndrome in which HTN is caused by increased aldosterone secretion driven by ACTH. The fusion of the 5′ regulatory sequences of 11β-hydroxylase (*CYP11B1*) with the distal coding sequences of aldosterone synthase (*CYP11B2*) leads to a chimeric gene which results in ACTH becoming the main controller for aldosterone secretion instead of angiotensin II or potassium [43]. Familial hyperaldosteronism type II (FH II) (OMIM #605635) is an autosomal dominant syndrome caused by the hyperplasia or adenoma of the aldosterone-producing adrenal cortex (APA), the genetic cause localised to chromosome 7p22 [44]. Apparent mineralocorticoid excess (OMIM #218030), accompanied by hypokalaemia and metabolic alkalosis and, is due to the absence or reduced activity of 11β-hydroxysteroid dehydrogenase (*HSD11B2*), resulting in HTN in which cortisol acts as if it were a potent mineralocorticoid [45]. Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by defects in enzymes of cortisol biosynthesis [46]. In some of these syndromes, plasma ACTH will increase to produce cortisol that causes the accumulation of aberrant products, some of which lead to HTN.

Enzyme mutations that are associated with HTN include (in order of frequency) 11β-hydroxylase (OMIM #202010, *CYP11B1*), 3β-hydroxysteroid dehydrogenase (OMIM #613890, *HSD3B2*), 17α-hydroxylase (OMIM #609300, *CYP17A1*) and cholesterol desmolase (OMIM #118485, *CYP11A1*). Furthermore, a common SNP near *CYP17A1* has emerged in multiple large BP GWAS meta-analyses [47–50]. It is estimated that ≤40% of aldosterone-producing adenomas (APAs) harbour somatic mutations in *KCNJ5*, *ATP1A1*, *ATP2B3*, *ATP2A2* and *CACNA1D* [51]. Pseudohypoaldosteronism type II (Gordon's syndrome, familial hyperkalaemia, OMIM #145260) is an autosomal dominant low-renin HTN syndrome resulting from either gain-of-function mutations in *WNK1* or loss-of-function mutations in *WNK4* and mutations in Kelch-like 3 (*KLHL3*) and Cullin 3 (*CUL3*) genes. Liddle's syndrome (OMIM #177200) is an autosomal dominant condition with a clinical picture of HTN and aldosterone excess but with very low aldosterone and renin levels. This is caused by gain-of-function mutations in the genes coding of the beta or gamma subunits of ENaC (*SCNN1B*, *SCNN1G*) [52, 53]. Two examples of low BP syndromes that include Bartter's (*SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND*, *CaSR*, *ClCK-A*) and Gitelman's (*SLC12A3*) syndromes are associated with mutations that reduce salt retention, tend to lower BP and protect against the development of HTN [42, 54]. Mutation in *CLCNKB* gene (1p36), encoding a basolateral chloride channel ClCKb, has been identified as the most frequent cause of classic Bartter syndrome. Mutations in *SLC12A1* and *KCNJ1* cause the classic, less severe phenotype.

In addition to the kidney, the heart secretes a family of vasodilatory and natriuretic hormones in response to increased wall stress—atrial natriuretic peptide (*NPPA*) and B-type natriuretic peptide (*NPPB*). Knockout of one copy of *NPPA* in mice increases BP, while overexpression of *NPPA* lowers BP [55, 56]. There is now a convincing evidence for common variations in the *NPPA-NPPB* locus influencing both levels of natriuretic peptides and BP in opposite directions [48–50, 57]. Furthermore, a SNP near the natriuretic peptide clearance receptor (*NPR3*) also showed genome-wide significant association in European, African and Japanese BP GWAS studies [48, 49, 58]. Interestingly, there is evidence of convergence between studies in animal models of HTN and their emerging signals from BP GWAS analyses [59–61]. Levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) increase with myocardial wall stress and are associated with HF. While natriuretic peptide gene variants have not been directly associated with HF, they have been associated with increased susceptibility to LVH [62].

A GWAS for HTN using an extreme case-control design identified a SNP in the 5′ region of uromodulin gene (*UMOD*) which is almost exclusively expressed in the thick ascending limb of the loop of Henle in the kidney, identifying a potentially novel pathway of BP regulation through an effect on sodium homeostasis [63]. Moreover, independent studies have identified SNPs highly correlated with the HTN SNP near *UMOD* to be associated with chronic kidney disease [64]. Trudu et al. [65] showed furosemide treatment significantly enhanced natriuresis and reduced BP levels both in the transgenic mice and in the hypertensive individuals homozygous for the *UMOD*-increasing allele making this a potentially interesting locus for both HTN and HF.

2.4.2 Autonomic Nervous System

Increased sympathetic nervous system activity has a role in causing HTN [66] which may be the result of background genetic susceptibility interacting with chronic psychogenic stress, obesity or high sodium intake. HTN could also arise or be sustained by defects in baroreceptor function [67]. Catecholamines can also exert a direct toxic effect on the myocardium through enhanced lipid mobility, calcium overload, free radical production or increased sarcolemmal permeability and lead to HF. Rare syndromes caused by mutations affecting function of the autonomic system and causing HTN are exemplified by phaeochromocytomas (PCCs) and paragangliomas (PGLs). Up to 10% of genetically determined PCC/PGLs are due to mutations in *SDHD*, *SDHC*, *SDHB*, *SDHA* and *SDHAF2* (or *SDH5*) genes [68]. Autosomal dominantly inherited PCCs are due to a variety of *RET* proto-oncogene mutations. Other PCC susceptibility genes including *RET* (multiple endocrine neoplasia syndrome type 2 (MEN-2)), the tumour suppressor gene *VHL* observed in families with von Hippel-Lindau syndrome, and the gene that encodes succinate dehydrogenase subunit B and D (*SDHB, SDHD*) cause familial PGL [68].

Polymorphisms in the alpha2c-adrenergic receptor and the beta1-adrenergic receptor are associated with an increased risk of HF in African-American individuals via increased synaptic norepinephrine release [69]. The simultaneous occurrence of both gene mutations had a synergistic effect with a tenfold increase in the risk of HF in double homozygotes [69].

2.4.3 Cardiac and Vascular Mechanisms

Vascular diameter and compliance of resistance arteries are important determinants of arterial pressure. Vascular changes in HTN may result from either an abnormal extracellular stimuli or an altered intracellular signalling cascade leading to enhanced vasoconstriction, blunted vasodilation and vascular wall hypertrophy/remodelling, all of which contribute to elevated peripheral vascular resistance.

Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesises and releases a spectrum of vasoactive substances, including nitric oxide (NO), a potent vasodilator. NO exerts vasodilating and anti-proliferative effects on smooth muscle cells and inhibits thrombocyte aggregation and leucocyte adhesion. Other vascular relaxation factors include endothelins and prostacyclin. Endothelin-1 (*EDN1*) activates specific ETA receptors (*EDNRA*) on vascular smooth muscle cells to cause vasoconstriction and cell proliferation. In contrast, endothelial ETB receptors (*EDNRB*) mediate vasodilatation via release of NO and prostacyclin (*PGI2*). GWAS of coronary artery disease (CAD) showed the SNP rs9349379 G allele (frequency 36%) was associated with an increased risk of CAD and coronary calcification but decreased risk for four conditions (migraine headache, cervical artery dissection, fibromuscular dysplasia and HTN [70, 71]). This SNP is located within the third intron of the gene encoding phosphatase and actin regulatory protein 1 (*PHACTR1*). However, functional analysis of this variant shows that it regulates

expression of endothelin 1 (*EDN1*), a gene located 600 kb upstream of *PHACTR1*. Interestingly, variants in the *PHACTR1* gene have been associated with fibromuscular dysplasia (FMD), a nonatherosclerotic vascular disease leading to stenosis, dissection and aneurysm affecting mainly the renal and cerebrovascular arteries [72]. Variants in the gene for vascular endothelial growth factor A (*VEGFA*) which induce proliferation and migration of vascular endothelial cells and stimulate angiogenesis are one of the replicated signals from GWAS. The GWAS locus containing urotensin-2 receptor (*UTS2R*) gene encodes a class A rhodopsin family G-protein-coupled receptor that upon activation by the neuropeptide, urotensin II, produces profound vasoconstriction. One of the GWAS loci is the relaxin gene which encodes a G-protein-coupled receptor with roles in uterine relaxation, vasorelaxation and cardiac function which signals via phosphatidylinositol 3-kinase (*PI3K*).

Ion transport by vascular smooth muscle cells may contribute to HTN-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH. An increased Na^+/H^+ exchanger (*SLC9A1*) can stimulate vascular tone and cell growth by increasing sodium reabsorption in renal proximal tubule cells [73]. Other ion transporters considered are the Na^+ bicarbonate transporter (*SLC4A10)* and the Na^+-Ca^+ exchanger NCX (*SLC8A1*). One hypothesis for the mechanism by which excess salt intake elevates BP is through the observed rise in cardiotonic steroids such as ouabain in response to salt intake [74]. It is believed that ouabain inhibits the plasma membrane Na^+/K^+ ATPase, leading to an increase in cytosolic Na^+ concentration which raises the cytosolic Ca^{2+} concentration through the involvement of the Na^+/Ca^{2+} exchanger NCX (*SLC8A1*) and thereby increases contraction in vascular or heart muscle [75].

The cardiomyopathies (intrinsic diseases of heart muscle), including dilated, hypertrophic and restrictive forms, can all lead to HF, although dilated cardiomyopathy (DCM) is the leading global cause for heart transplantation. Idiopathic dilated cardiomyopathy (DCM) is a form of HF defined by the presence of left ventricular dilatation and left ventricular systolic dysfunction in the absence of an obvious aetiology, such as CAD, HTN, valvular disease or congenital defect. It affects ~1/2500 adults and it is more common in men than in women [76]. There are over 50 currently recognised genes associated with this condition, most of which encode proteins in the cardiomyocyte sarcomere (Fig. 2.1 and Table 2.2).

GWAS has identified two loci for DCM: rs10927875 maps to a region on chromosome 1p36.13 which encompasses several genes among which *HSPB7* has been formerly suggested to be implicated in DCM. The second identified locus involves rs2234962, a non-synonymous SNP (c.T757C, p. C151R) located within the sequence of *BAG3* on chromosome 10q26 [77].Other GWAS studies of systolic HF have identified rs10519210 (nearest gene *USP3*) in Europeans and rs11172782 (nearest gene *LRIG3*) in Africans [41]. Two intronic SNPs rs1739843 (HSPB7) and rs6787362 (FRMD4B) were identified in a case-control study of advanced HF [37].

Among patients with thickening of the left ventricular wall that was not explained by HTN or valvular disease, nearly one in five individuals had a mutation in known sarcomeric (e.g. b-myosin heavy chain, myosin-binding protein C, troponin T, troponin I and myosin light chain) or storage (e.g. alpha-galactosidase A) genes [78].

Table 2.2 Genes associated with dilated cardiomyopathy

Gene	Protein	OMIM	% of familial DCM cases
LMNA	Lamin A/C	150330	6%
MYH7	β-myosin heavy chain	160760	4.2%
MYPN	Myopalladin	608517	3.5%
TNNT2	Cardiac troponin T	191045	2.9%
SCN5A	Sodium channel	600163	2.6%
MYBPC3	Myosin-binding protein C	600958	2%
RBM20	RNA-binding protein 20	613171	1.9%
TMPO	Thymopoietin	188380	1.1%
LAMA4	Laminin a-4	600133	1.1%
VCL	Metavinculin	193065	1%
LDB3	Cypher/ZASP	605906	1%
TCAP	Titin-cap or telethonin	604488	1%
PSEN1/2	Presenilin 1/2	104311/600759	1%
ACTN2	α-actinin-2	102573	0.9%
CRYAB	Alpha-B crystallin	123590	0.7%
TPM1	α-tropomyosin	191010	0.6%
ABCC9	SUR2A	601439	0.6%
ACTC1	Cardiac actin	102540	0.5%
PDLIM3	PDZ LIM domain protein 3	605889	0.5%
ILK	Integrin-linked kinase	602366	0.5%
TNNC1	Cardiac troponin C	191040	0.4%
TNNI3	Cardiac troponin I	191044	0.4%
PLN	Phospholamban	172405	0.4%
DES	Desmin	125660	0.3%
SGCD	δ-sarcoglycan	601411	0.3%
CSRP3	Muscle LIM protein	600824	0.3%
MYH6	α-myosin heavy chain	160710	Unknown
TTN	Titin	188840	Unknown
EYA4	Eyes absent 4	603550	Unknown
ANKRD1	Ankyrin repeat domain-containing protein 1	609599	Unknown
DMD	Dystrophin	300377	Unknown
GATAD1	GATA zinc finger domain-containing 1	614518	Unknown
BAG3	BCL2-associated athanogene 3	603883	Unknown
TAZ/G4.5	Tafazzin	300394	Unknown

2.5 Future Directions

Advances in genomics have accelerated over the last decade leading to an unparalleled leap in our understanding of the genetic architecture of BP and HF. While the technological and analytic aspects of genomics have been very successful in discovering DNA sequence variants associated with disease, the functional and biological significance of the vast number of these variants in the human genome are unknown. The *UMOD* loci from GWAS are now the basis of a clinical trial (clinicaltrials.gov NCT03354897) to reposition a loop diuretic in the HTN care pathway. Advances in the genetics of DCM and systolic HF have highlighted numerous rare

variants linked to DCM and fewer common variants linked to DCM and systolic HF. Unravelling the genetics of HF is challenging and requires great care in phenotypic definition and characterisation for efforts to be fruitful. Ultimately, understanding the genetic underpinnings of both BP and HF has the common goal which is early detection and precision treatment.

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Blood Pressure Variability and Blood Pressure Load

3

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3.1 Introduction

Blood pressure (BP) values change significantly over time as a result of the interaction between extrinsic environmental and behavioral factors and intrinsic cardiovascular regulatory mechanisms. Although these variations represent a continuous phenomenon, they may be evaluated over different time windows: from beat to beat [**very short-term** BP variability (BPV)], within 24 h (from minute to minute, hour to hour, and from day to night; **short-term** BPV), over different days (**mid-term** BPV), or between clinic visits performed over weeks, months, seasons, and years (**long-term** BPV) [1]. These different types of BPV appear to be influenced by several cardiovascular regulatory mechanisms and by subjects' individual characteristics. While in physiological conditions, these variations may represent a response to environmental stimulations from daily life, they may also reflect, however, alterations in mechanisms responsible for cardiovascular homeostasis. Over the last decades, a series of experimental and clinical studies have indicated that increased BPV (either in the short- or in the long term) is associated with development, progression, and severity of cardiac, vascular, and renal target organ damage (TOD) and with an increased risk of cardiovascular events and cardiovascular and all-cause mortality (Fig. 3.1). The analysis of 24 h ABP recordings allows not only the quantification of average BP levels and of BP fluctuations over the recording period but also the assessment of the so-called BP

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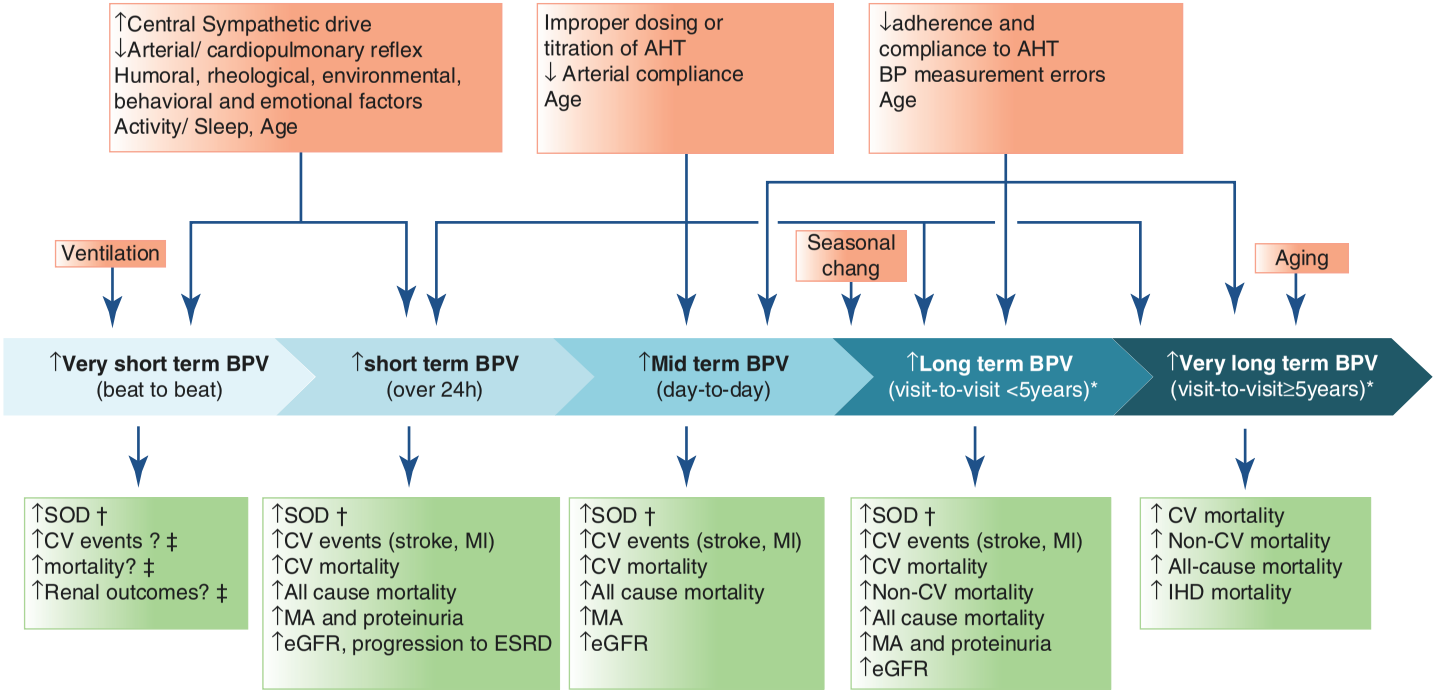

Fig. 3.1 Different types of blood pressure (BP) variability (BPV), their determinants, and prognostic relevance. Taken from [1] by permission. †Cardiac, vascular, and renal SOD; ‡BPV on a beat-by-beat basis has not been routinely measured in population studies. *AHT* antihypertensive treatment, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *IHD* ischemic heart disease, *MA* microalbuminuria, *MI* myocardial infarction, *SOD* subclinical organ damage

load. This is the percentage of readings above threshold values set for daytime and nighttime which might represent a clinically useful parameter complementing the quantification of average ABP levels and spontaneous BPV of the respective subperiods, although not free from limitations. Assessing BP load from 24 h ABPM might result useful, in particular in subjects with high normal office BP elevation in whom it could improve the diagnostic approach to hypertension. The aim of this chapter is to review the current evidence in the field of BPV including its mechanisms, the methodological aspects that should be considered for its assessment, and its relevance and significance for cardiovascular prognosis as well as its potential for application in clinical practice. In its last part, it also addresses the concept of BP load, discussing whether a proper interpretation of ABPM should include its assessment in addition to that of average BP values and BPV.

3.2 Mechanisms

Very short-term and short-term BPV. In physiological conditions, BP fluctuations occurring beat-to-beat and within the 24 h may represent a homeostatic response of neural [2–4], humoral, vascular [5–8], and rheological mechanisms to environmental, behavioral, and emotional stimuli modulated by a genetically determined susceptibility yet not completely understood. However, when increases in short-term BPV are sustained, they may also reflect alterations in regulatory mechanisms in the context of pathological conditions associated with autonomic dysfunction, characterized by enhanced sympathetic drive and impaired baroreflex function or by more complex neurological disorders. A list of the intrinsic cardiovascular mechanisms and extrinsic factors responsible for BP fluctuations occurring in the

Box 3.1: Mechanisms and Factors Responsible for BP Fluctuations Occurring Beat-to-Beat and Within 24 h

- **Neural mechanisms:** central sympathetic drive, arterial and cardiopulmonary reflexes
- **Humoral mechanisms:** catecholamines, insulin, insulin resistance, angiotensin II, bradykinin, endothelin-1, nitric oxide, endothelial dysfunction
- **Vascular mechanisms:** viscoelastic properties of large arteries, peripheral vasomotor modulation
- **Rheological mechanisms:** blood viscosity
- **Renal mechanisms:** salt sensitivity and sodium excretion
- **Environmental factors:** seasonal and altitude-related changes
- **Behavioral factors:** job strain, levels of physical activity, sleep/wakefulness cycles, quality and duration of sleep, postural changes, patterns of sodium intake
- **Emotional stimuli:** psychological stress
- **Genetic susceptibility**
- **Pathological conditions associated with autonomic dysfunction:** sleep-related breathing disorders (i.e., obstructive sleep apnea syndrome), carotid artery disease, arterial hypertension, chronic kidney disease, heart failure, diabetes mellitus, postural orthostatic tachycardia syndrome, Parkinson disease
- **Treatment-related factors and specific drug intake**

very short term and in the short term is summarized in Box 3.1. In particular, alterations in autonomic cardiovascular modulation and subject's behavioral factors such as daytime levels of activity and overall changes in the sleep/wakefulness cycle have been shown to exert an important influence on BP variations occurring from **day to night**. For instance, alterations in nighttime BP patterns (i.e., non-dipping or rising pattern of BP) have been shown to be influenced not only by an increased sympathetic activity during nighttime [4, 9] but also by salt sensitivity and sodium excretion [10, 11], sleep-related breathing disorders, obesity and insulin resistance [12], endothelial dysfunction [13], or specific drug intake [14, 15].

Mid-term BPV. Behavioral factors such as job strain, levels of physical activity, sleep/wakefulness cycles, quality and duration of sleep, postural changes, and patterns of sodium intake are likely to play an important role in determining day by day BP fluctuations. This has been clearly exemplified by some studies in which significant changes in BP levels between working days and the weekend have been reported [16]. Data from several population studies have found several factors, such as advanced age, female gender, increased arterial stiffness, elevated mean BP values, reduced body mass index, low heart rate, high heart rate variability, excessive alcohol intake, cigarette smoking, history of peripheral artery disease, cardiovascular disease, diabetes mellitus, diabetic nephropathy, and sedentary lifestyle, to be associated with increased values of day by day BPV derived from self-BP measurements performed at subjects' home [8, 17–21]. Studies focusing on treated hypertensive patients have found a higher day by day BPV among these individuals compared to untreated subjects [18, 20], also reporting higher values of home BPV in the case of treatment with b-blockers [8], short duration of treatment [22], and increasing number of antihypertensive drugs [21].

Long-term BPV. Although biological and behavioral factors may contribute to visit-to-visit BPV, it may be also importantly affected by treatment-related factors such as inconsistent BP control in subjects receiving treatment for arterial hypertension. In particular, poor patient's adherence to prescribed drugs, improper dosing/titration of antihypertensive drugs, dose omission, or delay in drug intake during the follow-up period, as well as improper BP measurement during assessment of BP control, may all induce important increases in BPV from visit to visit [23]. In the frame of large population studies, long-term BPV has been found to be associated with advanced age, female gender, insomnia and long sleep duration, history of myocardial infarction or stroke, higher mean systolic BP, and pulse pressure [24, 25]. Besides, observational studies have shown that long-term BPV may be importantly influenced by seasonal related climatic changes [26, 27] and in particular by changes in outdoor temperature [27, 28]. This has been supported by the finding that BP levels (either office, ambulatory, or home BP) are consistently lower during the summer and higher during the winter [29]. However, not only the changes in outdoor temperature but also an improper downward titration of antihypertensive drugs on the basis of office BP reductions during the summer (with the consequent

reduction of the extension of 24 h BP coverage) [28] may lead to a paradoxical increase in nighttime BP levels.

3.3 Methods for Assessment of BPV

The measures of BPV can be obtained with different BP monitoring methods [i.e., continuous beat-to-beat BP recordings, repeated conventional office BP (OBP) measures, 24 h ambulatory BP monitoring (ABPM), home BP self-monitoring

Table 3.1 Different components of BPV and methods for their measurement

Characteristic	Very short-term BPV (beat by beat)	Short-term BPV (within 24 h)	Mid-term BPV (day by day)	Long-term BPV (visit-to-visit)
Method for BP measurement	Continuous BP recordings in a laboratory setting or under ambulatory conditions	ABPM	HBPM ABPM over ≥48 h	OBP HBPM ABPM
Measurement intervals	Beat-to-beat	15–20 min intervals for day and night, respectively. A 15-min interval for the whole 24 h time desirable but not always feasible	Day-by-day	Spaced by visits over weeks, months, and years For treatment changes, allow a 3-month window before estimating BPV
Number of measurements	Variable depending on patients' heart rate and recording duration	Ideally 87–96, at least 72 valid measurements when focusing on BPV	Duplicate BP measurements in the morning and in the evening (1 min apart) for each day over 7 days	At least 2–3 BP measurements during a visit (1 min apart) when using OBP Duplicate BP measurements in the morning and in the evening (1 min apart) for each day over 7 days before each clinic visit when using HBPM At least 48 valid measurements for ABPM

(continued)

Table 3.1 (continued)

Characteristic	Very short-term BPV (beat by beat)	Short-term BPV (within 24 h)	Midterm BPV (day by day)	Long-term BPV (visit to visit)
Time of measurement in treated patients	NA	NA	Morning BP measurements before drug intake	Before drug intake (or maybe drug intake within 24 h before office visit)
Duration of the recording period	Variable recording periods (1 min to 24 h)	24–48 h	Several days, preferably 7 (at least 3 days), over weeks or months	Months to years
Time of measurement	Variable	24 h/daytime/nighttime	Morning and evening	Time of visit when using OBP to be standardized within a study Morning and evening when using HBPM
Main indices of BPV	SD, CV, AVR Indices of BPV in the frequency domain can be estimated also through spectral analysis (that is, very low-, low-, and high-frequency components). Indices of nonlinear BP changes	SD, CV, ARV, VIM of 24 h, daytime, and nighttime BP; time rate of BP changes; 24 h weighted SD Indices of slower BP fluctuations (nighttime BP dipping, morning surge); slower BP fluctuations and residual components through spectral analysis	SD, CV, ARV, VIM, morning-evening changes, maximum values	SD, CV, ARV, VIM
Stable treatment	NA	Yes	Yes	Not always
Advantages	Beat-to-beat recordings allow assessment of indices of autonomic cardiovascular modulation	Extensive information on 24 h BP profile (nighttime BP dipping, morning surge) Assessment of efficacy of antihypertensive drug treatment over 24 h	Appropriate for both midterm and long-term monitoring devoid of the white coat effect	Assessment of consistency of BP control by treatment over time Detection of seasonal BP changes

Table 3.1 (continued)

Disadvantages	Stability of measurements might not be guaranteed outside the laboratory setting. Possibility of measurement artifacts	ABPM: Cannot be repeated frequently Not well tolerated Not widely available difficult to standardize subjects' behavior over 24 h	Patients' training required for HBPM 48 h ABPM not well tolerated	OBP and HBPM provide limited information on diurnal BP profiles Based on retrospective analysis of available data

Taken from Parati et al. [1] modified by permission. *BP* blood pressure, *BPV* blood pressure variations, *ABPM* ambulatory blood pressure monitoring, *HBPM* home blood pressure monitoring, *OBP* office blood pressure, *SD* standard deviation, *CV* coefficient of variation, *ARV* average real variability, *VIM* variability independent of the mean

(HBPM)] and over different time intervals. Appropriate implementation of the different BP monitoring methods, according to current hypertension guidelines, is critical for the proper estimation of BPV indices, either for research purposes or in a clinical setting [30–34] (Table 3.1).

Very short-term and short-term BPV. An accurate assessment of fast BP fluctuations occurring in the very short term, either in the laboratory setting or under ambulatory conditions, requires implementation of continuous beat-to-beat BP recordings over variable recording periods (i.e., 1 min to 24 h). These recordings not only allow estimation of the standard deviation (SD) of average BP levels (a traditional index of BPV) but also of very low-, low-, and high-frequency components of BP spectra contributing to overall BPV, thus allowing an indirect evaluation of autonomic cardiovascular modulation [35]. However, the difficulties in implementing continuous invasive recordings outside the laboratory setting in a daily life situation, the instability of measurements, and the cost and technical difficulties in performing noninvasive beat-by-beat recordings have prevented this method from being widely used in clinical practice. Although continuous beat-to-beat BP recording would represent the optimal solution also for the assessment of short-term BPV, its assessment is also possible through noninvasive, intermittent 24 h ABPM, at intervals between measurements from 15 to 20 min [36, 37]. This allows the straightforward estimation of short-term BPV for the whole 24 h period and separately for the daytime and nighttime subperiods (i.e., a major advantage of 24 h ABPM if considered the important prognostic value of nighttime BP changes). Important aspects to be considered for estimation of short-term BPV from ABPM include measurement intervals and criteria for determining day- and nighttime subperiods (predefined wide-fixed or narrow-fixed time periods, self-reported diaries, actigraphy), as well as the BPV metrics to be analyzed, and whether individuals' behaviors should be standardized in terms of daily activities, time in bed, working and resting hours, physical activity, etc. Regarding the determination of the interval between measurements and the minimum number of BP measurements to be obtained over 24 h, an analysis of a large 24 h ABPM registry found 48 BP readings (spaced at 15 and 30 min intervals during day and night,

respectively) to be the minimum number of BP readings required to compute average real variability (ARV) without loss of prognostic information [32]. However, such a number may be responsible for inaccuracies, as shown by a simulation study carried out on 24 h intra-arterial recordings [38]. Given that highly frequent measurements might cause discomfort, thus reducing compliance and acceptance of ABPM, measurements at 15–20-min intervals could be a reasonable compromise for BPV assessment in clinical practice. Regarding the definition of the daytime (awake) and nighttime (asleep) periods, a study with ABPM in 330 participants showed that there was a high degree of agreement between the definitions of subperiods by actigraphy and by self-reporting, with the narrow fixed time periods representing an alternative approach [39]. Table 3.2 summarizes some suggestions regarding the implementation of ABPM for the assessment of short-term BPV.

Mid-term BPV. A thorough assessment of mid-term BPV can be obtained by performing ABPM over 48 h or repeatedly during a week or a month. However, this approach is limited by the fact that ABPM is neither available in all clinical

Table 3.2 Recommendations for assessment of different types of BPV using in-office or out-of-office BP measurement techniques (ambulatory or home BP monitoring)

Assessment of short-term BPV using ABPM
• Use of validated devices • Measurements at 15–20-min intervals (day-night) • Minimum number of 48 valid readings required, best if 96 (a measure every 15 min over 24 h) • ABPM during a usual working day (usual physical activity) • Predefine meal and bed times • Definition of daytime and nighttime intervals using patients' diaries or simultaneous actigraphy recordings • Editing is not recommended at present, but percent of accepted readings should be reported
Assessment of mid-term BPV using HBPM
• Use of validated devices • HBPM during usual working days • Duplicate morning and evening measurements, taken at 1-min interval after a 5 min rest (for the comparative assessment of morning vs. evening vs. morning-evening) • At least 3 days of measurements required with a 7 day schedule suggested as optimal • For treated subjects, morning BP measurements should be performed before drug intake • No editing is recommended at present (not discarding first day)
Assessment of long-term BPV using OBP/HBPM
• Use of validated devices for both OBP and HBPM • Use of both OBP measurements at each visit and HBPM before each visit (for the comparative assessment of data obtained by OBP measurements and HBPM) • At least 2–3 OBP measurements (1-min interval) per visit required • At least a 3-day HBP before each visit, better if 7 days • Standardization of room temperature for OBP measurements • For treated subjects, morning OBP measurements should be performed before drug intake (or maybe drug intake no more than 24 h before OBP) • In case of change in treatment, a 3-month stabilization period should be allowed before calculation of BPV • No editing is recommended at present

settings nor is always well accepted by patients at such a repetition rate. Although HBPM cannot provide extensive information on nighttime BP and 24 h BP profile as ABPM does, it provides enough BP measures for the estimation of day by day BPV, devoid of the white coat effect. Besides, HBPM is widely available and well accepted by patients, being thus a feasible alternative for the evaluation of day-by-day BPV, in particular if BP measurements at home are performed according to current guidelines. Overall, HBPM schedule should consist of duplicate morning and evening BP measurements with validated devices for a 7 day period (at least 3 required) [34]. A recent outcome study based on the analysis of morning HBP measurements has indeed indicated that indices of home BPV may retain their prognostic value even when calculated from a 3 day schedule as compared to the suggested 7 days [40]. Because of the large heterogeneity among studies in terms of measurement schedules (number of readings, number of days, morning and/or evening) and BP measurement devices and indices of BPV assessed, it has not been possible to standardize an evidence-based approach for the assessment of home BPV in clinical practice. However, some suggestions based on the available evidence for the assessment of midterm BPV based on HBPM are provided in Table 3.2.

Long-term BPV. A series of studies in the past decade have indicated that visit-to-visit BPV is a highly reproducible phenomenon with demonstrated predictive value for cardiovascular prognosis [24, 25]. Long-term BPV is most commonly assessed from visit-to-visit conventional BP measurements obtained in the medical office, which are characterized, however, by several intrinsic limitations such as the "white coat effect" and may thus not accurately reflect patients' actual BP profile and BPV. Although ABPM performed on repeated visits might represent an ideal approach for the accurate assessment of visit-to-visit BPV in the long term, this technique is not always available, and patients may not easily accept its frequent use on a regular basis. An optimal, alternative approach to overcome the limitations of OBP and ABPM for the assessment of long-term BPV might be an implementation of HBPM over the days preceding each office visit. Although HBPM cannot provide the extensive information on BP levels over 24 h as ABPM does, it can provide information on BP levels in daily life conditions devoid of the subject's alarm reaction during the medical visit. In recognition of its advantages and prognostic superiority over OBP, the use of HBPM has been recommended for the long-term follow-up of treated hypertensive patients and might thus be also employed for the assessment of long-term BPV [24, 37, 41–44]. Identifying a standard method to obtain reproducible and valid estimates of visit-to-visit BP variability, using either OBP or HBPM, has been difficult due to the inconsistency of the available evidence. However, a higher number of visits considered for the assessment of visit-to-visit BPV have been associated with a greater reproducibility [45] and a stronger prognostic value [25]. Some suggestions based on the available evidence for implementation of OBP and HBPM for the assessment of long-term BPV are presented in Table 3.2**.**

Table 3.3 Indices for estimation of different types of BPV

Overall BPV	
Type of index	Type of BPV assessed
Frequency:	
– Spectral indices (HF, LF, VLF) – Residual variability	Short-term BPV Very short-term BPV (spectral analysis)
Dispersion:	
– Standard deviation (SD) – Coefficient of variation (CV) – Variability independent of the mean (VIM) – Weighted 24 h SD (wSD)[a]	Short-term BPV Mid-term BPV Long-term BPV
Sequence:	
– Average real variability (ARV) – Interval weighted SD (wSD) – Time rate of BP fluctuations[b]	Short-term BPV Mid-term BPV Long-term BPV
Instability:	
– Range (maximum-minimum BP)	Short-term BPV Mid-term BPV
– Peak size (maximum BP) – Trough size (mean-minimum BP)	
Specific patterns of BPV	
Nocturnal BP fall Night/day ratio Morning blood pressure surge (MBPS) Afternoon siesta dipping Postprandial blood pressure fall	Short-term BPV

[a]Assessment of short-term BPV only
[b]Not for assessment of short-term BPV

3.4 Indices for Estimation of BPV

In general, BPV indices can be classified into two main groups: (a) i**ndices of overall variability**, i.e., assessing the frequency components of BP spectra, the degree of dispersion, and the sequence or the instability of BP values over a certain period of time, and (b) i**ndices for estimation of specific BP patterns of BPV**, i.e., associated with the day/night cycle (representing slower fluctuations within a 24 h time period) or with other behavioral factors (i.e., "siesta") (see Table 3.3).

Indices for the assessment of very short-term BPV. Assessment of very short-term BPV is only possible from continuous beat-to-beat BP recordings [35]. In addition to calculation of standard deviation (SD) and other traditional indices of BPV, continuous BP recordings allow to estimate indices of autonomic CV modulation by applying power spectral analysis. It decomposes the overall BP variance or power into its different components oscillating at different frequencies. The corresponding spectral indices are usually obtained by integrating the BP power spectrum over different frequency bands by focusing on those reported to have a pathophysiological or clinical relevance. This is usually done by computing BP spectral powers over a high-frequency band (HF power, between 0.15 and 0.50 Hz),

a low-frequency band (LF power, between 0.15 and 0.07 Hz, centered around 0.1 Hz), and a very low-frequency band (VLF power, <0.07 Hz). The HF power usually reflects BP changes induced by respiratory mechanics. The LF power mainly quantifies oscillations generated by a resonance in the baroreflex loop, with an important contribution by sympathetic modulation [46]. Evidence exist of an adrenergic origin of the VLF powers [47], which may be potentiated in case of autonomic dysfunction by the inability of CV control mechanisms to "gate" BP fluctuations around 0.1 Hz. Also, alterations in respiratory activity may contribute to the VLF power in pathological conditions like congestive heart failure and obstructive or central sleep apnea, due to the impact of so-called periodic breathing. Thus, spectral BPV indices yield information on the autonomic control of circulation, on the baroreflex function, and on pathological aspects of respiration. Their assessment should be accompanied by the assessment of the corresponding heart rate variability spectral powers, which can provide complementary and pathophysiologically and clinically relevant information.

Indices for assessment of short-term BPV. Short-term BPV may be estimated from noninvasive, intermittent 24 h ABP recordings at intervals from 15 to 20 min [36, 37] by calculating 24 h SD and also the respective SD for the day and nighttime subperiods [36, 38]. SD represents the most commonly used index for assessment of BPV and provides a measure of value dispersion over selected time windows (24 h, day and night). SD is affected by trends in BP (e.g., day-night change) and increases with increasing average BP values. In order to account for such a dependence of SD and other absolute measures of BPV on mean BP levels, the coefficient of variation (CV, SD* 100/BP mean) may be applied [38]. The **weighted 24 h SD (wSD)** selectively removes the contribution provided by nighttime BP fall to 24 h SD, by weighting daytime and nighttime BP SD for the duration of the day- and nighttime periods, respectively, and by averaging the SD of these two time subperiods [48]. The corresponding weighted CV may be calculated as well. **Average real variability (ARV)** is an index of overall variability based on reading sequence. It is computed as the average of the absolute differences between consecutive BP measurements over 24 h. It focuses on the sequence of BP readings, thus reflecting short-term, reading-to-reading, within-subject variability in BP values [49]. ARV has been shown to be a more specific estimate of 24 h BP variability and a more effective predictor of outcome than SD. Indeed, subjects with different 24 h ABPM profiles may have similar SD but different ARV [30, 49, 50]. ARV effectively removes the contribution of trends in mean BP to overall BPV and is correlated with mean BP levels. Other indices of overall variability based on reading sequence include **time rate of BP fluctuations** (similar to ARV but quantified as a function of time to provide information also on speed of BP changes) and **interval weighted SD** (similar to SD), both of which take into account the interval between measurements giving larger weight to more distant pairs of readings. **Variability independent of the mean (VIM)** excludes the effect of mean BP on BPV by applying nonlinear regression analysis (i.e., plotting SD against mean) [25]. For its estimation, it requires calculation of a factor x from overall population data. Short-term BP

variability may also be assessed by estimation of instability indices that take into account extreme readings of the distribution of BP values within a given time window such as **range (maximum-minimum BP), peak and trough values, peak size (maximum-mean BP), and trough size (mean-minimum BP)**. Although some studies have demonstrated their clinical value, a major limitation of these indices is that extreme readings have limited reliability value within a given distribution of values, including ABPM data, especially when focusing on individual subjects, being unstable and prone to show measurement artifacts more than actual BP values.

It is also possible, from 24 h ambulatory BP recordings, to evaluate **specific patterns of BPV** associated with the day/night cycle (representing slower fluctuations within a 24 h time period) or with other behavioral factors (i.e., "siesta"). One of the most common among these indices of BPV estimated from 24 h ABPM is the n**octurnal BP fall.** The reduction in BP during the night can be expressed as percentage of daytime BP [Nocturnal BP fall = (Daytime BP − Nighttime BP) * 100/Daytime BP)] which is mathematically equivalent to the night/day ratio. When considering the degree of nocturnal BP fall (dipping), subjects may be classified into four different categories: (1) normal dipping (fall in nighttime systolic and diastolic BP between 10 and 20%), (2) non-dipping (or more precisely reduced dipping, with a fall in nighttime systolic and diastolic BP <10%), (3) rising or "inverted dipping" (increase in nighttime BP compared to daytime values), and (4) extreme dipping (BP fall during night >20%) [44].

Another index of short-term BPV that can be estimated from 24 h ABPM and which has been suggested to carry a prognostic value is the **morning BP surge (MBPS)**. It is computed in different ways, as a function of the different time points set by the researcher to define wake and sleep time periods. The most commonly employed method is the calculation of the difference between the lowest BP value at night and the highest BP value recorded shortly after awakening. However, when computed in this way, its correlation with nocturnal BP fall may represent a challenge in the interpretation of its impact on outcome data. Indeed, there are still issues to be defined regarding the best way of computing morning BP surge and its actual clinical value, due to the interference of the degree of nocturnal BP dipping both with morning BP surge estimates and with the assessment of its prognostic value. Other patterns of BP variations that can be evaluated from 24 h ABPM are the **siesta dipping (**i.e., the BP fall observed in populations where having an afternoon nap (siesta) is a common habit) and the **postprandial BP fall** (i.e., when excessive, postprandial hypotension may indicate altered autonomic function). However, up to date, no standards have been provided regarding the calculation of these indices.

Indices for assessment of mid-term BPV. Changes occurring in home BP values obtained over a number of days may be estimated by applying some of the same indices employed for the assessment of short-term BP variability such as SD, CV, VIM, and ARV described in Table 3.3**.** Also indices of instability such as range (maximum-minimum BP), peak size (maximum BP), and trough size (mean-minimum BP) can be estimated in order to assess midterm BPV. These indices appear to have different strengths and limitations. Until data showing the superiority of one or more of these indices become available, it is difficult to yield any recommendation on which among them should be selected.

Indices for assessment of long-term BPV. Several of the indices employed for estimation of short-term BPV may be employed for the assessment of BPV in the long term (i.e., SD, CV, ARV, VIM). Although metrics of long-term BPV are highly correlated to each other, it is not clear which metrics are better representative of true long-term BPV [51, 52]. Most studies have evaluated classical (i.e., SD and CV) but not novel indices of BPV such as ARV or VIM [53]. It is likely that ARV, CV, and SD may reflect different primary determinants of BPV as they are only partly correlated [25]. In the future, clinical trials aimed at establishing the relationship of BPV with CV outcomes should ideally evaluate all metrics of overall ordered and extreme long-term BPV.

3.5 Clinical Relevance of BPV

The clinical relevance of BPV has been supported by the evidence accumulated in the last decades showing significant associations between different types of BPV with TOD and cardiovascular and mortality outcomes. A recent meta-analysis of observational cohorts and of clinical trials reported significant hazard ratios for cardiovascular events as well as for cardiovascular and all-cause mortality in relation to an increased visit-to-visit BPV, also showing similar results in relation to increased midterm and short-term BPV [54]. It is important to note that this meta-analysis reported standardized hazard ratios to account for the heterogeneity in reporting of risk per different units across studies [54]. Although evidence from some recent studies has indicated an incremental contribution of BPV for cardiovascular risk stratification, over and above the impact of average BP values, the relevance of such contribution has been shown to be influenced by the methodology employed for the assessment of BPV and by the characteristics and baseline cardiovascular risk of the study populations. Future studies should establish whether there are specific categories (high versus low risk, treated or untreated) of patients where BPV more clearly provides additional predictive information over and above the impact of average BP levels. Although some outcome studies addressing the prognostic value of BPV have suggested reference values and thresholds for BPV, the heterogeneity in the indices of BPV used and the different characteristics of study populations have not allowed to definitely conclude in this regard. In recent years, a series of studies or *post hoc* analyses of clinical trials in hypertension have also addressed the important issue of whether there are drugs able to specifically reduce BPV and whether such reduction is translated into an improved cardiovascular risk.

Short-term BPV. In the last decades, several studies have provided evidence supporting the predictive value of short-term BPV either for TOD or for cardiovascular events. Most evidences supporting the association of very short- and short-term BPV with target organ damage are derived either from cross-sectional studies reporting on such relationship or from prospective studies on the predictive value of BPV regarding the development and progression of TOD [1]. Early studies implementing intra-arterial beat-to-beat BP recordings in hypertensive subjects showed that [1] at nearly any level of 24 h mean BP, the prevalence and severity of TOD were higher in subjects with higher 24 h BPV [55] and [2] BPV at baseline was a significant predictor of target organ damage, in particular of left ventricular hypertrophy, at the end of follow-up [56]. Regarding

the value of short-term BPV as assessed from intermittent ABPM recordings, a recent meta-analysis has shown a significant, although moderate, association between left ventricular mass index and SD of 24 h systolic BP, SD of daytime systolic BP, wSD of 24 h systolic BP, and ARV of 24 h systolic BP (with correlation coefficients of 0.22, 0.19, 0.23, and 0.37, respectively) [57]. Other studies have shown an independent, although moderate, relationship between short-term BPV and carotid atherosclerosis, arterial stiffness, and renal function [7, 58–60]. However, not all studies have reported significant associations [61, 62]. In the European Lacidipine Study on Atherosclerosis (ELSA), short-term BPV predicted carotid damage by the end of treatment [63], while this was not the case for visit-to-visit BPV [64]. Regarding CV outcomes, several studies and analyses of ABPM registries have confirmed the prognostic role of short-term BPV. An analysis of the International Database on Ambulatory blood pressure in relation to Cardiovascular Outcomes (IDACO) composed of 8.938 subjects (41% hypertension, 48% treated) showed a significant predictive value for short-term BPV for most outcomes, with ARV of 24 h systolic/diastolic ambulatory BP being a better predictor than SD [50]. The analysis of the ABP-International database, composed of 7.112 untreated hypertensive subjects, showed SD of nighttime systolic ambulatory BP to be an independent predictor of cardiovascular events, cardiovascular death, and all-cause mortality in contrast to daytime values [65]. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, there was an independent relationship between the risk of death and SD of 24 h, daytime, and nighttime BP [66]. Moreover, the adjusted risk of cardiovascular death was inversely related to day-night diastolic BP difference and showed a significant positive relationship with residual diastolic BPV, as computed by spectral powers of 24 h ABP recordings, after removing the contribution of day-night BP changes [66]. Accumulating evidence suggests that specific patterns of the diurnal BP variation may indeed have an important prognostic role. Nighttime ambulatory BP carries superior prognostic value as compared to other BP monitoring methods [67–69]. In this context, several studies have investigated whether BP fluctuations occurring from day to night or vice versa may have additional prognostic value. More specifically, a non-dipping or even a rising pattern at night has been shown to be associated with increased cardiovascular risk, although recent evidence suggests that it is the nighttime average BP level that mainly matters [68]. Likewise, an increased morning BP surge is associated with a high incidence of cardiovascular events and mortality, but this should be interpreted in the context of the significant relationship between the degree of morning BP surge (carrying high risk) and the degree of nighttime BP fall (carrying low risk), which may affect calculation of the extent of BP rise in the early morning and the interpretation of its prognostic value [70, 71].

Evidence on whether short-term BPV might improve cardiovascular risk stratification over and above average BP levels has been provided by some studies. While in the ABP-International study, the relative integrated discrimination improvement for an increased value of the SD of nighttime systolic BP ranged from 8.5% to 14.5% for cardiovascular and mortality outcomes [65], in the IDACO analysis, however, ARV added only 0.1% to prediction of the risk of a composite cardiovascular event [50]. It should be mentioned, however, that there were significant differences in the methodology (ambulatory BP readings obtained at 10–30-min intervals during daytime and at 15–30-min intervals during nighttime versus 15–30-min and

30–60-min, respectively, for the ABP-International and IDACO databases) and in the characteristics of the two populations (untreated hypertensives versus population-based cohorts including treated hypertensives, respectively).

Regarding possible threshold values for short-term BPV, evidence has been provided by some outcome studies. An analysis of the ABP-International database showed that a SD of nighttime systolic ambulatory BP ≥12.2 mm Hg (compared with SD <12.2 mm Hg) was associated with greater risk of cardiovascular events (41%), cardiovascular death (55%), and all-cause mortality (59%) [65]. The corresponding values for the SD of diastolic BP ≥7.9 mmHg were 48%, 132%, and 77% [65]. The IDACO analysis also presented the risk of total and cardiovascular mortality by fifths of distribution of ARV showing progressively increased risk among quantiles with higher event rate at systolic/diastolic ARV values of 16.2/12.4 mmHg, respectively [50].

Studies have also been conducted addressing whether short-term BPV may be reduced by specific classes of antihypertensive drugs. In the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients (X-CELLENT) study, the effect of different antihypertensive agents (candesartan, indapamide sustained release, and amlodipine) on ambulatory BPV was examined. Amlodipine and indapamide were the only agents associated with a significantly decreased ambulatory BPV after a 3-month treatment [72]. In another study in 2780 hypertensive subjects, it was shown that those treated with CCBs or diuretics alone, or in addition to other drugs, had significantly lower SD of 24 h systolic BP compared with those not treated with these classes [73].

Current antihypertensive treatment usually consists of once-daily administration of long-acting antihypertensive drugs upon awakening. Since the vast majority of drugs have a trough-to-peak ratio lower than 100%, it is expected that a diminished effect occurs during nighttime and the early morning hours. This phenomenon may have important implications for subjects with nighttime hypertension and/or non-dipping profile and/or pronounced morning surge. Preliminary results derived from a single research center in Spain (MAPEC study) appear to support bedtime dosing of at least one of the antihypertensive drugs in terms of cardiovascular prognosis [74]. However, the findings of this particular study and the concept of restoring a disturbed nighttime BP profile with chronotherapy need to be confirmed by other groups.

Mid-term BPV. Overall, the studies addressing the predictive value of mid-term BPV for TOD have been characterized by significant heterogeneity in the methodology for evaluating BPV (home BP monitoring schedule, variability indices, characteristics of subjects) and by discrepant results regarding impact on outcome [75]. Overall, it seems that there is not a single index of BPV or an index of TOD presenting consistent and independent relationships in both positive and negative studies [61, 62, 75–81].

Regarding CV events, the most solid evidence supporting the prognostic value of mid-term BPV is derived from the IDHOCO database, composed of four populations (n = 6.238, 22% treated hypertensive subjects) [40]. An analysis of this database based on day-to-day morning home BP measurements showed all indices of systolic/diastolic

BPV (SD, CV, ARV, VIM) to be independently associated with all-cause and cardiovascular mortality [40]. Although a direct head-to head comparison between all types of BPV in terms of prognosis has not been addressed so far, it is important to note that the meta-analysis by Stevens et al. showed similar hazard ratios for all-cause mortality among all types of systolic BPV [visit-to-visit, 1.12 (95% confidence intervals, 1.05, 1.20); home, 1.15 (1.06, 1.26); 24 h ambulatory, 1.11 (1.04, 1.18)] [54]. In addition, it appears that morning day-by-day home BPV has the strongest prognostic value as compared to morning-evening or evening home BPV [82, 83]. Regarding the question on whether mid-term BPV may independently add to cardiovascular risk stratification, the IDHOCO analysis revealed only a minor nonsignificant incremental improvement for home BPV in terms of net reclassification and integrated discrimination improvements [40]. Regarding potential threshold values for mid-term BPV, the IDHOCO study provided some evidence indicating that the risk of cardiovascular morbidity and mortality was steeply increased in the highest decile of systolic/diastolic home BPV (CV ≥11/12.8%, respectively) [40]. Regarding the response of mid-term BPV to antihypertensive treatment, the study by Matsui et al. showed that the olmesartan/azelnidipine compared to olmesartan/hydrochlorothiazide combination improved home BPV (home BP monitoring was performed before each office visit for a total of seven visits during a 24-week period) in addition to home BP reduction and that the reduction in home BPV was associated with the reduction in the arterial stiffness in the group of azelnidipine [79]. On the contrary, in a study conducted in 310 hypertensive subjects, the treatment-induced reduction in urine albumin excretion after a 6-month period of antihypertensive treatment with candesartan (+diuretics) was significantly associated with that of average home BP but was not associated with that of the SD of home systolic BP or that of maximum home systolic BP [84].

Long-term BPV. Rothwell et al. were the first to systematically emphasize the prognostic relevance of visit-to-visit BPV [25, 53]. Regarding TOD, the largest amount of evidence addressing the predictive value of long-term BPV comes mainly from studies in diabetic patients in whom the incidence or the progression of renal dysfunction in relation to long-term BPV has been evaluated [19, 85–89]. In one of these studies, visit-to-visit BPV, assessed by CV of systolic BP, was associated with a significantly increased hazard of developing albuminuria in patients with type 2 diabetes [85]. Visit-to-visit BPV has been also shown to be associated with left ventricular dysfunction [87, 88], as well as with carotid atherosclerosis and stiffness [19, 88, 89]. Regarding CV events, there is a large amount of evidence, i.e., mainly derived from *post hoc* analyses of large randomized trials and meta-analyses, supporting the prognostic value of long-term BPV. Indeed, recent meta-analyses using different methodologies have shown an independent prognostic value for visit-to-visit BPV [54, 90, 91]. In one of these meta-analyses, visit-to-visit BPV independently predicted all the examined outcomes [hazard ratios for increase in systolic visit-to-visit BPV (95% confidence intervals): all-cause mortality, 1.12 (1.05, 1.20); cardiovascular mortality, 1.15 (1.03, 1.30); cardiovascular events, 1.13 (1.04, 1.23); coronary heart disease events, 1.07 (1.00, 1.14); and stroke events, 1.19 (1.11, 1.27)] [54]. The most commonly assessed BPV index across the included studies was SD of systolic BP. Of note, the available evidence regarding long-term BPV is derived from studies in the general population, postmenopausal women, patients with hypertension, type 2 diabetes, chronic kidney disease,

coronary heart disease, and history of stroke [24, 25, 54, 90–98]. On the other hand, in a recent analysis of the SPRINT data, systolic visit-to-visit BPV failed to predict outcome, although a marginal association was observed with all-cause mortality [94]. However, since the SPRINT study implemented a different approach to measure BP levels (i.e., automated unattended office BP in most cases), its results should be interpreted with caution. It should be noted that visit-to-visit BPV in treated hypertensive subjects may reflect the inconsistency of BP control over time, which might, at least in part, explain its independent prognostic value [64].

The question on whether long-term BPV might add to risk stratification over and above average BP levels and baseline cardiovascular risk has been addressed by some recent studies. A report of the ADVANCE-ON study which included patients with type 2 diabetes showed that, besides the independent prognostic value of the SD of systolic clinic BP, its addition in the model significantly improved the 8-year risk classification beyond the contribution by traditional risk factors including average systolic BP [93]. Also in another study including 2157 patients with cardiovascular disease, addition of CV of systolic BP resulted in a modest but significant improvement in the prediction model [99]. On the contrary, in the ELSA, visit-to-visit BPV did not contribute to cardiovascular risk prediction [64]. It should be mentioned that the latter study included middle-aged patients with treated, mild-to-moderate, systolic-diastolic hypertension at relatively low cardiovascular risk [64]. Very recently additional information on the prognostic value of BP visit-to-visit BPV has been offered by the analysis of the prognostic value of long-term BPV in the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study [100]. The VALUE trial was a randomized controlled trial of valsartan vs. amlodipine in patients with hypertension and different risks of cardiovascular events, followed for a mean of 4.2 years. In this study, visit-to-visit BPV was calculated as standard deviation (SD) of mean systolic blood pressure computed over visits from 6 months onward in patients with >3 visits and no events during the first 6 months. The risk of cardiovascular events in the highest and lowest quintile of VVV visit-to-visit BPV was assessed by using Cox regression (100). For analysis of death, visit-to-visit BPV was analyzed as a continuous variable. Of 13,803 patients included, 1557 (11.3%) had a cardiovascular event and 1089 (7.9%) died. Patients in the highest quintile of visit-to-visit BPV had an increased risk of cardiovascular events [hazard ratio (HR) 2.1, 95% confidence interval (95% CI) 1.7–2.4; $P < 0.0001$], and a 5-mmHg increase in SD of systolic BP was associated with a 10% increase in the risk of death (HR 1.10, 95% CI 1.04–1.17; $P = 0.002$). Associations were stronger among younger patients and patients with lower systolic BP and similar between patients with different baseline risks, except for higher risk of death among patients with established cardiovascular disease [100].

Despite the large amount of evidence on the prognostic value of long-term BPV, there is no specific suggestion of thresholds for its clinical application, at present. The largest study addressing the clinical value of long-term BPV conducted among 2.865.157 US veterans reported the risk of cardiovascular events among quantiles of SD of systolic BP with an incremental risk for SD quartiles 2 through 4 for all-cause mortality, coronary heart disease, stroke, and end-stage renal disease [92]. The SD of systolic BP which corresponded to the highest quartile was 15.6 mmHg [92].

The question on whether long-term BPV might be modulated by antihypertensive treatment and whether this might be translated into improved CV prognosis has been addressed by post hoc analyses of randomized clinical trials. Overall, these analyses have indicated a favorable effect of calcium-channel blockers (CCBs) versus other drugs, especially beta-blockers, in reducing visit-to-visit BPV and the risk of stroke. In particular, the *post hoc* analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed that amlodipine-based compared to atenolol-based regimen was associated with a reduction in BPV (data available for visit-to-visit and ambulatory BPV) [53]. In addition, Webb et al. performed a meta-analysis regarding the effect of antihypertensive treatment on interindividual office BPV (as a surrogate for intraindividual variability) and on the associated clinical outcomes [101]. Compared to other drugs, interindividual variability in systolic BP was reduced by CCBs and by non-loop diuretic drugs and increased by renin-angiotensin system blockers and beta-blockers [101]. Compared to placebo, CCBs were the most effective drug class to reduce interindividual variability in systolic BP [101]. In another recent meta-analysis of five studies, amlodipine was found to be more effective than other active comparators in reducing intraindividual visit-to-visit BPV [102].

It should be noted that the prognostic value of the treatment-induced changes in BPV appear to be of clinical importance. In this regard, in the ASCOT-BLA study, the reduction in the risk of stroke was partly attributed to the reduction of BPV [53]. In the meta-analysis by Webb et al., the reduction in the risk of stroke was attributed not only to the reduction of average systolic BP but also to the reduction of systolic BPV, although the latter regarded interindividual variability only, which represents a major limitation of such an analysis [101]. Moreover, a recent study by Kollias et al. showed a trend toward greater reductions in odds ratios for several endpoints—mainly stroke across randomized clinical trials as a function of greater decreases in coefficient of variation of intraindividual systolic BP achieved by amlodipine versus other comparators [103].

3.6 Blood Pressure Load

Definition, rationale, and assessment. As mentioned above, the analysis of 24 h ABPM allows not only the quantification of average BP levels over 24 h, daytime, and nighttime but also the assessment of BP fluctuations over the recording period. This is relevant on the background of the evidence showing that not only average BP levels but also an increased BPV within the 24 h has a significant impact on cardiac, vascular, and renal organ damage [55, 56] as well as on cardiovascular events and mortality [1, 104]. Along this line of thinking, assessment of the percentage of ambulatory BP readings above threshold values set for daytime and nighttime (i.e., systolic/diastolic BP levels ≥135/85 mmHg during daytime and ≥ 120/70 mmHg during night) might represent a useful parameter complementing the quantification of average ABP levels of the respective subperiods [105]. Such a percentage has been termed “BP load” [105, 106].

Following its initial description, evidence was also provided that not only average BP levels but also measures of BP load are consistent and reproducible when

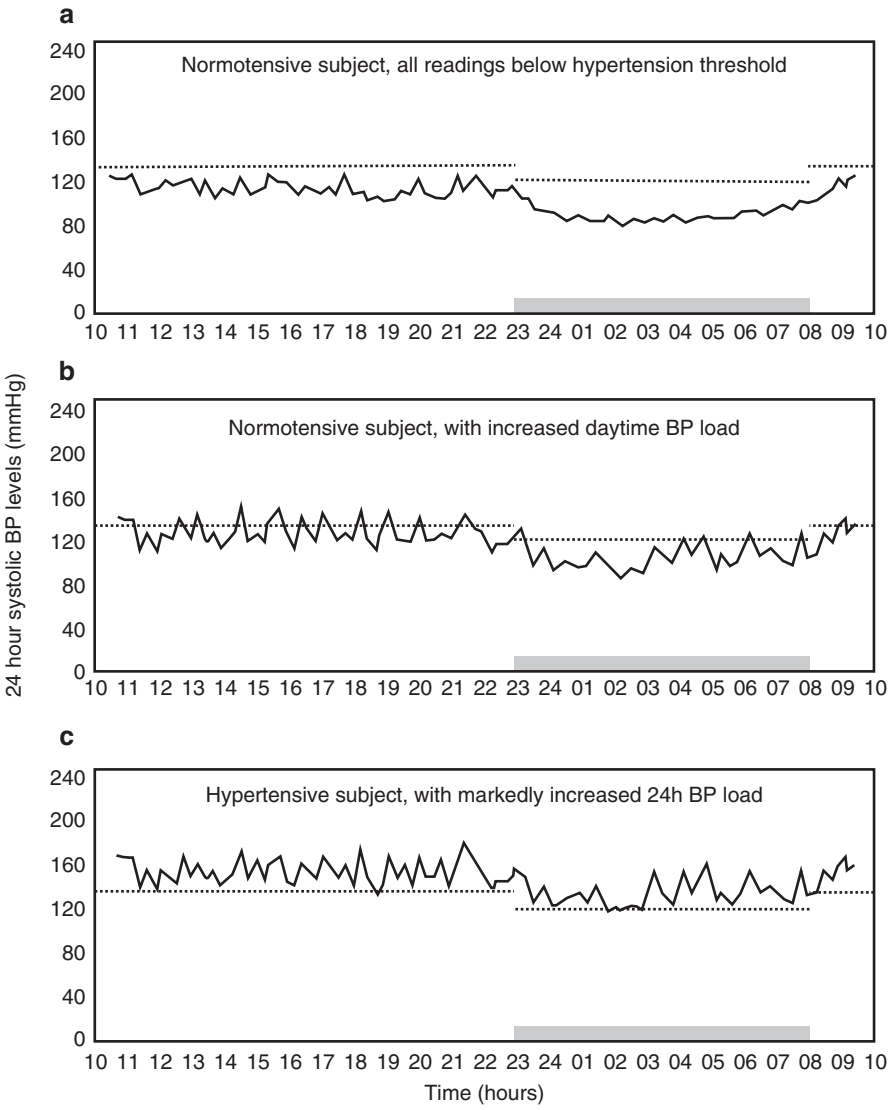

Fig. 3.2 Examples of 24 h ambulatory SBP tracings obtained in normotensive and hypertensive patients. Taken from Parati et al. [117] by permission. (**a**) Normotensive patient with all ambulatory SBP levels below threshold, (**b**) normotensive patient (average 24 h SBP within normal limits) with increased BP load during daytime, (**c**) hypertensive patient with markedly increased BP load over 24 h (close to 100%). Dotted lines indicate threshold values for ambulatory systolic hypertension during daytime (≥135 mmHg) and during nighttime (≥120 mmHg). Gray bars indicate nighttime sleep

computed over 24 h ABPM tracings obtained on successive days [107]. As illustrated in Fig. 3.2**,** while in patients with sustained BP elevation over 24 h, calculation of BP load is of limited relevance, being by definition always greater that 100%,

its assessment in subjects with normal and even more so with high normal office BP elevation is of much greater interest. Indeed, in these subjects BP load might quantify the degree of BP fluctuations above normal limits during daily life activities, thus possibly representing an additional measure of BPV. This calculation might be of clinical relevance as it could improve the diagnostic approach to hypertension, by detecting the number of abnormally elevated BP readings in ambulatory conditions, in spite of the finding of office BP values still within normal ranges. Identification of subjects with normal office and/or average ambulatory BP values but with increased BP load, who are theoretically at a higher risk of future sustained hypertension as compared to subjects with sustained normotension, might allow implementation of early interventions aimed at improving subjects' lifestyle and at detecting/preventing TOD [108, 109]. Even in treated hypertensive patients, assessment of BP load was proposed as an additional measure of the efficacy of antihypertensive drugs in effectively covering the 24 h BP profile [110].

Clinical relevance. Based on the abovementioned assumptions, a series of studies either in treated or untreated hypertensive patients have been conducted in order to explore the relationship between average ambulatory BP values, BP load, and indices of TOD, giving particular attention to cardiac structural and functional alterations (i.e., left ventricular mass and left ventricular function). In many of these studies, an increased BP load, expressed as a percentage value or as an integrated area under the BP curve, was shown to be significantly associated with left ventricular hypertrophy [109, 111–113] with alterations at ocular fundus examination [114], microalbuminuria [114], and endothelial dysfunction [115]. Of note, some of these reports showed BP load to be a better determinant of cardiac or vascular abnormalities than either casual or mean ambulatory BP levels [109]. Recently, a prospective study in elderly subjects found increasing values of systolic BP load (i.e., daytime systolic BP load $\geq$24.5%) to be independently associated with an increased risk of cardiovascular events [116]. However, this study was limited by the sample size and the low number of events recorded during the follow-up period.

Despite the interesting results provided by these studies, which related BP load to TOD and cardiovascular outcomes, most of them were limited by several factors such as the small sample size, methodological problems related to performance of ABPM recordings, the skewed distribution of BP load values, as well as the collinearity between BP average level and BP load. It should also be mentioned that not all studies have univocally shown a significant association of BP load with all measures of target organ damage and cardiovascular outcomes, independent of 24 h average BP levels [117].

Besides, since average BP levels and BP load are affected by significant collinearity (i.e., increasing BP load is associated with increasing frequency of elevated average ambulatory BP levels), it is not surprising that after adjustment for mean 24 h BP levels, BP load had lost its prognostic value in some studies [118].

Considerations for a proper interpretation of BP load. In the previous paragraphs, it has already been described how much BP values fluctuate within the 24 h around a reference set point as a consequence of behavioral, environmental, humoral, and neural central or reflex influences [1]. Then, an increased blood

pressure load may reflect an increase in BPV. Besides, It should be considered that BP load (estimated as % of ABP values being defined as "increased") only measures how frequently ambulatory BP readings are above a predetermined threshold, without providing any quantitative information on how much each BP reading was elevated above such a threshold. Thus BP load provides only semiquantitative information, by focusing on the frequency of BP elevation and by telling us how often, but not how much, BP is increased over the 24 h. This is why we may find a high BP load even in subjects with normal average BP, in whom BP readings might well be frequently elevated but only by a small amount. Thus, a proper assessment of BP load should also consider the magnitude of the elevation in BP levels.

3.7 Conclusions

Blood pressure variability can be measured with different BP monitoring methods, i.e., continuous beat-to-beat BP recordings, repeated conventional office BP measures, 24 h ABPM through oscillometric BPM devices, and HBPM. This can be done over different time windows: from beat-to-beat [**very short-term** BPV], within 24 h (from minute to minute, hour to hour, and from day to night; **short-term** BPV), over different days (**mid-term** BPV), or between clinic visits performed over weeks, months, seasons, and years (**long-term** BPV) [119]. Thus, a proper implementation of the different BP monitoring methods as a function of specific aims of a given survey, according to current hypertension guidelines, is critical for a proper estimation of BPV indices, either for research purposes or in a clinical setting [30–34].

Accumulating evidence supports the concept that BPV may contribute to cardiovascular risk prediction over and above the impact of average BP levels. These findings suggest the possible usefulness of assessing BPV in clinical practice and of considering an elevated BPV as a possible target for treatment to further improve prognosis. However, currently available studies are characterized by a significant heterogeneity in the methodology applied for estimating BPV indices. Specifically, the different designs of most of the studies addressing the prognostic value of BPV (mainly post hoc analyses of clinical trials), the heterogeneity of the populations studied (general population, or patients with hypertension, diabetes, nephropathy), as well as the variable follow-up duration and the diversity of protocols used to estimate indices of BPV have not so far allowed to adequately answer a number of practical questions nor to clarify several important issues related to a clinical implementation of BPV assessment. In addition, although many indices of BPV have been shown to be of prognostic value, no interventional longitudinal outcome study has yet been conducted specifically addressing what BPV levels should be regarded as normal and which BPV level should be achieved as target for antihypertensive treatment. Similarly, no intervention study has yet explored the key question of whether a reduction in BPV by treatment translates into a better outcome. Regarding the type of BPV that should be considered in clinical practice (short-term, mid-term, or long-term), the poor correlation and agreement between indices of

short-term (24 h) and long-term variability (visit-to-visit) indicate that they may reflect different pathophysiological and clinical phenomena and may thus not be interchangeable but rather represent variables to be separately quantified.

Assessing BP load from 24 h ABPM might have some clinical relevance, in particular in subjects with high normal office BP elevation in whom it could improve the diagnostic approach to hypertension, by detecting the number of abnormally elevated BP readings in ambulatory conditions, in spite of the finding of office BP values still within normal ranges. Whether a proper interpretation of ABPM should include analysis of BP load in addition to the assessment of average BP values, this is still an issue which should be better defined, ideally in the context of prospective studies assessing the risk of developing sustained hypertension as well as the risk of TOD and cardiovascular outcomes in the presence of elevated BP average levels and variability.

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Hemodynamic Mechanisms

4

Tatiana Kuznetsova and Nicholas Cauwenberghs

4.1 Introduction

The normal heart is an efficient muscle that is designed to serve both as pump and integrator of two independent vascular systems, the pulmonary and systemic circulations. The capacity of the body to augment cardiac output, regulate systemic blood pressure (BP), and respond appropriately to elevations in heart rate and pre- and afterload depends on the properties of both the heart and the vasculature into which the left ventricle (LV) ejects blood [1]. Two components of systemic BP could be identified: the steady component, represented by mean arterial pressure, and the pulsatile component, represented by pulse pressure. Mean arterial pressure is determined by peripheral arterial resistance, which depends on the physical characteristics of the arterial tree and the volume of blood that the LV ejects. On the other hand, LV stroke volume and aortic compliance are major determinates of pulse pressure. In the absence of aortic stenosis, conventionally measured brachial BP provides a clinically useful estimate of LV afterload.

When a high afterload opposes LV ejection, reduction of the LV stroke volume could be observed in a short term. This reduction is further compensated by shifting the LV pump function to a higher energy level (the Frank-Starling mechanism) and by activating an autoregulatory mechanism (the Anrep response). However, the long-term increased afterload and, consequently, the chronically increased cardiac performance lead to adverse LV remodeling and dysfunction and increased LV oxygen requirements and eventually cause symptomatic heart failure (HF). Because the process of myocardial remodeling/dysfunction starts long before the onset of symptomatic HF, it is of importance to better understand the pathophysiological mechanisms leading to subclinical (asymptomatic) LV maladaptation and the timely identification

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of patients who are at risk for developing overt cardiac events. Hereby we discussed the different aspects of cardiac maladaptive responses to a chronically increased load.

4.2 LV Deformation

LV deformation (strain) is determined by the fiber structure and curvature of the myocardium and its interaction with local wall stress at the beginning of ejection, which decreases from the endocardium to epicardium and from the LV base to the apex [2]. During LV ejection, longitudinal deformation of the heart results from contraction of longitudinally oriented subendocardial and subepicardial fibers, whereas radial LV wall thickening mainly originates from contraction of circumferential fibers located in the mid-wall [3]. Gould et al. [4] assessed the relation between the directional components of LV contraction and ejection fraction in 122 subjects with or without heart disease, by using angiocardiography. The contribution of the longitudinal and radial components to total cardiac work was 14% and 40%, respectively [4]. It was suggested that separate analysis of the various components of LV systolic deformation might help us to understand the progression of LV systolic dysfunction at different stages of heart disease [5, 6].

4.2.1 Changes in LV Longitudinal Strain in Response to Increased Afterload

Theoretical computer models of the heart predicted that LV systolic deformation in a longitudinal direction increased with higher cardiac output (preload) and decreased with increasing mean arterial pressure (afterload) (Fig. 4.1) [7]. Because high systemic arterial pressure leads to increased LV wall stress, particularly on the

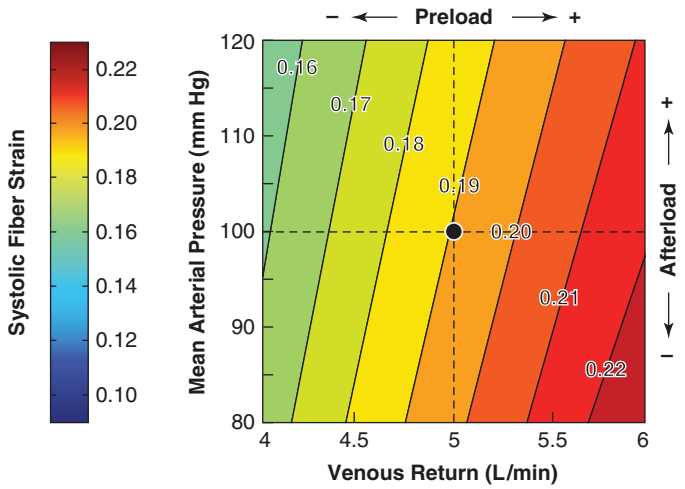

Fig. 4.1 Dependence of LV global LS (color gradient) to preload (venous return) and afterload (mean arterial pressure) in a normal heart. Reproduced from Lumens et al. [7] with permission

longitudinally oriented and less curved subendocardial fibers, deformation of the myofibers in this direction is impaired. Thus, longitudinal systolic dysfunction could already been observed at the early stages of progressive myocardial maladaptation related to chronically increased hemodynamic load [8].

Along similar lines, an experimental study involving an aortic banding model showed disparate changes in longitudinal and radial myocardial strain in response to acute alternation in LV afterload [9]. Longitudinal systolic function dramatically fell as afterload increased, whereas LV fractional shortening and radial strain were still preserved after a mild banding [9]. Previous clinical studies reported depressed LV longitudinal function even in asymptomatic patients with hypertension as compared with normotensives controls [10, 11]. In our large-scale general population study, we observed in the continuous analysis that global longitudinal strain decreased significantly with higher mean arterial pressure (by 0.29% per 10 mmHg, $P < 0.01$) [12].

4.2.2 Changes in LV Radial Strain in Response to Increased Afterload

At systole, the heart ejects a volume of blood into the aorta and generates a forward pressure wave that is reflected at various sites in the arterial system. If the aorta is compliant, the aortic walls elastically expand to accommodate the ejected blood. An elastic aorta, therefore, dampens pulsatility and maintains a continuous blood flow from the heart to the periphery. Hypertension accelerates the age-related stiffening of the large arteries including aorta, which plays an important role in the development of HF due to additional mechanical load on the heart [13]. Indeed, to expand stiffened arteries, the heart needs to produce greater pressure, and therefore its energy expenditure increases [14–16]. In addition, increased pulse wave velocity (PWV) in stiffening arteries leads to an early return of the reflected wave which might, in turn, also augment late systolic LV load. On the other hand, as suggested recently, entrapment of reflected waves in the periphery might limit the influence of peripheral reflected waves on central hemodynamic and late systolic load [17].

Previous population studies showed that measures reflecting increased aortic stiffness, such as a higher aortic PWV, are associated with a higher risk of cardiovascular events including HF beyond traditional cardiovascular risk factors [18–20]. For instance, in the Framingham study, greater aortic stiffness as reflected by increased aortic PWV was associated with increased risk of HF [19]. In multivariable-adjusted analyses, a one-SD increase in aortic PWV was associated with 29% higher risk for incident HF (hazard ratio per SD unit, 1.29; 95% CI, 1.02–1.64; $P = 0.037$).

Along these lines, we previously reported an age-dependent relationship between changes in LV radial systolic deformation and early and late systolic load in a general population [12]. Radial strain increased significantly with higher central pulse pressure and PWV in middle-aged participants (50–60 years) only, whereas it decreased with these indexes in older subjects (above 70 years) (Fig. 4.2). Our finding suggested that chronic rise in pulse pressure increases LV load and enhances LV radial systolic performance but in the long run might lead to adverse LV remodeling

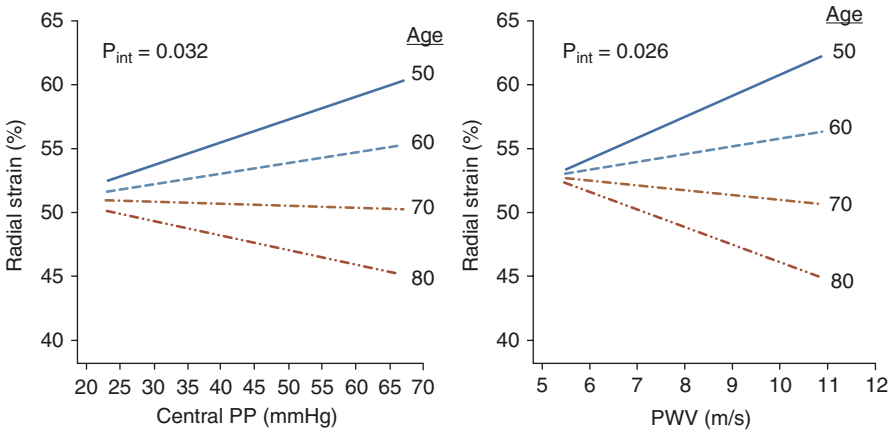

Fig. 4.2 Extrapolation from the multivariable-adjusted model of radial strain in relation to the continuous components of arterial stiffness at fixed levels of age. The number at the extrapolation line indicates the fixed level of age. P_{int} indicates the P values for interaction between arterial characteristics and age. Reproduced from Cauwenberghs et al. [12] with permission

and impairment of radial deformation. This mechanism probably contributes to development and progression of LV dysfunction in hypertensive patients. However, future serial imaging studies should clarify the progression of LV radial strain changes in response to chronically increased LV loading due to arterial stiffening.

4.3 LV Remodeling

For better understanding of cardiac mechanics, it is important to describe a relationship between pressure, volume, and wall stress of the LV. The Laplace law is commonly used as a mathematical model to predict LV wall stress from given pressure and geometry [21]. According to this equation, LV wall stress is directly proportional to LV pressure and radius and is inversely proportional to the wall thickness of the LV (Fig. 4.3). Higher pressure can cause thickening of LV walls in order to accommodate an increased load and maintain normal wall tension. Indeed, hypertension induces a compensatory thickening of the ventricular wall, so-called concentric hypertrophy, in order to normalize wall stress. Thus, patients with hypertensive heart disease usually present with concentric remodeling or concentric LV hypertrophy but have a normal-sized LV chamber and normal ejection fraction [22]. On the other hand, the hypertrophic LV is stiffer, so it requires elevated pressures to fill it, leading to a condition known as diastolic dysfunction.

Cardiac maladaptation in response to increased hemodynamic load such as worsening of LV geometry is not a benign condition and is associated with increased risk of cardiovascular outcome. A number of studies documented the relationship between LV hypertrophy (increased LV mass index) detected by electrocardiography and echocardiography and an adverse prognosis. A meta-analysis combined

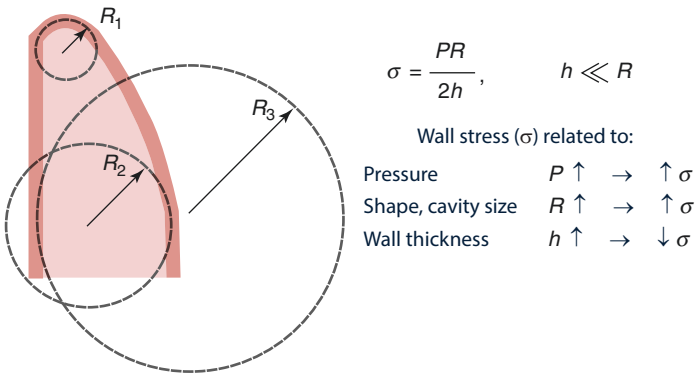

Fig. 4.3 Schematic representation of the law of Laplace, which states that wall tension is proportionate to the pressure (P) times radius (R). Therefore, wall stress (σ) is wall tension divided by wall thickness (h). At a given intraventricular pressure, wall stress increases with an increase in radius of the ventricular cavity

48,545 subjects from 20 prospective studies and showed that the adjusted risk of future cardiovascular morbidity associated with baseline LV hypertrophy ranged from 1.5 to 3.5, with a weighted mean risk ratio of 2.3 for all studies combined [23]. Several mechanisms may explain why adverse LV remodeling/hypertrophy is a harbinger of adverse cardiovascular outcomes. Firstly, LV hypertrophy or remodeling may lead to diastolic filling abnormalities that predispose to symptomatic HF. Secondly, maladaptive LV remodeling may lead to dysfunction of the autonomic nervous system, reduce coronary reserve, and increase LV oxygen requirements. Thirdly, it may predispose to ventricular arrhythmias and a greater risk of sudden death.

4.4 LV End-Diastolic Filling Pressure (Diastolic Function)

As we mentioned in the previous section, LV diastolic function tends to worsen over the adult life course in patients with hypertension in parallel to changes in systolic performance and cardiac geometry [24]. Diastolic dysfunction refers to a condition in which abnormalities in LV function are present during diastole.

Early stage of LV diastolic dysfunction, as impaired myocardial relaxation, is characterized by decreased transmitral early (E peak) and enhanced atrial (A peak) LV filling as well as less vigorous mitral annulus motion (e' peak) during early diastole. The more advanced stage of diastolic dysfunction is typically presented by increased LV end-diastolic filling pressure in response to increased LV stiffness. Noninvasively we might estimate LV filling pressure by combining early transmitral blood flow velocity with early mitral annular velocity (E/e' ratio) [25]. Of notice, an accurate prediction of LV filling pressures for an individual patient requires further characterization of the intermediate E/e' group, for instance, by measurement of left atrial volume and blood flow in the pulmonary vein.

Previous studies demonstrated that elderly women appear the most susceptible to the detrimental effects of increased pulsatile load on LV diastolic function [17, 26, 27]. This observation might be explained by the higher aortic pulsatile load and aortic stiffness, enhanced LV systolic performance, and lower LV compliance in women as compared to men [12, 17, 28, 29].

4.5 The Correlation Network of BP and LV Traits

Figure 4.4 illustrates a complex network of interactions between the multivariable-adjusted components of BP and echocardiographic indexes of LV systolic and diastolic function and structure. To construct this network, we used a population data of 791 participants (mean age was 50.9 years, 51.8% were women and 41.2% had hypertension) randomly recruited within the FLEMENGHO study [30]. The figure represents a partial regression diagram including multivariable-adjusted components of BP such as mean arterial pressure and pulse pressure and echocardiographically measured LV phenotypes. This approach fits covariance selection models, estimating the correlation between two components of the network adjusted for the correlations of these two components with all other variables in the network (i.e., partial correlations).

While accounting for all BP and LV traits' interactions, the partial regression analysis confirmed the relationships between hemodynamic variables and LV phenotypes as described in previous sections. Namely, lower global longitudinal strain is significantly correlated with higher mean arterial pressure and increased LV mass index. Moreover, we observed the strong relation of higher pulse pressure with increased LV filling pressure (as estimated by E/e' ratio) and LV mass index (Fig. 4.4). Lower radial strain was related to higher relative wall thickness (index of concentric remodeling) and greater LV filling pressure (by E/e' ratio). Thus, higher BP evokes a complex network of functional and structural changes in the heart. As such, early detection and effective management of BP may prevent or delay the development of subclinical LV remodeling and dysfunction preceding symptomatic HF. The preventive strategies might tackle the rising contribution of poorly controlled BP to the epidemic of symptomatic HF.

4.6 Assessment of LV and Arterial Elastance

As we highlighted in the previous section, the interaction of the heart with the systemic vasculature, or ventricular-arterial coupling, is a key determinant of cardiovascular performance. Therefore, simultaneous measurement of arterial and LV stiffness or elastane is important to better understand hemodynamic mechanisms leading to HF. The measurements of elastance could be derived from invasive or noninvasive registration of LV pressures and LV volumes (pressure-volume curves), which might also be recorded over a wide range of LV loading conditions (Fig. 4.5). By definition elastance reflects volume change per unit of pressure change; it is the

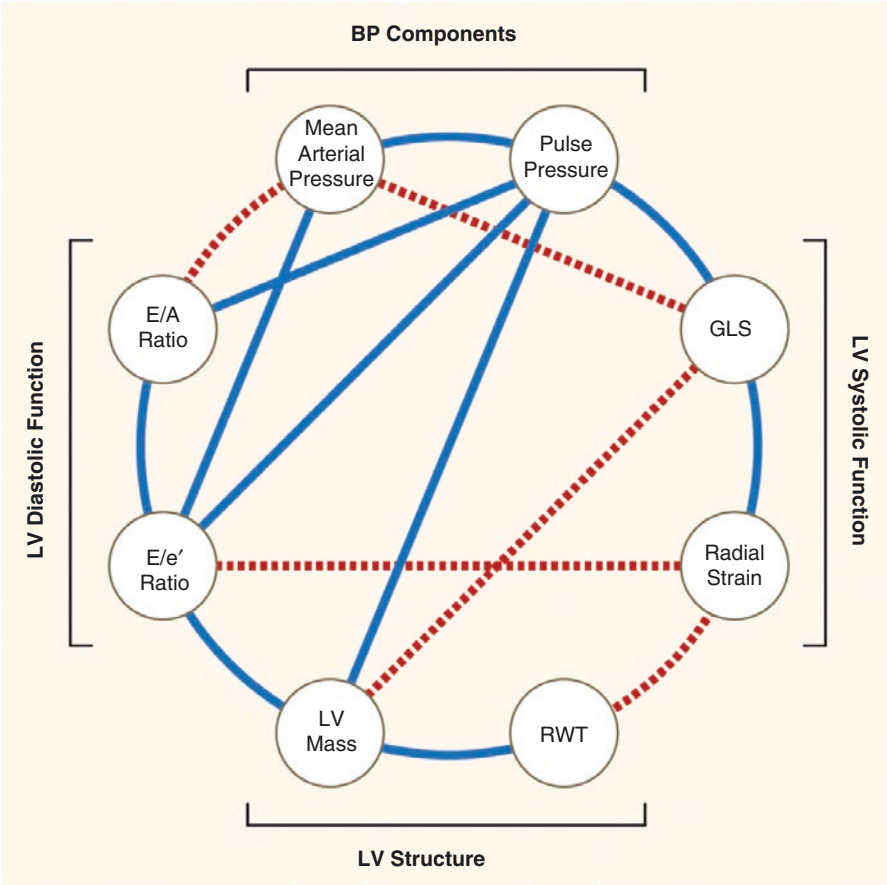

Fig. 4.4 Partial correlation diagram between blood pressure components and echocardiographic indexes of LV function and structure based on the data of 791 participants from the FLEMENGHO population study [30]. The full blue lines represent direct (positive) correlations, and dashed red lines represent inverse (negative) correlations ($P < 0.05$ for all). All indexes were adjusted for age, sex, heart rate, body height, and body weight. Models for LV mass index did not include body height and weight. *BP* blood pressure; *GLS* global longitudinal strain; *LV* left ventricular; *RWT* relative wall thickness

reciprocal of compliance. For instance, effective arterial elastance (E_a) could be calculated as the ratio of LV end-systolic pressure to stroke volume, and it reflects the net arterial load imposed on the LV [31].

LV end-systolic elastance (E_{lv}) provides an estimate of overall LV performance and is calculated by measuring the slope of the end-systolic pressure-volume relations registered over a range of LV loads [31]. Alternatively, E_{lv} could be calculated as a ratio of LV end-systolic pressure to LV end-systolic volume (Fig. 4.5). Therefore, E_{lv} as an index of myocardial performance reflects the ability of the LV to eject blood opposed to a given pressure. An increase in E_{lv} is generally associated with enhanced

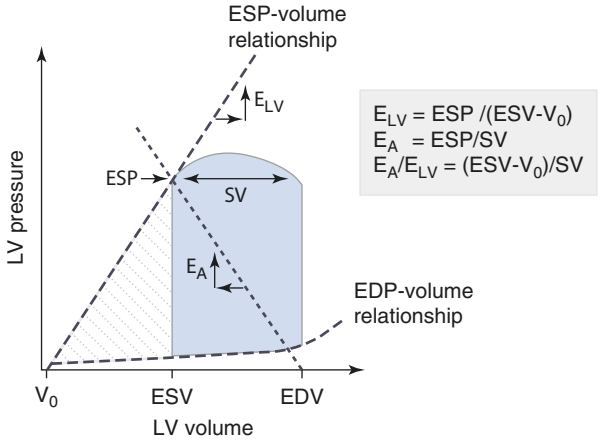

Fig. 4.5 Schematic representations of a pressure-volume loop and derived ventricular-arterial indexes. *EDV* end-diastolic volume; *ESV* end-systolic volume; *ESP* end-systolic pressure; E_A arterial elastance; E_{LV} left ventricular end-systolic elastance; *LV* left ventricular; *SV* stroke volume

myocardial contractility. On the other hand, E_{lv} also reflects in some degree chamber geometry and passive myocardial stiffening, which could be altered in hypertensive patients. Indeed, numerous clinical studies [32–35] show that effective arterial and LV elastances based on invasive or noninvasive determination of LV volumes and end-systolic pressure are both increased in hypertensive patients. For instance, Cohen-Solal et al. [33] showed that E_a and E_{lv} as measured by angiography were significantly higher in 19 hypertensive patients as compared to 25 normotensive men. Later on, Saba et al. [35] confirmed this finding using echocardiography for measurement of LV volumes and carotid pressure waveforms for assessment of ESP in 81 normotensive and 174 hypertensive patients. Furthermore, Chantler et al. [32] reported that the ventricular-arterial coupling ratio (E_a/E_{lv}) was about 25% lower in hypertensive compared with normotensive women. Along similar lines, we also found that in hypertensive patients the ventricular-arterial coupling ratio at rest was 16.4% lower compared with normotensive subjects [34]. The lower ventricular-arterial coupling ratio in hypertensive patients was due to a disproportionate increase in E_{lv} compared with E_a (32% vs. 10%) [34]. Therefore, in asymptomatic hypertensive patients, a higher E_{lv} at rest might not only mean greater myocardial performance but also reflect geometrical and passive structural changes in hypertensive hearts.

4.7 Area of the Pressure-Strain Loop During Ejection as Noninvasive Index of LV Performance

Additional information about changes in LV performance due to increased loading conditions might also be derived from a simultaneous assessment of pulse wave and myocardial deformation (strain) curves. Two-dimensional speckle tracking allows

quantification of the relative myocardial deformation (strain) [36] whereas applanation tonometry could be used to derive pulse waveform during each cardiac cycle. From these recordings, the myocardial work density could be calculated as a quantitative measure of regional LV performance as previously described [37]. In analog to pressure-volume curves, we constructed LV pressure-strain loops by plotting the instantaneous pressures against the instantaneous strain values (Fig. 4.6) with indications of different mechanical phases of the cardiac cycle [34]. The area of these loops during ejection phase was considered as the LV ejection work density (EWD)

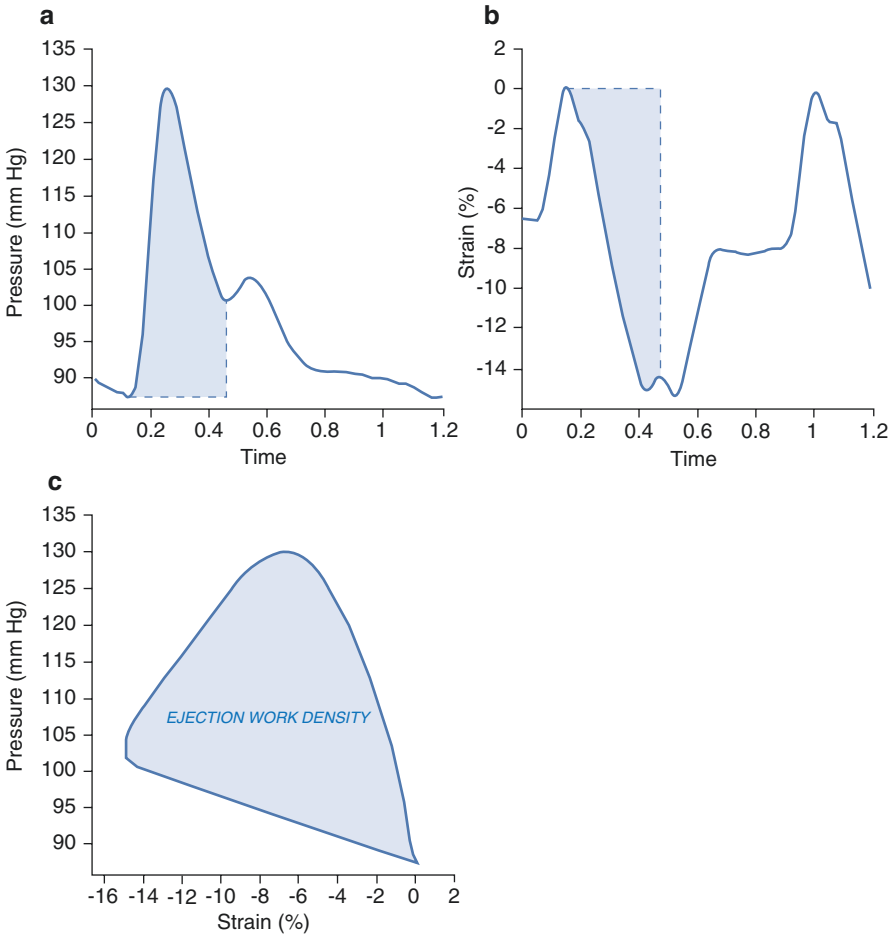

Fig. 4.6 Noninvasive assessment of LV ejection work density. From grayscale echocardiographic imaging and simultaneously recorded brachial pressure waveforms, we derived brachial artery pressure wave (**a**) and two-dimensional LV strain (**b**) curves to construct the pressure-strain loop (**c**). The myocardial work index (i.e., ejection work density) was calculated as the area of the pressure-strain loop during LV ejection (shaded area in **c**). LV indicates left ventricular. Reproduced with modification from Kouznetsova et al. [34] with permission

as it represents the cumulative work done by the cardiac muscle in order to instantaneously shorten a given amount (i.e., change in strain) at a given instantaneous resistance (i.e., pressure) [34].

In our study of random cohort of 148 subjects, we observed that the higher arterial load in asymptomatic hypertensive patients matched with enhanced LV myocardial performance [34]. As a result, ejection work density as a measure of ventricular-arterial coupling was 24% higher in hypertensive subjects as compared to normotensives [34]. This finding is similar to those previously reported with regard to E_a/E_{lv} in hypertensive patients. Moreover, an experimental study showed that the peak rate of changes in LV pressure (dP/dt), an invasive index of myocardial contractility, was 51% greater in hypertensive than in normotensive rabbits [38]. However, so far this noninvasive index of LV performance remains insufficiently studied in patients and populations.

4.8 Conclusion

As shown by epidemiological studies, hypertension is one of the most important modifiable risk factors for the development of symptomatic HF. Identifying patients at the early (asymptomatic) stages of HF would allow the institution of more aggressive risk management strategies and will likely decrease the progression to symptomatic disease.

In this regard, better understanding of pathophysiological mechanism of cardiac maladaptation in patients with hypertension is crucial for early detection of this condition. The chronically increased cardiac performance due to high afterload leads to LV concentric remodeling, impairment of LV systolic deformation and diastolic dysfunction. LV systolic and diastolic dysfunction coexists to varying degrees and appears very early in the course of hypertensive heart disease. Community-based studies revealed a higher than hitherto expected prevalence of LV systolic and diastolic dysfunction and their independent prognostic significance.

Hypertension also accelerates the age-related stiffening of the large arteries which plays an important role in the development of HF due to additional mechanical load on the heart. The heart typically adapts to confront higher systolic loads by both hypertrophy and LV stiffening. Increased vascular loading on the heart also contributes to LV dysfunction. Ventricular-arterial coupling disease has to be further explored in subjects with subclinical LV dysfunction.

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Neural Mechanisms

5

Dagmara Hering, Gino Seravalle, Guido Grassi, and Krzysztof Narkiewicz

5.1 Sympathetic Nervous System Activation in Human Hypertension

It is not clear whether the hemodynamic characteristics of the initial phase of primary hypertension are induced by increased peripheral resistance or raised cardiac output [1]. Approximately one third of younger adults with borderline and/or mild hypertension present with hyperkinetic hypertension with increased heart rate, cardiac output, forearm blood flow and plasma noradrenaline (NA) levels [2]. Other abnormalities also commonly characterize the hyperkinetic state including increased renal blood flow and plasma renin activity [3]. The

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hyperkinetic state is likely to indicate increased sympathetic activity. The activation of the sympathetic nervous system (SNS) in human hypertension has been convincingly demonstrated through the use of two state-of-the-art methods, namely, the isotope dilution method for quantifying NA spillover rates and the postganglionic efferent sympathetic nerve recording with microneurography technique. NA is the main neurotransmitter of sympathetic nerves, and the rate of its release from nerve terminals allows for the measurement of sympathetic nerve activity. Quantifying NA kinetics with spillover technique was a major breakthrough in studies on the sympathetic nervous system. Although the overall (total body) NA spillover in hypertension is moderate, a selectively augmented sympathetic outflow from the heart and the kidney characterizes primary hypertension, likely contributing to established hypertension [4, 5]. Augmented NA from the renal sympathetic nerves is evident in untreated patients with essential hypertension (EH), mostly adults below the age of 40, and is a prime mover for blood pressure (BP) rise [4, 6]. Increased cardiac NA spillover and decreased NA neuronal reuptake further potentiate sympathetic activation in maintaining elevated BP [7]. In comparison to younger hypertensives, NA release from sympathetic nerves has been found to be lower as a result of an age-dependent fall in NA plasma clearance in essential hypertension [8]. With ageing and disease progression, cardiac output generally becomes normal in uncomplicated hypertension; however a shift towards increased vascular resistance potentiates sympathetic activation which is a hallmark of established hypertension, leading to vascular remodeling, organ damage and adverse cardiovascular (CV) complications [9].

It is noteworthy that at rest in the healthy human heart, the amount of adrenaline release from the sympathetic nerves is negligible as the majority (80%) of adrenaline is secreted from the adrenal medulla into the bloodstream, with only a slight amount released from sympathetic nerve endings. On the contrary, in untreated primary hypertension, augmented adrenaline release from cardiac sympathetic nerves enhances cardiac NA release through adrenaline co-transmission [10]. Mental stress is another factor to potentiate adrenaline plasma concentrations and increase the amount of neuronal uptake of adrenaline in cardiac sympathetic nerve endings, leading to subsequent release of adrenaline, potentiating NA co-release, thus acting as co-transmitter mechanism, supporting the ‘adrenaline hypothesis’ [10]. Adrenaline contribution to the pathogenesis of hypertension has been demonstrated by other findings documenting an 18-h elevation in BP following a 6-h adrenaline infusion [11]. These data suggest that adrenaline exerts a delayed pressor effect during sympathetic stimulation through activation of presynaptic β2-adrenoreceptors.

Microneurography studies have demonstrated elevated levels of muscle sympathetic nerve activity (MSNA) in high-normal BP [12, 13] indicating that sympathetic activation may precede overt arterial hypertension even in very low-risk subjects with high-normal BP [14]. Tonic sympathetic activation evident in patients with prehypertension appears to contribute to time-related increase in BP and development of sustained hypertension and asymptomatic arterial stiffness [15]. Persistent sympathetic activation is commonly found in patients with uncontrolled hypertension and resistant hypertension (RH). High levels of multiunit MSNA (often

50–70 bursts/min.) with burst activity often synchronized with every heartbeat typically characterize patients with RH when compared to healthy controls (<20 bursts/min.) and patients with untreated EH (25–40 bursts/min.). Furthermore, patients with RH display markedly elevated activity of single-unit muscle vasoconstrictor fibres including firing rate, firing probability and incidence of multiple spikes within a cardiac cycle [16]. These findings indicate that high sympathetic drive is a hallmark of RH despite the use of all available antihypertensive drug classes [16, 17] which are supposed to target hypertension pathophysiology. Notably, an increased prevalence of sympathetically mediated co-morbidities including diabetes, chronic kidney disease, obesity and obstructive sleep apnoea is commonly found in RH patients [18, 19], thereby further potentiating high sympathetic drive.

5.2 Neural Reflexes in the Pathogenesis of Hypertension

Tonic sympathetic activation is generated by neurons residing in the rostral ventrolateral medulla (RVLM) which integrates neural reflex mechanisms from afferent arterial baroreceptors, afferent arterial chemoreceptors and cardiopulmonary mechanoreceptors [20]. Baroreflex acts as an important inhibitory regulatory mechanism induced by BP changes mediated by the parasympathetic and sympathetic component. Reduced baroreflex sensitivity has been demonstrated in patients with hypertension and also subjects with a family history of hypertension and normal BP levels [21]. Augmented gain of the cardiopulmonary baroreflex control of sympathetic activity, unrelated to the attenuation of the arterial baroreflex, has also been demonstrated in hypertension compared to normal counterparts [22]. A further important causative mechanism of sympathetic activation, contributing to the pathogenesis of human hypertension, is potentiated sensitivity of arterial chemoreceptors in response to hypoxia [23–25].

5.3 Interaction Between the Sympathetic Nervous System and the Renin-Angiotensin System

The SNS is directly related to the renin-angiotensin system (RAS), both playing an important role in BP and blood volume control, acting at different levels on the central nervous system (CNS) and peripheral sites leading to the synthesis and release of angiotensin II and NA, the fundamental neurotransmitters implicated in the development and progression of a disease [26]. Sympathetic activation increases the activity of the RAS via direct effects on the three renal neuroeffectors: (1) the juxtaglomerular granular cells enhancing renin release (via stimulation of β_1-adrenoreceptors), (2) the renal tubular epithelial cells increasing sodium reabsorption (via stimulation of α_{1B}-adrenoreceptors) and (3) the renal vasculature (via stimulation of α_{1A}-adrenoreceptors) reducing renal blood flow. These result in increased efferent renal sympathetic nerve activity (ERSNA) [5]. Notably, in physiological conditions ERSNA stimulates afferent renal sensory nerves which via the

renorenal reflex mechanism lead to a subsequent reduction in ERSNA and resultant diuresis and natriuresis. In the presence of elevated BP, increased signals arising from the injured and/or ischemic kidney via afferent renal sensory nerves are projected to the central integrative structure in the brainstem (RVLM) potentiating sympathetic outflow to the periphery, causing end-organ damage and adverse sequelae.

5.4 Brain Neural Activity in Hypertension

There is evidence to indicate that sympathetic activation in EH is of CNS origin and contributes to the efferent sympathetic outflow to the periphery. Studies assessing the combined overflow of brain NA have demonstrated increased NA release within the CNS [27, 28]. Direct blood sampling from the internal jugular veins and concomitant cerebral blood flow scans revealed that suprabulbar noradrenergic projections from the brainstem to the hypothalamus play a key role in neurogenic hypertension [29]. Subcortical NA turnover in brain regions (not cerebral cortex) was found significantly higher in EH when compared to healthy subjects and directly related to neurochemical indices of the SNS activity and renal NA spillover in EH [29].

The association between 'hypertension and the brain' is reciprocal. Hypertension alone has led to cerebral hypoperfusion and a reduction in cortical thickness independent of the use of antihypertensive drugs [30]. Further proof linking functional neural reorganization early in the course of hypertension development comes from functional magnetic resonance imaging studies demonstrating substantial variations in brain activation in a reasonably controlled hypertensive cohort compared to age-matched counterparts [31].

5.5 Heart Failure Attributable to Hypertension

Chronically elevated BP critically contributes to the progression of hypertensive heart disease resulting in a constellation of abnormalities in the myocardium, coronary vasculature, heart function and conduction [32]. Changes in cardiac chamber geometry induced by hypertension include asymptomatic left ventricle (LV) hypertrophy, ischaemic heart disease, systolic and diastolic dysfunction and resultant clinical manifestations including arrhythmia and heart failure (HF). The relationship of antecedent hypertension to the development of HF has been documented in a large study cohort (n = 5143) followed over a 20-year duration [33]. Of note, hypertension accounted for 39% of new HF cases in men and 59% in women. Among hypertensive subjects, myocardial infarction, diabetes, LV hypertrophy and valvular heart disease predicted increased risk for congestive HF in both genders. Outcomes following the onset of hypertension-related HF were poor with only 24% of men and 31% of women surviving for 5 years [33].

The pathophysiology of hypertensive heart disease involves a complex interplay of hemodynamic, structural, cellular, neurohormonal, molecular and genetic factors. Nevertheless, sympathetic activation plays a critical role in cardiac, arterial and

vascular remodeling and further progression. High levels of NA release from cardiac and renal sympathetic nerves accompanying increased MSNA has been linked to LV remodeling in untreated hypertension including LV hypertrophy and LV dysfunction [34–36]. Activation of RAS is a further major contributor to the development of myocardial hypertrophy. The associated sympathetically mediated rise in BP and induced organ damage are likely to contribute to further adverse events.

5.6 Role of Sympathetic Nervous System Activation in Heart Failure

Neurohormonal activation with heightened sympathetic activity and withdrawal of vagal activity are hallmarks of HF. Altered sympathetic CV regulation is at the core of disease development, progression and associated increased CV morbidity and mortality. Augmented MSNA is already evident in early-stage HF and is directly related to the clinical severity of congestive HF as classified by NYHA (New York Heart Association) [37]. Moreover, the potentiated high sympathetic drive in HF has been associated with markedly impaired baroreflex control when compared to healthy subjects [37]. Higher levels of MSNA have been linked to end-organ damage including reduced LV function, LV stroke work index, stroke volume and cardiac chamber size [38], indicating that sympathetic activity at rest parallels impairment of cardiac performance in HF. Further support for sympathetic activation in HF has been shown in studies applying NA spillover. Increased NA releases from the renal and cardiac sympathetic nerves are typical features in patients with chronic HF (CHF) [39].

Previous studies found that in acute HF, high levels of catecholamines augment ventricular contractility in order to maintain sufficient cardiac output. Heightened NA released from the sympathetic nerves predominantly stimulates β_1-adrenergic receptors (AR) with its higher binding affinity to β_1-AR than to β_2-AR, irrespective of the physiological and pathophysiological condition [40]. In the healthy heart, the concentration of β_1-AR is four times higher than β_2-AR, whereas in the chronically failing heart, β_1-AR is selectively down-regulated shifting the proportion of β-AR resulting in high levels of circulating NA. In the failing heart, NA has been found to be exceptionally cardiotoxic producing cardiac myocyte injury via NA-mediated cell toxicity through β- rather than α-AR [40]. Additionally, high cardiac NA levels contribute to the selective decrease of β_1-AR density in HF. Although initially this is a protective compensatory mechanism preventing a deleterious surge in intracellular cAMP mediating the catecholaminergic control of HR and contractility, it ultimately leads to a loss of inotropy and damage to the failing heart [41].

5.7 Role of the Kidney in the Pathophysiology of Heart Failure

Neural control of the kidney is of particular relevance in HF with subsequent increase in renin release, sodium reabsorption and reduction in renal perfusion [6]. The resulting increase in venous return triggers a rise in end-diastolic volume and

stroke volume to the heart. An excessive and prolonged exposure to sympathetic activation produces adverse systemic effects on various organs, critically contributing to the progression of HF including myocardial ischemia and remodeling with enlargement of the ventricular chamber [42] and a decrease in ventricular fibrillation threshold resulting in sudden cardiac death and worsened prognosis [6]. Increased elevated cardiac NA spillover rate independently predicted mortality in CHF patients [43]. Additionally, CHF patients with higher levels of renal NA spillover had substantially reduced transplantation-free survival rates [44]. Moreover, chronic kidney disease has been demonstrated to be a predictor of repeated HF hospitalizations [45]. Stimulation of the RAAS accompanying sympathetic activation is an additional fundamental contributor to the progression of CHF [46, 47] producing adverse systemic consequences on the myocardium, blood vessels and peripheral vasoconstriction resulting in increased afterload, reduced cardiac output and renal perfusion.

5.8 Neural Reflexes in the Pathogenesis of Heart Failure

Altered reflex, neurohumoral and metabolic factors substantially contribute to the initiation and maintenance of increased sympathetic activation in HF. This includes an impairment of arterial baroreceptor function in mediating changes in tonic sympathetic nerve activity to the heart and blood vessels in HF [48–50]. While in healthy subjects the arterial baroreflex exerts a powerful inhibitory influence on SNS and arterial chemoreceptors [51], baroreflex impairment with subsequent loss of sympathetic inhibition in HF is likely to increase chemoreflex sensitivity and further potentiate sympathetic activation which is unopposed by inhibitory influences from reflex mechanisms. HF patients display a marked and selective augmentation of the central chemoreflexes (located in the brainstem on the ventral surface of the medulla) in response to hypercapnia [52, 53]. An increase in central chemoreflex sensitivity may contribute to the development of central sleep apnoea (CSA) in HF. Direct intraneural recordings of MSNA showed conflicting results in HF patients regarding chemoreflex activation. High resting levels of MSNA evident in HF patients were not influenced by hyperoxia (deactivation of peripheral chemoreceptors) indicating that increased efferent MSNA is unrelated to tonic activation of excitatory chemoreflex afferents even in the presence of mild hypoxemia [52]. This has been further confirmed in another study demonstrating that CHF patients despite higher ventilation (which inhibits sympathetic activity) are characterized by a selective potentiation of ventilatory and sympathetic responses to central chemoreceptor activation induced by hypercapnia but not hypoxia or cold pressor test when compared to healthy subjects [53]. In contrast, another study demonstrated reduced MSNA in response to hyperoxia in patients with HF-associated anaemia [54]. Moreover, deactivation of peripheral chemoreceptors led to a reduction in MSNA and was closely associated with impaired baroreflex function in HF [55]. Nevertheless, CSA and cyclic episodes of hyperpnoea-apnoea breathing (Cheyne-Stokes, C-S respiration) are commonly present in HF patients [56] eliciting a further augmentation of

sympathetic activation [52] likely contributing to CV events, brady-arrhythmias and worsening prognosis. Increased peripheral chemoreflex sensitivity has been shown to be an independent prognostic factor in ambulatory patients with HF [57]. An additional important contributor to sympathetic activation in HF is reduced ability of the inhibitory influences from arterial and cardiopulmonary mechanoreceptors to exert tonic restraint on sympathetic outflow [58]. Chronic sympathetic activation with reduced parasympathetic tone present in HF is critical in the development and progression of disease including ventricular remodeling and arrhythmia resulting in increased CV morbidity and mortality [59, 60].

5.9 Device-Based Therapeutic Interventions

Inhibition of the neurogenic pathways has been a major target for the management of hypertension and heart failure. Therapeutic modulation of the SNS activity via interruption of afferent signalling arising from (1) the kidney (RDN), (2) carotid arterial baroreceptors (BAT) and (3) carotid arterial chemoreceptors (CBD) projected to the RVLM (centre for BP and sympathetic outflow control) has been demonstrated in the treatment of uncontrolled/resistant hypertension and HF.

5.10 Renal Denervation in Hypertension

Since the first-in-man proof-of-concept Symplicity HTN-1 trial, most interventional advancements for the treatment of drug-RH have focused on renal denervation [61]. Evidence from the unblinded studies applying catheter-based RDN demonstrated a significant decrease of ~10–15 mmHg in mean ambulatory systolic BP [62–64]. However, the first prospective randomized double-blind sham-controlled Symplicity HTN-3 study has not confirmed the BP lowering effect in the treatment of RH [65]. Conflicting results derived from other sham-controlled trials of RDN exist demonstrating no significant changes in the primary efficacy endpoint between the RDN and sham-controlled groups [66] or comparable reductions in daytime systolic BP between both groups [67]. Another yet randomized controlled trial study demonstrated that effectiveness in BP lowering is greater when RDN is added to a standardized stepped-care antihypertensive treatment when compared to the same medication alone [68].

The uncertainty of the BP reduction following RDN has been addressed in the SPYRAL HTN-OFF MED trial [69] with the use of the next-generation RDN multi-electrode Symplicity Spyral catheter which delivers radiofrequency energy treatment to all four renal artery quadrants for 60 s, likely to provide sufficient nerve ablation circumferentially. The SPYRAL HTN-OFF MED included drug-naïve hypertensives or patients who were able to discontinue existing pharmacological therapy and demonstrated a significant reduction in daytime SBP (−5.5 mmHg) in the RDN group compared to −0.5 mmHg in the sham-controlled group at 3 months post procedure [69]. While there is a biological proof of principle for the BP

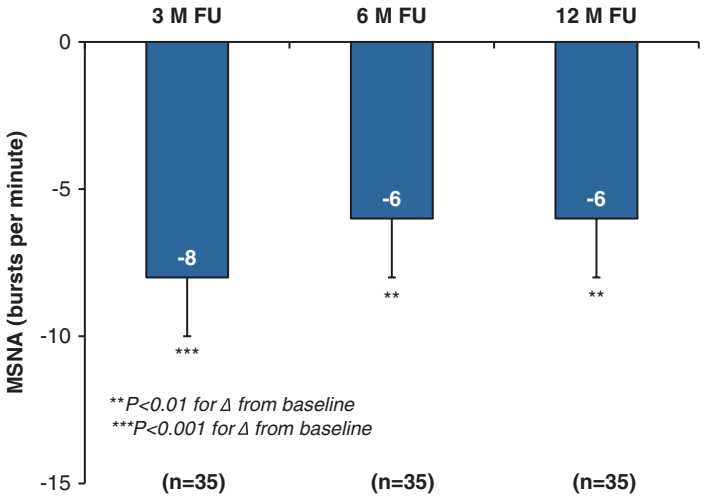

Fig. 5.1 Mean fall in muscle sympathetic nerve activity (MSNA) at 3, 6 and 12 months (M) follow-up (FU) after renal denervation. Adapted with permission from [17]

lowering efficacy [69] and a sustained reduction in MSNA out to 12 months post procedure [17] (Fig. 5.1), the broad clinical utility of RDN for the management for hypertension merits further clinical trials.

5.11 Renal Denervation in Heart Failure

With a proven safety profile and substantial continued BP reduction in a large proportion of patients with uncontrolled hypertension, the safety and efficacy of bilateral RDN have been demonstrated in the Renal Artery Denervation in Chronic Heart Failure (REACH) trial which included 7 HF patients [70] and the Symplicity HF Feasibility Study with a total of 39 HF patients [71]. Importantly, the procedure was well-tolerated, and no major drops in BP were observed [70]. No changes in left ventricular ejection fraction (LVEF) and cardiac function were observed in the REACH trial at 6 months follow-up and in the Symplicity HF trial at 12 months post procedure. A significant improvement in the 6-min walk test was found in the REACH trial but not in the Symplicity HF trial [71]. While there are potential benefits of RDN in patients with HF, no randomized controlled and long-term data is yet available.

5.12 Baroreflex Activation Therapy in Hypertension

Electric stimulation of carotid sinus baroreceptors is a further attractive approach for the treatment of uncontrolled hypertension. The initial proof-of-concept study (DEBuT-HT trial) has demonstrated the safety and efficacy of the CVRx Rheos

System device in producing a substantial and durable BP-lowering effect [72, 73]. The implantation of the first-generation system was associated with procedure-related serious adverse events and the short-term battery life which limited its utility. The next-generation minimally invasive Barostim neo led to a significant BP reduction in RH patients at 3- and 6-month follow-ups, even in a subset of patients (n = 6) previously treated with RDN, and was associated with less device-related side effects [74]. Further proof for additive BP lowering and antiproteinuric effects achieved by BAT was demonstrated in a cohort of 28 patients who presented with elevated BP despite previous RDN performed 5 months prior [75]. Two recent case reports demonstrating the beneficial clinical utility of BAT in acute clinical scenarios deserve to be mentioned. Generally, the BAT device is activated 2–4 weeks after surgical implantation to allow the site to heal; however, its immediate activation in a young male with hypertensive crisis following aortic dissection due to RH that was unresponsive to sympatholytic agents resulted in a rapid, significant and sustained reduction in BP out to 12 months post procedure with no further incidence of hypertensive crisis [76]. Clinical utility of the second-generation Barostim neo has been also successfully demonstrated in a first-in-man treatment of severe BP variability >30 mmHg in a patient diagnosed with a progressive central and peripheral dysautonomia secondary to Sjogren's syndrome and impaired CV reflex regulation [77]. These case reports highlight further clinical applicability of BAT in severe forms of difficult-to-manage hypertension. While the application of BAT in an emergency situation may not be feasible, it emphasizes the potential of this treatment option.

5.13 Baroreflex Activation Therapy in Heart Failure

The beneficial results of BAT in patients with RH have led to further proof-of-concept studies in HF patients characterized by impaired baroreflex function [78, 79]. In one of these studies, 11 HF patients with NYHA III class and an average LVEF of 31 ± 7% receiving optimal drug therapy; 7 of which had a previous implanted cardioverter defibrillator and 1 with a pacemaker underwent BAT, and were followed up for 6 months [78]. The reduction in MSNA was more pronounced between 1 and 3 months post procedure and remained at this level in 8 out of 11 patients at 6 months follow-up (Fig. 5.2) [78]. The sympathetic inhibition was accompanied by progressively increasing improvement in baroreflex sensitivity from 1 month post procedure through to 6 months follow-up. BAT was associated with improved clinical symptoms as demonstrated by increased exercise tolerance and LVEF, reduced NYHA class and hospitalization rate in addition to improved quality of life, with no significant changes in BP or symptoms of orthostatic hypotension [78]. Two patients died over the course of the study due to causes deemed to be unrelated to the procedure. Nevertheless the remaining nine patients who experienced clinical benefits with BAT at 6 months continued to maintain the improvements over the longer term at 12 and 21.5 ± 4.2 months post procedure [79]. Given the causal link between baroreflex dysfunction and its prognostic significance in HF, these preliminary findings appear reassuring for the potential applicability of BAT in patients with

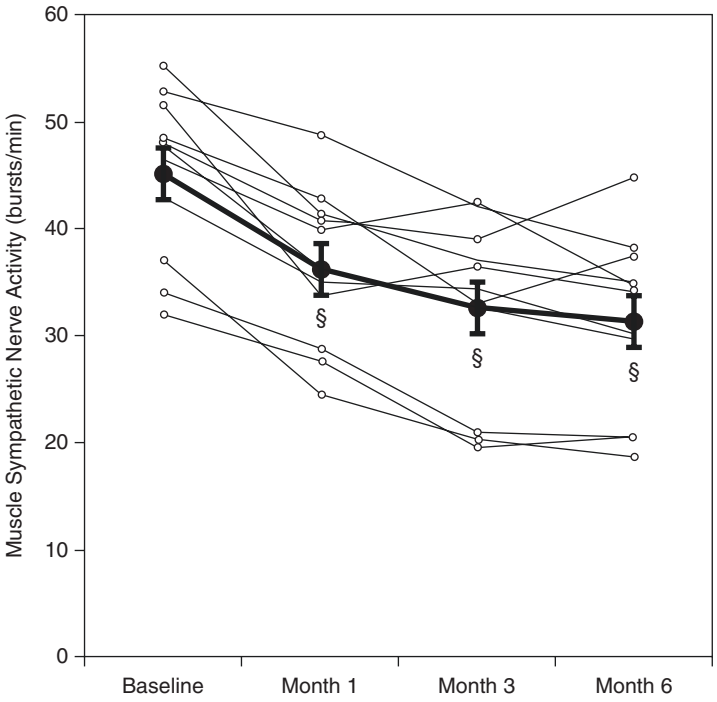

Fig. 5.2 Change in muscle sympathetic nerve activity (MSNA) during treatment with baroreflex activation therapy. Adapted with permission from [78]

reduced LVEF. However, larger clinical trials need to confirm these clinical observations and assess whether BAT may complement current management in the treatment of HF, both in patients with preserved and reduced LVEF.

5.14 Carotid Body Denervation in Hypertension

The association between potentiated tonic chemoreflex sensitivity and increased sympathetic activation in hypertension pathophysiology has encouraged the initiation of studies investigating the feasibility and efficacy of a therapeutic intervention directed at modulation of peripheral arterial chemoreceptors located in the carotid body. Results from the first-in-human proof-of-concept study of a total of 15 patients with RH who underwent unilateral ($n = 4$ on left side, $n = 11$ on right) carotid body removal found that 8 out of 15 patients, who underwent carotid body removal on the right side, experienced a reduction in daytime and night-time systolic BP at 3 (-23 ± 3 mmHg, -20 ± 4 mmHg), 6 (-26 ± 4 mmHg, -16 ± 5 mmHg) and 12 (-12 ± 8 mmHg, -15 ± 6 mmHg) months follow-up [80]. Lowering the BP was accompanied by a reduction in MSNA and improved baroreflex sensitivity in responders but not in nonresponders (Fig. 5.3). In a patient previously treated with RDN and removal of left carotid body, no short-term and long-term BP changes

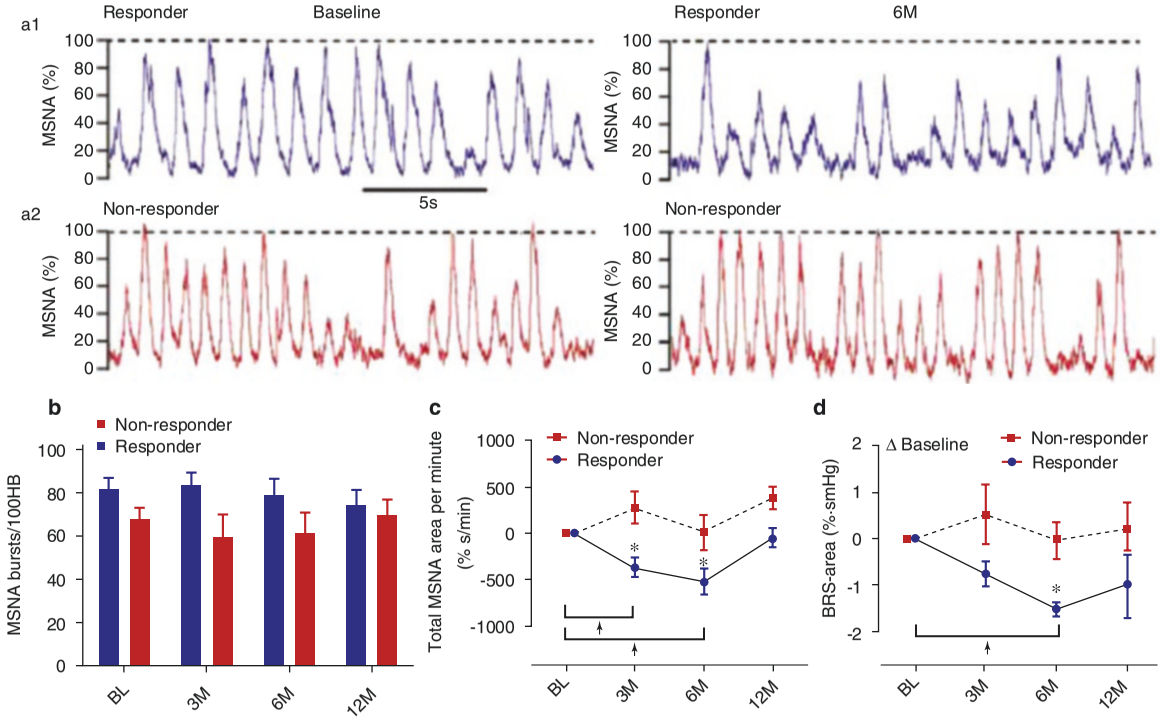

Fig. 5.3 Representative recordings of muscle sympathetic nerve activity (MSNA) for a responder ($\mathbf{a}_1$) and nonresponder ($\mathbf{a}_2$) at baseline (left trace) and 6-month follow-up (right trace). There was no difference in MSNA burst incidence between responders and nonresponders (**b**). However, MSNA area reduced after carotid body removal in the responders but not in the nonresponders (**c**), and spontaneous MSNA area baroreflex gain improved in responders but not in nonresponders (**d**). Two-way repeated measure analysis of variance was used (within groups $*p < 0.05$; between groups $\dagger p < 0.05$), bursts/100HB = bursts per 100 heart beats. Adapted with permission from [80]

were noted post procedure. Another novel finding is the association between the BP responses and increased chemoreflex sensitivity indicating the underlying contributing mechanism of RH [80]. Currently ongoing clinical trials are aimed at determining the effects of CBD via a venous-based catheter approach for the treatment of uncontrolled hypertension.

5.15 Carotid Body Denervation in Heart Failure

The prognostic significance of augmented peripheral chemoreflex sensitivity in HF patients has prompted the extension of therapeutic removal of carotid body in patients with systolic CHF [81]. Surgical carotid body removal was well-tolerated in a treated patient and reduced peripheral chemoreceptor sensitivity while improving exercise tolerance, LVEF, sleep disorder breathing and quality of life. Although the patient's medication remained unchanged, no symptoms of hypotension following unilateral carotid body removal were observed. Further investigation is merited into whether surgical or endovascular carotid body denervation may be offered as a therapeutic approach to improve CV outcomes in HF. The effect of carotid body removal on sympathetic activity in HF is unknown.

5.16 Future Directions

Hypertension is the leading and most preventable risk factor for cardiovascular disease. Despite the wide range of available pharmacological approaches, there is a proportion of patients with uncontrolled BP. Innovative device-based and procedural interventions that directly manipulate the mechanisms underlying hypertension have been successful in demonstrating their ability to lower BP in the vast majority of patients. The high variability in BP response to these therapies indicates that the pathophysiology including complex neural reflexes that may trigger a disease in an individual is still not completely understood.

HF and its progression remain a challenging clinical problem. Preliminary findings from HF pilot studies with recently introduced therapeutic interventions appear promising; however their long-term outcomes including the rate of hospital admission for HF deterioration and associated death need to be confirmed in larger clinical trials.

Disclosure Authors declare no conflict of interest.

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Natriuretic Peptides

6

Massimo Volpe and Speranza Rubattu

6.1 Introduction

The natriuretic peptide (NP) family includes three well-characterized hormones, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), which play a key role in the maintenance of cardiorenal and body fluid homeostasis [1].

ANP is largely produced from cardiac atria [1], whereas BNP is predominantly secreted from the heart ventricles [1]. NPs are produced to a lesser extent in other organs, including the brain, kidney, and vessels [2]. Within the heart, they are mostly synthetized in response to increased volume overload and myocyte stress [1]. In addition, a neuroendocrine regulation of cardiac NPs involves angiotensin II, endothelin-1, and phenylephrine that, by signaling through receptors coupled to Gq proteins, increase ANP and BNP in a more gradual manner than stretch [3]. On the other hand, CNP is mainly produced by endothelial cells and is considered a noncirculating hormone [1]. In addition, urodilatin, an amino-terminal 4-amino acid extended form of ANP, is considered a renal ANP [4]. Additional components of the family, dendroaspis natriuretic peptide (DNP) and vasonatrin peptide (VNP), have been identified in the green mamba snake and in the eel [5].

ANP, BNP, and CNP derive from separate genes. ANP and BNP genes are located in the distal arm of chromosome 1 (1p36.2). Their structure is similar and includes three exons and two introns. The signal sequences are located in exon 1,

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whereas the coding sequences are located in exon 2; exon 3 encodes the terminal tyrosine and the 3' untranslated region [1]. The CNP gene is located on chromosome 5 (5p13.3) and includes 13 exons [1].

NPs are synthetized as pre-prohormones and are subsequently cleaved to obtain a biologically active α-carboxy-terminal peptide along with the amino-terminal end (Fig. 6.1). Human ANP is released as a 152-amino acid pre-prohormone. After removal of the signal peptide, the $proANP_{1–126}$ is released and stored into granules within the atrial cardiomyocytes. Before secretion, $proANP_{1-126}$ is processed by corin, a type II transmembrane serine protease, into the circulating forms of $ANP_{(1–98)}$ and of $ANP_{(99–126)}$. Of note, the active corin protease is obtained through the cleavage of procorin by proprotein convertase subtilisin/kexin type 6 (PCSK6) [6]. The major form of biologically active ANP is the 28-amino acid carboxy-terminal peptide, $ANP_{(99–126)}$. More recently, a biological functional relevance has been proven also for $ANP_{(1–98)}$ [7]. In addition, three peptides are cleaved from the $ANP_{(1–98)}$: the long-acting natriuretic peptide, LANP (1–30), the vessel dilator (31–67), and the kaliuretic peptide (79–98) [8]. All of them appear to exert some diuretic and natriuretic effects.

BNP is synthetized as a 134-amino acid pre-prohormone. After processing by furin, a subtilisin/Kex2p-like endoprotease, the biologically active peptide consisting of a 32-amino acid peptide, $BNP_{(77–108)}$, is released.

CNP is synthetized as a 103-amino acid prohormone which is processed by furin. The active CNP form is a 22-amino acid peptide [1].

All mature bioactive peptides contain a 17-amino acid ring structure that is essential for their biological activities [1]. Eleven of the 17 amino acids are identical in ANP, BNP, and CNP. On the other hand, the amino- and carboxy-terminal

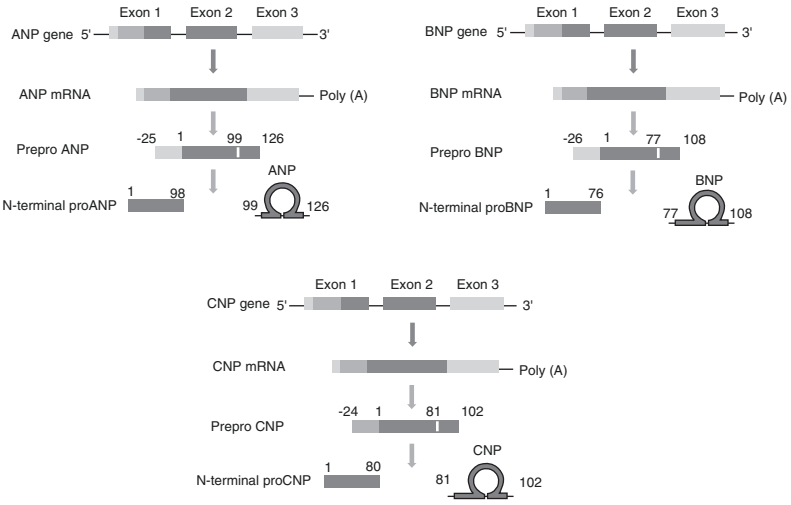

Fig. 6.1 Schematic genes and proteins structure of ANP, BNP, and CNP

sequences vary in length and composition among the three peptides. The primary structure of NPs is conserved across species apart few variations. With regard to the ANP sequence, an isoleucine is present at position 10 in rats, mice, and rabbits, whereas humans, dogs, and bovines have a methionine at this position.

The half-life of ANP ranges from 2 to 2.5 min in humans. BNP has both a short half-life (3–4 min) and a long half-life (20–23 min). Finally, CNP has a half-life of 2–3 min.

ANP, BNP, and CNP bind to specific cell membrane receptors which mediate the biological functions [1]. In particular, soluble guanylyl cyclase (GC) receptors mediate NP effects in target tissues [1]. GC-A receptor (or type A natriuretic peptide receptor, NPR-A) is the main effector of both ANP and BNP actions, whereas GC-B (or NPR-B) mediates CNP actions. GC-A and GC-B receptors contain three domains: an extracellular ligand-binding domain that binds to NPs, a short transmembrane domain, and an intracellular domain that acts as a docking site for other proteins. An increase in cyclic guanylate monophosphate (cGMP) levels reflects the activation of both GC-A and B receptors (Fig. 6.2).

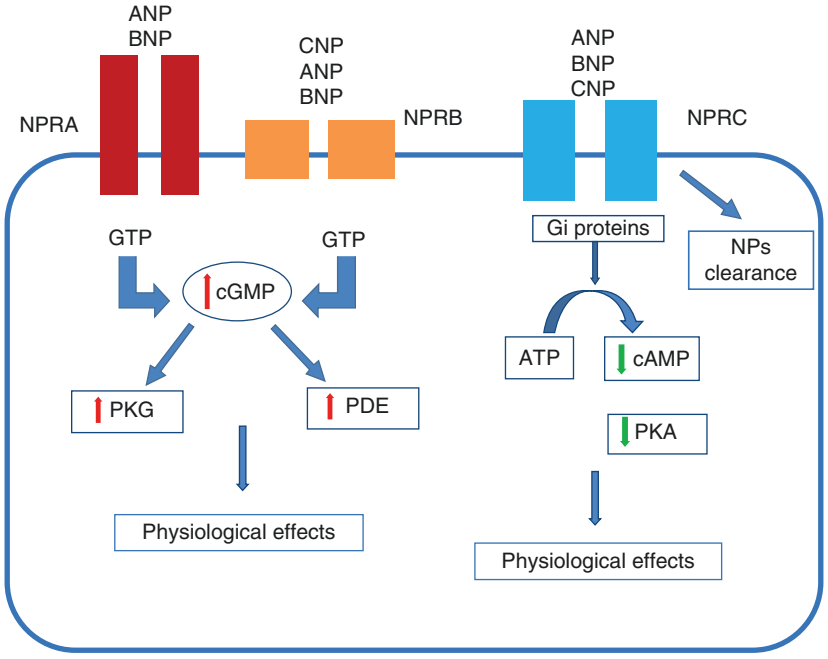

Fig. 6.2 Type A and type B natriuretic peptide receptors mediate the biological effects of the NPs through the activation of guanylyl cyclase and release of cGMP, with consequent increase of protein kinase G (PKG) and of phosphodiesterase (PDE). On the other hand, type C natriuretic peptide receptor is mainly responsible of NP clearance. In addition, NPR-C inhibits, through the Gi proteins, the adenylate cyclase with consequent decrease of protein kinase A and production of biological effects

An additional natriuretic peptide receptor (type C natriuretic peptide receptor, NPR-C) plays a fundamental role in NP clearance [9]. This receptor is mostly expressed in the glomerular and vascular structures of the kidney and also in the adrenals, lungs, brain, heart, and vascular wall. It recognizes an eight-amino acid linear fragment of ANP molecule to perform the peptide clearance. This process requires the ANP-NPR-C internalization and is followed by the ANP hydrolysis by lysosomes. Of interest, different from GC-A and B receptors, NPR-C contains a 37-amino acid cytoplasmic domain with a Gα inhibitory protein-activating sequence, and it is devoid of kinase and GC activities [9]. By activating NPR-C a decrease in cyclic adenylate monophosphate levels follows (Fig. 6.3). It has been shown that NPR-C mediates vasoprotective properties of CNP, and it has been also involved in cellular signaling pathways leading to antiproliferative and pro-apoptotic effects in specific circumstances [10]. In fact, a molecular variant of ANP (T2238C) acts through NPR-C to exert vascular effects opposing those of the regular peptide [11].

In addition to NPR-C, the circulating NPs are cleared by proteolytic cleavage by neutral endopeptidase (NEP) [1] (Fig. 6.3). NEP is a zinc-dependent type II integral membrane metallopeptidase with ubiquitous distribution [12]. Among the NPs, αANP is the main known target of NEP. Additional target peptides of NEP are angiotensins I and II, endothelin 1, bradykinin, and substance P.

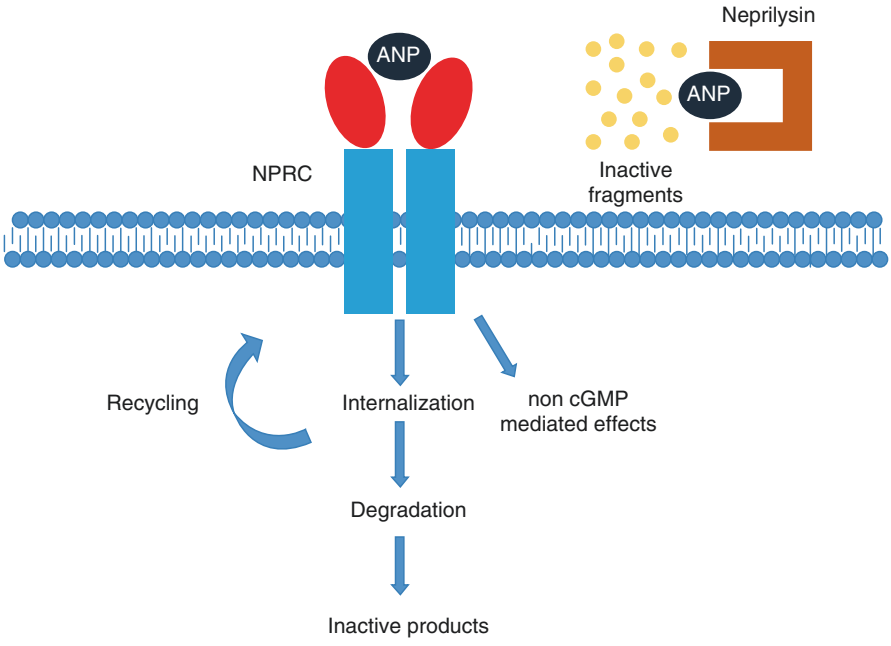

Fig. 6.3 ANP degradation is achieved through the interaction with NPR-C on the cellular membrane and subsequent internalization and through the action of NEP

Through the activation of GC-A receptor, ANP and BNP produce natriuretic and diuretic effects [13]. These effects are achieved mostly through an increase of glomerular filtration rate and filtration fraction by dilating afferent arterioles and constricting efferent arterioles with an increase of glomerular capillary hydrostatic pressure. They reduce sodium reabsorption at the level of collecting ducts, and this effect is achieved also by a decrease of vasopressin secretion from the pituitary gland. Moreover, by limiting renin production and release from the juxtaglomerular cells and aldosterone secretion at the zona glomerulosa level [14], ANP interferes with sodium reabsorption at the proximal tubular level and sodium transport at the distal tubule.

In addition, ANP and BNP contribute to modulate systemic vascular resistance mainly by inhibiting the contraction of vascular smooth muscle cells through cGMP-dependent kinases [1]. At the heart level, ANP inhibits cardiac and pulmonary chemo- and baroreceptor activity causing a suppression of sympathetic outflow to the heart [15]. The inhibition of sympathetic activity associated with an increase of vagal afferent activity and the interference with SNS leads to reduction of heart rate and of cardiac output [16]. Moreover, ANP and BNP reduce salt and water appetite [1].

As a consequence of their multiple functions, the biological signature of NPs is to reduce body fluid and maintain blood pressure and cardiovascular homeostasis. On this basis, NPs become the physiological antagonist of both renin and angiotensin II.

They also modulate endothelial function [17]. Consistently with the latter effect, ANP level showed the best correlation with endothelial function among several tested biomarkers in the Framingham population [18].

Apart from the well-known hemodynamic functions, NPs are known to preserve vascular health in both endothelial and vascular smooth muscle cells by interfering with the key mechanisms of atherosclerosis, i.e., proliferation, angiogenesis, apoptosis, and inflammation [19]. In this regard, a low dose of ANP induced an increase in endothelial cell numbers, DNA synthesis, and cell migration through an increased expression of cGMP-regulated protein kinase (cGK) and, consequently, of protein kinase B (Akt) and extracellular signal-regulated kinase (ERK)1/2 [(p44/42 mitogen-activated protein kinases (MAPK)] pathways [20]. Thus, physiological concentrations of ANP promote endothelial regeneration and could be useful in the regeneration of endothelial cells after injury in atherosclerosis. On the other hand, supraphysiological levels of ANP exert an opposite effect leading to reduced endothelial cell regeneration, DNA synthesis, and cell migration [20]. In addition, NPs exert anti-hypertrophic and anti-fibrotic effects within the heart [21] by activating several signaling pathways including the calcineurin/nuclear factor of activated T cells (NFAT), the sodium-hydrogen exchanger (NHE)-1, and the transforming growth factor (TGF)β1/Smad [22]. Interestingly, a negative inotropic effect of ANP has been described in normal left ventricular myocytes [19].

Finally, a role of NPs in the control of lipid metabolism [19], in the promotion of mitochondria biogenesis in adipocytes, and in the process of "browning" of white adipocytes to increase energy expenditure has been described [23]. The cardiac

cachexia of HF patients has been partially attributed to the increased levels of NPs that are present in HF.

As a proof of their fundamental cardiovascular properties, several dramatic effects can be observed in the absence of either NPs or of their receptors. In fact, lack of ANP leads to salt-sensitive hypertension [24]. Disruption of NPR-A causes hypertension, cardiac hypertrophy, interstitial fibrosis, and sudden death [25]. Moreover, lack of BNP leads to cardiac fibrosis [26]. Finally, lack of CNP causes bone deformation with skeletal overgrowth [27].

NPs are currently viewed as key players in the process of cardiovascular function and remodeling as well as in the natural history of cardiovascular diseases including heart failure (HF) [28].

6.2 Natriuretic Peptides in HF

ANP and BNP levels increase in HF, and their properties could at least partially balance the overactivation of the RAAS and of the SNS, hence contributing to cardiovascular and fluid-electrolyte homeostasis [29, 30]. However, their increase is not sufficient to preserve the cardiovascular hemodynamics, particularly with the progression of the disease. Thus, the physiological responses to NPs are blunted in HF patients. As a consequence, HF is recognized as a disease state characterized by defective NP processing and synthesis and by a resistance to NPs. Consistently with these observations, a decreased expression of corin gene and protein, with consequent reduced conversion of proANP or proBNP into ANP and BNP, was reported in the left atrium of experimental HF [31]. Moreover, serum corin levels decrease over time during progression of HF [32]. Consistently, corin overexpression improves cardiac function and survival in a mouse model of dilated cardiomyopathy [33]. Moreover, low levels of $BNP_{(1–32)}$ were detected in HF patients by the use of mass spectrometry immunoassay technology [34], raising the issue that commonly used BNP assays are unable to distinguish between different peptide fragments and that relatively greater abundance of immature BNP forms, that are less active biologically, are present in HF. These experimental and clinical observations may contribute to explain the paradoxical compromised natriuretic response in HF. The latter condition can also be explained by a reduced responsiveness due to natriuretic peptide receptor downregulation, with reduced guanylyl cyclase activity, in certain tissues including the heart [35], by increased local degradation [36], and by increased degradation of cGMP [37].

Interestingly, ventricles express ANP in the developing embryo and fetus with a rapid decline of gene expression during the prenatal period [38]. Ventricular ANP expression is reinduced in adult life in cardiac disease states [39].

6.2.1 Diagnostic Implications

The diagnostic role of NPs in both acute and chronic HF is well established [28–30]. In fact, both ANP and BNP plasma levels increase in parallel with the degree of left

ventricular dysfunction and hemodynamic stress, although they are not useful to discriminate between reduced and preserved ejection fraction (EF) [28]. Both ANP and BNP reduce preload and afterload of the heart. The increase of BNP is 10- to 100-fold greater than that of ANP, and it appears to perform better than ANP. Furthermore, since the N-terminal prohormones are more stable and their half-lives in the plasma are longer than that of the carboxy-terminal peptides, the NT-proBNP and NT-proANP (particularly, the mid-regional NT-proANP, MR-proANP) are currently considered suitable and informative biomarkers in cardiovascular diseases [28].

The highest levels of NPs are expected in HF with reduced EF (HFrEF) compared to HF with preserved EF (HFpEF). However, when considering the levels of circulating NPs in both HFrEF and HFpEF, other factors, apart from the hemodynamic stress and left ventricular function, should be taken into account. In fact, age, sex, NP gene variants, BMI, renal function, sodium levels, and comorbidities such as atrial fibrillation exert a significant impact on circulating BNP and NT-proBNP levels. In particular, obesity is associated with reduced NP levels, whereas atrial fibrillation and renal failure are associated with increased NP levels [28]. Carrier status for the rs5068 ANP gene variant is associated with higher NP levels [19, 28].

At present, BNP and NT-proBNP are the established diagnostic biomarkers for HF, as well as for ventricular remodeling after myocardial infarction, cardiomyopathies, left ventricular hypertrophy, and pulmonary hypertension [28]. BNP and MR-proANP provide similar and useful diagnostic information in HF, particularly in the context of acutely destabilized HF (ADHF) [28]. This evidence suggests that the combination of either BNP or NT-proBNP and MR-proANP can provide superior diagnostic accuracy than either NP alone, and they greatly contribute to exclude noncardiac causes of acute dyspnea [40]. In fact, the current ESC guidelines recommend measuring levels of BNP, NT-proBNP, or MR-proANP [41].

The important clinical diagnostic implications of NPs in HF indicate that NP level measurement may represent a useful marker to monitor the course of the disease in relation to the benefits of therapeutic strategies [28]. In ADHF, BNP measurement led to better accuracy in diagnosis and reduced rate of hospitalizations and of admissions in intensive care units and had favorable effects on treatment costs and mortality rates. In fact, a useful algorithm for BNP-guided treatment of ADHF has been developed [28]. In patients with chronic HF due to systolic dysfunction, a meta-analysis performed in the attempt to overcome existing controversies and including 12 randomized clinical trials has shown that NP-guided therapy reduced all-cause mortality and HF-related hospitalizations. It was observed that individuals older than 75 years are those who benefit less, as a possible result of increased rate of comorbidities in this age range [28]. However, the recently published GUIDE-IT study has reported that a strategy of NT-proBNP-guided therapy was not more effective than a usual care strategy in improving outcomes in high-risk patients with HFrEF [42]. As a consequence of the uncertainties produced by the different studies, a low level of recommendation for NP-guided therapy in chronic HF has been assigned by AHA-ACC-HF guidelines [43]. Future studies will add important insights on this topic.

6.2.2 Prognostic Implications

The value of NPs as reliable markers for the long-term prognostic stratification both in acute and chronic HF conditions is well established. The prognostic value of NPs has been shown in both HF with reduced and preserved EF [44].

In chronic HF, subsequent measurements of either BNP or NT-proBNP levels provide independent information regarding the risk for disease progression across a wide spectrum of adverse outcomes: ventricular remodeling, malignant ventricular arrhythmias, hospitalization for HF, need for transplantation, and death. Due to its longer half-life and higher circulating concentrations, NT-proBNP may behave as a more accurate marker than BNP in disease prognosis. In fact, in the Valsartan in Heart Failure Trial (Val-HeFT), NT-proBNP, compared to BNP, had a greater predictive value for mortality, morbidity, and hospitalization for HF [45]. In one of the longest available follow-up study of patients with chronic HF, evaluating the prognostic power of multiple biomarkers (not including BNP), plasma ANP levels turned out to be the strongest long-term predictor of death in all disease stages [28].

In a study of patients presenting with acute HF, measurement of BNP, NT-proBNP, and MR-proANP levels showed significant diagnostic performance, although only MR-proANP had long-term prognostic value [46]. In a large collection of patients hospitalized for acutely destabilized HF (ADHF), the prognostic performance of both NT-proBNP and MR-proANP levels was confirmed by the evidence of an incremental prognostic value with respect to clinical risk factors for predicting mortality at 1 year [47].

6.2.3 NPs as Marker of Transition from Cardiac Diseases to HF in the General Population

Based on the knowledge that NPs increase in the attempt to maintain cardiorenal homeostasis, it has been postulated that higher circulating NP levels may anticipate the development of a cardiovascular disease. Over the last decade, several efforts have been performed in the attempt to establish the potential predictive role of NP levels toward the risk of developing cardiovascular diseases including HF in the general population.

A preventive role of NP-based screening toward HF development has been documented in different populations, being confirmed in both sexes, in older men and even among individuals with obesity [28]. Among patients with CV risk factors, at risk of HF, BNP assessment, associated with collaborative care, reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and HF [48].

More recently, the Natriuretic Peptides Studies Collaboration demonstrated the ability of NT-proBNP level to predict future HF development, as well as ischemic heart disease and stroke occurrence, in subjects without baseline cardiovascular disease from a large cohort of the general population, obtained through the analysis of 40 different populations collected worldwide [49].

Therefore, it appears that NP measurement predicts the risk of HF development beyond current routine assessment, and it may be a useful, cost-effective screening test for the identification of individuals at high risk of HF.

6.2.4 NPs for the Treatment of HF

It would be ideal to use oral NP in HF. However, this has not become a feasible approach in the clinical setting. Moreover, the subcutaneous administration of NPs did not reveal a complete absorption, and it was substantially ineffective [50].

Synthetic peptides for intravenous administration have been made available in the recent past to overcome the abovementioned difficulties. Among them, anaritide and carperitide are synthetic forms of ANP. Nesiritide is a synthetic form of BNP. Ularitide and cenderitide are the synthetic forms of urodilatin and of CNP, respectively. These synthetic peptides have shown some positive effects in the treatment of HF, particularly in acute HF (AHF) [51–53]. Carperitide led to a satisfactory recovery from AHF [53] and also to renal protection following infusion of contrast medium. Only carperitide was approved for the treatment of AHF in Japan in 1995, whereas there is not enough evidence to support the clinical use of the other peptides. Among others, CD-NP is a chimeric natriuretic peptide in which the 15-amino acid C-terminal tail of DNP is coupled to the 22-amino acid human C-type natriuretic peptide. CD-NP is able to bind to all three natriuretic peptide receptors (NPR-A, NPR-B, and NPR-C). Animal and human studies demonstrated that CD-NP improves cardiovascular and renal function without inducing significant levels of hypotension [54]. Although preliminary data suggested improved renal function in human HF patients, no indication has ever been obtained for the use of CD-NP in the treatment of HF.

Notably, the ANP gene delivery was also tested as an alternative way of administration. However, its use in experimental models of hypertension did not lead to conclusive results [50].

Interestingly, either stimulation of corin expression or of its activity should favor the proANP processing to ANP. In fact, by increasing corin expression, a significant improvement of cardiac function was observed in a mouse model of dilated cardiomyopathy [33].

Degradation of ANP takes place by NPR-C and by NEP. Since NPR-C plays pleiotropic functions other than NP clearance, its inhibition in order to increase ANP levels does not appear feasible.

The inhibition of NEP, aimed at increasing ANP levels, was first attempted several years ago through the introduction of the first inhibitor, omapatrilat. Its use in HFrEF led to a greater improvement compared to enalapril [55]. However, omapatrilat was stopped because of the higher occurrence of angioedema due to the coincident action on the substrates of angiotensin-converting enzyme (ACE) and NEP (bradykinin and substance P). More recently, the combined inhibition of NEP and AT1R (ARNi) was realized with the target to prevent a rise of Ang II and its effects during NEP inhibition that may offset the advantages of the increased action of NPs.

This was accomplished in a compound (LCZ696) formed by the NEP inhibitor sacubitril and the AT1 receptor blocker valsartan. In the first proof-of-concept trial, the PARADIGM-HF, the ARNi LCZ696, today commercialized as Entresto, reduced the risk of death and of rehospitalization in HFrEF compared to enalapril, and it did not promote angioedema [56]. The use of Entresto, the first drug of this new class, has been indicated in patients affected by HFrEF, and it promises to be a valid tool in the treatment of HF [57].

The relevance of NEP inhibition in order to reinforce the natriuretic peptide actions led to the design of M-ANP, a synthetic peptide which consists of the 28 amino acids of native ANP and of a 12-amino acid terminus extension, which is highly resistant to NEP degradation [58]. M-ANP lowers blood pressure, induces natriuresis and glomerular filtration rate (GFR), and inhibits aldosterone [50]. In a model of hypertensive HF, M-ANP exhibited significant renal enhancing and left ventricular unloading properties that were greater than those of a conventional vasodilator (nitroglycerin) [50] and make M-ANP an attractive candidate for the treatment of HF.

As a key interesting issue, the knowledge that miR425 binds to a region of the 3′ untranslated region (UTR) of the ANP gene to stimulate its expression [59] underscores the potential usefulness of a miR425-based therapeutics to modulate ANP expression in HF. Additional miRNAs, able to interfere with ANP expression, may also provide future potential targets for the treatment of HF [60].

6.3 Conclusions

Thirty-six years after the discovery of the first component of the family, we keep reinforcing our knowledge on NPs as a class of cardiovascular hormones with fundamental regulatory functions on hemodynamics, as well as on atrial, ventricular, and vascular remodeling processes. Following the initial pioneering physiological studies, the subsequent application of several molecular biology and genetic approaches has allowed a full characterization of the multiple roles of NPs in physiology and pathology within the cardiovascular system. In the context of HF, NPs emerge as useful biomarkers with important diagnostic and prognostic implications. More importantly, based on the notion that HF is a disease state characterized by a deficient natriuretic peptide response, NPs merit full consideration as a rational therapeutic target for the treatment of this disease. From the latter point of view, several attempts have been made to define efficacious therapeutic strategies that, either by increasing NP levels through reduced degradation or by mimicking the physiological peptides actions through synthetic molecules, can restore the cardiovascular hemodynamics in both acute and chronic HF conditions. Many other approaches deserve to be tested in the near future to establish novel NP-based therapeutic drugs that can help to fight a dreadful common disease such as HF.

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Renal Mechanisms and Heart Failure

7

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Chronic kidney disease (CKD) is a well-established cardiovascular (CV) risk factor, and as Dr. Dargie said, "The kidneys have always been at the heart of heart failure treatment." Few years ago, the interrelationship between the heart and kidney was described as cardiorenal syndrome(s) by Ronco et al. [1]. However, recently this classification was criticized as being oversimplistic and biologically not completely plausible [2]. The pathophysiological relationships between heart failure (HF) and renal dysfunction are not fully understood, but it is obvious that dysfunction of one organ could cause deterioration of other organ function.

Renal dysfunction is one of the most important independent risk factors for poor outcomes and all-cause mortality in patients with HF. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. In meta-analyses of studies on HF which included almost 19.000 subjects, 25% of patients exhibited an increase of serum creatinine more than 18 μmol/L or decrease of estimated GFR (eGFR) more than 5 mL/min/1.73 m^2. This worsening renal function (WRF) was associated with a higher risk for mortality and hospitalization. Both elevated serum creatinine on admission and WRF during hospitalization predicted prolonged hospitalization, rehospitalization, and death [3]. In the Acute Decompensated Heart Failure National Registry (ADHERE) of >105.000 individuals admitted for acute decompensated HF (ADHF), 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >176.2 μmol/L, and 9% had creatinine

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concentrations >264.3 μmol/L [4]. McAlister et al. found that only 17% of patients with HF had creatinine clearances >90 mL/min [5]. In their cohort, 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance <30 mL/min. Renal function is a strong determinant of HF patients' survival. In a cohort of more than 80.000 patients with CHF, annual mortality was 25% in patients with normal renal function, 38% in those with eGFR 53–89 mL/min, and 51% in those with GFR <53 mL/min.

Cardiac and renal diseases commonly present in the same patient have been associated with increased cost of care, complications, and mortality. The mechanisms by which the onset of acute HF or acutely decompensated chronic HF leads to WRF are multiple and complex, being different in acute versus chronic HF. In opposite way, multiple mechanisms are involved in the deterioration of heart function in patients with impaired renal function. Cardiac abnormalities like left ventricular hypertrophy and "uremic cardiomyopathy" were described complicating CKD. HF significantly increases mortality in patients with CKD, and Herzog et al. reported HR for annual mortality of 1.64, 2.25, and 3.30 in patients with only CKD, with only CHF, and in those having both CKF and CHF, respectively [6]. However, there is lack of data on "acute renocardiac failure."

In cardiorenal association, besides many pathophysiological mechanisms (underlying diseases, hemodynamic alterations, inflammation, oxidative stress, ineffective or maladaptive counter-regulatory systems), there are also several iatrogenic causes of WRF in patients with HF, diuretics being one of the most intriguing. In addition WRF and CKD are the most important causes of "therapeutic nihilism" in HF patients.

7.1 Renal Dysfunction as a Consequence of HF

Traditional theories explained the progressive decline in GFR observed in HF with inadequate renal perfusion secondary to reduced cardiac output. However, recent investigations pointed on that this so-called low-flow theory is neither solely nor most important cause of renal dysfunction in HF and focused more on elevation in central venous pressure and consecutive attenuation of the gradient across the glomerular capillary network. The theory on venous congestion as an important mechanism of renal impairment is mostly supported by data obtained in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, in which only baseline right atrial pressure correlated with baseline serum creatinine [7].

7.1.1 Acute Decompensated HF

The presence of WRF in ADHF patients is associated with a poor prognosis. Even small increases in serum creatinine (26.4 μmol/L from baseline) were reported to

be independently associated with both short-term and long-term clinically important outcomes. Further, even when the small changes in serum creatinine are transient and renal function improves, patient's clinical prognosis remains worse than those whose renal function remains intact throughout their hospital stay. As with the heart, venous congestion has been associated with WRF in patients with ADHF [8]. However, debate is going on as the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial found no relationship with baseline or changes in hemodynamic on renal outcomes [7].

Box 7.1: Prognostic Importance of WRF in ADHF

- Approximately one third of the patients developed WRF.
- The presence of WRF did not appear to have an impact on overall mortality but extended hospital stay [9].
- Patients with ADHF who experienced WRF in the hospital had a significantly higher rate of the primary outcome—urgent hospitalization for HF or CV mortality.
- WRF was found to be an independent risk factor for rehospitalization for ADHF or all-cause mortality.
- It was observed that WRF alone is not an independent determinant of outcomes in patients with acute HF; it has an additive prognostic value only when it occurs in patients with persistent signs of congestion.

Box 7.2: Clinical Characteristics of Subjects with ADHF and WRF

- Baseline renal function, diabetes, prior HF, and initial presentation with hypertension are established risk predictors for WRF in ADHF.
- In Prospective Outcomes Study in Heart Failure (POSH) study, only ADHF patients with WRF who concurrently developed hemodynamic compromise, infection, or MACE were observed to have a higher 6-month mortality [9].
- Individuals with WRF were more likely to have pre-existing renal dysfunction, rales above the lung bases on auscultation, presence of increased jugular venous pressure, lower mean ejection fraction, greater likelihood of left ventricular dilation, higher mean pulmonary artery pressure, and a greater likelihood of a having a restrictive pattern of filling.
- Ventricular ejection fraction did not differ between those who did and did not develop WRF.
- Only mean central venous pressure was predictive of WRF. Interestingly, cardiac output was actually higher in patients developing WRF [8].

7.1.1.1 Hemodynamic Mechanism

Arterial underfilling contributes to WRF during HF. When low aortic pressure results in a renal perfusion pressure ≤80 mmHg, kidney autoregulation is no longer possible [10]. Hemodynamic responses depend on endothelial function. Reduced kidney perfusion pressure upregulates the sympathetic nervous and renin-angiotensin aldosterone (RAS) systems. Both angiotensin II and catecholamines further induce glomerular arteriolar vasoconstriction, decreasing renal plasma flow (RPF). Angiotensin II has a more exaggerated vasoconstrictive effect on the efferent arteriole, preserving GFR despite reduced RPF, and initially, the filtration fraction and GFR are preserved. However, eventually increased angiotensin II and/or catecholamine levels become maladaptive causing more preglomerular vasoconstriction and decreasing GFR. This was followed with enhanced proximal tubular sodium and water reabsorption contributing to systemic and renal congestion. Elevated central venous pressure in HF promotes renal congestion (also known as backward failure). These changes occur independently of reduction in cardiac output and/or mean arterial pressure. In healthy subjects with normal heart function, a transient hypervolemic state leads to increased renal fluid and salt excretion decreasing blood volume and cardiac output and returning the pressure back to normal. On contrary, in patients with HF in hypervolemic state, the elevated right atrial and central venous pressure affects salt excretion by the kidney. In that way vicious cycle of sodium retention, volume expansion, and HF is initiated, leading to more renal congestion which leads to increased renal interstitial pressure that affects the entire capillary bed and the tubules, possibly also inducing local hypoxia. Tubular compression raises the luminal pressure, further attenuating the transglomerular pressure gradient and lowering the GFR. Such increase in renal interstitial pressure due to venous congestion is physiologically different from that caused by elevations in arterial pressure, which is on contrary associated with natriuresis. Intra-abdominal venous hypertension is inversely related to renal blood flow and could cause systemic hypotension and low cardiac output [11].

A potential causative link is suggested by the observation on the effect of fluid removal on increased intra-abdominal pressure and renal function in patients with ADHF [9]. After fluid removal, the mean intra-abdominal pressure fell from 13 to 7 mmHg which was associated with a significant fall in serum creatinine [12]. These findings do suggest that intra-abdominal pressure is the determinant of changes in renal function in the patients with ADHF and increased intra-abdominal pressure.

7.1.1.2 Non-Hemodynamic Mechanisms

Neurohormonal Activation

The RAAS has an important role in the initiation and maintenance of WRF in HF. Increased renin secretion occurs early in HF, with consecutive increase of angiotensin II. The extreme sodium resorption, functional and morphological changes in the kidney, and ventricular remodeling induced by RAAS in HF are a maladaptive response to further alter hemodynamic changes, sympathetic activity contributing to WRF. Catecholamines play a crucial role in the pathogenesis and progression of HF. It is well known that elevated plasma norepinephrine levels in patients with HF correlate with increased mortality. In addition, renal effects occur

secondary to sympathetic activation. Concentration of arginine vasopressin is increased in HF and could lead to water retention and hyponatremia [13]. At present, vasopressin appears important as a cause of water retention but does not appear to be an integral part of processes associated with WRF.

Adenosine concentrations are increased in patients with HF [14]. Adenosine-A1 receptors are found in afferent arterioles, juxtaglomerular cells, the proximal tubule, and thin limbs of Henle, and GFR and urine output could improve by countering the effects of adenosine. However, the role of adenosine in WRF in patients withHF is not yet established.

Box 7.3: Some Facts about Neurohormonal Activities in Patients with ADHF and WRF

Angiotensin II

- Increased thirst.
- Heightened activity of ganglionic nerves via its effects on the autonomic nervous system.
- Systemic vasoconstrictor to compensate for the initial decrease in stroke volume.
- Increased contractility.
- Stimulator of the sympathetic nervous system (systemic vascular resistance, venous tone, and congestion).
- Direct trophic effects on cardiomyocytes and renal tubular cells (hypertrophy, apoptosis, and fibrosis).
- Accounts for approximately 50% of the stimulation of aldosterone.
- Upregulates the cytokines, transforming growth factor beta, tumor necrosis factor alfa, nuclear factor-kappa-B, and interleukin-6.
- Stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma.
- Activates NADPH oxidase and myeloperoxidase (MPO) within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells (superoxide, a reactive oxygen species).

Aldosterone

- Renal sodium reabsorption.
- "Escape" from renal salt-retaining effects does not occur in HF patients continued sodium retention contributes to the pulmonary congestion and edema, particularly in those with angiotensin-converting enzyme DD genotype [15].
- Stimulates macrophages in the heart and kidney to secrete galectin-3 (stimulates fibroblasts to secrete procollagens I and III that are cross-linked to collagen, resulting in fibrosis) [16].
- Patients with biventricular failure have poor hepatic perfusion and decreased clearance of aldosterone (additional elevation of the plasma aldosterone concentration) [17].

Sympathetic activation

- Enhanced reabsorption of sodium in proximal tubular cells.
- Decreased clearance of catecholamines in renal failure.

Oxidative Stress

A vast majority of literature supports oxidative injury as a common link between progressive cardiac and renal dysfunction. Oxidative stress is a hallmark in ADHF, as evidenced by a significant increase in circulating reactive oxygen species (ROS) and reactive nitrogen species (RNS). Powerful oxidants increase and upregulate proinflammatory mediators and cytokines. Myeloperoxidase (MPO) acts as primary enzyme in ROS generation by promoting hydrogen peroxide (H_2O_2) conversion into nitrogen dioxide (NO_2) [18]. MPO is considered a marker of altered myocyte metabolism, oxidative stress, and inflammation and contributes to myocyte apoptosis and necrosis, and it is associated with arrhythmias and endothelial dysfunction.

Inflammation may also promote and be a consequence of renal congestion [19]. High levels of proinflammatory cytokines and proapoptotic factors were found in ADHF patients with WRF [20]. Inflammation causes endothelial activation enhancing arterial stiffness, reducing myocardial contractility, and increasing myocardial cell death, as well as contributing to WRF and fibrosis [19]. Increased intra-abdominal pressure and abdominal congestion (i.e., splanchnic) affect abdominal lymph flow contributing to elevated cardiac filling pressures [21], which initiates/adds to the cascade of events causing WRF and renal congestion. In addition, recent evidence suggests that alteration of gut flora during HF may play an important role in WRF and renal congestion. Gut under-perfusion and endotoxin release in patients with ADHF have also been proposed as pathophysiological mechanisms accelerating progression of HF and WRF [22]. Impaired intestinal barrier function secondary to congestion allows the entrance of bowel toxins into the circulatory system contributing to further depression of cardiac and renal function. These toxins are mainly produced by microorganisms in the gut lumen and are altered in advanced congestive HF [23].

Failure of Counter-Regulatory Mechanisms

The regulatory and counter-regulatory systems in ADHF are in focus of scientists for last decades. In response to wall tension and ischemia, the cardiomyocytes produce large quantities of natriuretic peptides that work to reduce wall tension, vasodilate, and promote natriuresis and diuresis. Reduced sodium reabsorption is achieved via natriuretic peptide receptors which are located in the glomerulus and the renal tubules. In supraphysiological doses, B-type natriuretic peptide reduces levels of catecholamines, angiotensin II, and aldosterone [24]. However, this counter-regulatory mechanism seems to be overwhelmed in patients with ADHF and WRF, and clinical course worsens (oliguria, edema) despite markedly elevated levels of natriuretic peptides.

Thus, despite high levels of serum BNP in HF, its physiological effects (vasodilatory, diuretic, and natriuretic) do not prevent the disease progression. Recent findings suggest a resistance to BNP and higher concentrations of biologically inactive precursor of BNP [25]. Consequences of inappropriate high levels of angiotensin II, aldosterone, and catecholamines are already discussed.

Anemia

Anemia is common in HF and is associated with increased mortality, morbidity, and worsening renal function. Because of its frequency and importance, a new term was coined: cardiorenal anemia syndrome. It is usually anemia of chronic disease type. The pathogenesis of anemia in HF is multifactorial, encompassing hemodilution due to water retention, blockade of normal iron transport, inflammation/cytokine-induced erythropoietin deficiency, and tissue resistance, malnutrition, cachexia, and vitamin deficiency, which all amplified in the presence of pre-existing CKD and WRF [26]. It must be mentioned that RAS blockade could contribute to anemia. Anemia enhances renal oxidative stress. Although anemia should induce increased erythropoietin, there is evidence that observed decreased concentrations in patients with ADHF may directly exacerbate the renal abnormalities. Iron deficiency should be also taken into account and treated in anemic patients with HF.

Box 7.4: Some Facts about Anemia in ADHF and Renal Dysfunction

- The high frequency of anemia in HF has repeatedly been demonstrated [27, 28].
- In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), patients with HF having anemia had increased mortality, length of hospital stay, and hospital readmission rates [29].
- Anemia in advanced kidney diseases is due to an absolute deficiency in erythropoietin production.
- HF alone is marked by insensitivity to elevated erythropoietin concentrations secondary to sustained inflammation [28].
- Relative or absolute erythropoietin deficiency in CHF contributes to a more pronounced anemia in these patients than might be expected for renal failure alone.
- ACE inhibitors and angiotensin receptor blockers (ARB) may reduce erythropoietin in patients with HF [30].
- Erythropoietin receptor activation in the heart may protect it from apoptosis, fibrosis, and inflammation [31].
- Erythropoietin-stimulating agents in patients with chronic HF, CKD, and anemia lead to improved cardiac function, reduction in LV size, and lower B-type natriuretic peptide (BNP) [32].
- However, long-term exposure of higher-dose erythropoiesis-stimulating agents has been associated with higher rates of cardiovascular events, including HF in CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) and stroke in the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) trials [33].

- Reduced responsiveness to erythropoietin in patients with HF and WRF/CKD has been associated with high levels of hepcidin-25, a key regulator controlling iron intestinal absorption and distribution throughout the body [34].
- Hepcidin-25 may be useful in predicting erythropoietin responsiveness in stable chronic HF patients.
- Iron deficiency is presented in 17–36% anemic patients with HF [35].
- According to Ferric Iron Sucrose in Heart Failure and Ferinject assessment in patients with iron deficiency and chronic heart failure studies, diagnosis of iron deficiency should be made by combination of absolute and relative deficiency:
- Definition of absolute iron deficiency in HF: ferritin <100 μg/L
- Definition of functional iron deficiency in HF: transferrin saturation <20% if serum ferritin is 100–300 μg/L [36, 37].

7.1.2 Chronic HF

The prevalence of renal dysfunction in CHF has been reported to be approximately 25% [38]. Even slight decreases in eGFR significantly increase mortality risk and are considered a marker of severity of vascular disease [38]. WRF in CHF is less clear and may be due to chronic hypoperfusion, venous congestion, or intra-abdominal hypertension or, simply, a concomitant manifestation of the underlying disease processes that have led to the cardiac dysfunction. CHF is likely to be characterized by a long-term situation of renal venous congestion and reduced intrarenal perfusion and filtration gradients. The pathophysiology of renal congestion in HF is complex and involves multiple simultaneous pathways. Aging, hypertension, and diabetes are cofactors both in CHF and WRF accelerating atherosclerosis, myocardiopathy, and CKD. In addition, microvascular and macrovascular renal disorders (so-called chronic ischemic nephropathy) may be present and contribute to harm renal function. Responses to acute and chronic damage can involve the recruitment of immune cells, activation of resident fibroblasts and myofibroblasts, and deposition of procollagen into the extracellular matrix, eventually leading to collagen-generating cardiac and renal fibrosis [39]. Iatrogenic factors may account for renal damage as much as the congestive nephropathy itself [40].

There is very limited understanding of the pathophysiology of renal dysfunction in advanced HF. The ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness) trial [7] found that the only link was with right atrial pressure, suggesting that renal congestion is most important characteristic indicating that hypoperfusion alone cannot explain renal dysfunction in those patents.

Box 7.5: Kidney Function in Chronic HF

- WRF in chronic HF is caused by renal venous congestion and by decreased renal perfusion (decreased cardiac output) and/or hypotension (decreased preload).
- In addition activation of the neurohormonal cascade causes sustained renal reactive vasoconstriction ("vasomotor nephropathy").
- High venous pressure is described as a key factor in WRF in HF patients, especially in those with preserved ejection fraction.
- Patients with decompensated HF and venous congestion often have significant RAAS activation without decreased circulating volume as stimulus [41].
- Kidneys of HF patients seem to release large amounts of circulating renin with consequent abnormal angiotensin II production, resulting in efferent arteriolar constriction and increase in oncotic pressure of peritubular capillaries [42].
- Use of iodinated radiocontrast agents or nonsteroidal anti-inflammatory drugs may predispose to renal dysfunction and renal congestion.
- Drugs used in the management of CHF may worsen renal function (diuresis-associated hypovolemia, enhanced RAAS activation).
- "Resistance to diuretics" also may play a role when excessive increases in diuretic dosing induce various harmful phenomena (exaggerated stimulation of the tubuloglomerular feedback mechanism and activation of RAAS, with consequent reactive vasoconstriction of the renal afferent arterioles and fall of GFR).

Box 7.6: Clinical Data on Congestion and WRF in CHF

- In the SOLVD (Studies of Left Ventricular Dysfunction), eGFR was statistically significant independent predictor of mortality [43].
- The risk of mortality increased significantly when eGFR is <60 mL/min, and the rate of CKD progression is also an important predictor of overall mortality [44].
- Interestingly, in patients whose eGFR fell, the highest risk for rapid progression was observed in subjects with an eGFR >90 mL/min at baseline [44].
- It appears that preserved renal function does not protect an individual with systolic dysfunction from developing WRF [44].
- In the Atherosclerosis Risk in Communities (ARIC) cohort and the Cardiovascular Health Study (CHS) cohort, patients with the highest CV morbidity risk were the individuals with a sustained eGFR <60 mL/min [45].

- Elevated central venous pressure predicted mortality and was associated with low eGFR independent of cardiac index.
- Significant association of small decrements in renal function with CV morbidity was observed even when renal function may transiently improve [45].
- Decongestion was associated with a greater risk of in-hospital WRF; every 5% increase in hematocrit was associated with a 19% decreased risk of all-cause death (HR 0.81 95% CI 0.70–0.95), after adjustment for baseline clinical risk factors [46].
- Hemoconcentration was associated with a lower risk of mortality, despite an increased risk for WRF [46].

7.2 Renal Dysfunction as a Risk Factor for Heart Failure

7.2.1 Acute Deterioration of Renal Function

Pathophysiological interactions between the kidney and heart during WRF episode have been referred to "cardiorenal connectors" which include immune modulation (pro- and anti-inflammatory cytokines and chemokines release) and sympathetic nervous systems and RAAS hyperactivity and activation of the coagulation cascade [47]. WRF may negatively impact heart function as electrophysiological, ischemic, myocardial, and/or pericardial. The theoretical pathophysiological mechanisms responsible of myocardial ischemia during WRF may include (1) acidemia, (2) neurohormonal activation (SNS and RAAS), and (3) acute accumulation of uremic toxins and cytokines [48].The strongest evidence of a cardiorenal link between WRF and the development of cardiac fibrosis is the β-galactoside-binding lectin galectin-3 [49]. Galectin-3 mRNA expression in renal tubules was shown to be upregulated early after ischemic and toxin-induced WRF and persisted for 7 days following injury [49].

7.2.2 Chronic Kidney Disease

Cardiovascular risk factors such as hypertension, anemia, hyperphosphatemia, volume overload, and uremic toxins are frequently present when eGFR is <60 mL/min/1.73 m^2, while in many patients, all those modifiable factors are presented from early CKD stages affecting renal circulation and contributing to WRF. CKD accelerates ischemic heart disease and contributes to pressure and volume overload causing left ventricular hypertrophy. Hyperphosphatemia and secondary hyperparathyroidism are risk factors for ossification of cardiac vessels and valves ("osteoblastic" transformation of vascular smooth muscle cells). It promotes both

Box 7.7: Direct Effects of Acute WRF on Heart

- Tumor necrosis factor-alpha (TNFa), interleukin-1 (IL-1), and interleukin-6 (IL-6) have direct cardio-depressant effects (reduction in left ventricular ejection fraction and elevation of left ventricular end-diastolic and end-systolic volumes and areas) [50].
- Hyperactivity of the SNS with abnormal secretion of norepinephrine impairs myocardial activity by increasing myocardial oxygen demand, myocardial cell b1-adrenergic mediated apoptosis, stimulation of a1 receptors, and activation of RAAS.
- Uncontrolled RAAS activation leads to systemic vasoconstriction and elevation of vascular resistance and promotes cellular hypertrophy and apoptosis inducing diminished coronary response to adenosine, bradykinin, and L-arginine [51].

Box 7.8: Indirect Effects of WRF on Heart

Oliguria—Sodium and water retention: consequent fluid overload and development of volume overload, hypertension, pulmonary edema, and myocardial injury.

Hyperkalemia—Raised risk of fatal arrhythmias and sudden death.

Acidemia—Worsen pulmonary vasoconstriction, increased right ventricular afterload, and contribute to a negative cardiac inotropic effect through changes to β-receptor expression and altered intracellular calcium handling [52].

Uremic toxins*—Affect myocardial cell contractility through myocardial depressant factors and promoting pericardial effusions and pericarditis [53].

*(i.e., indoxyl sulfate, *p*-cresol conjugates, β2-microgliobulin, FGF-23).

Box 7.9: Detrimental Clinical Effects of WRF on the Heart

- Increase in preload (intravascular fluid accumulation).
- Increase in afterload (increased mean systemic blood pressure).
- Increase in diastolic dysfunction (loss of calcium homeostasis).
- Increase in systolic dysfunction (inflammatory mediators and uremic toxins).
- Coronary autoregulation is preserved but with shift to a higher coronary perfusion pressure.
- Coronary vascular reserve and coronary vascular conductance are diminished.
- Coronary vessel reactivity to vasodilators is substantially reduced.

atherosclerosis and arterial stiffness [54]. Increase of FGF-23 promotes LVH and cardiac remodeling; a 5% left ventricular mass index rise was observed for every log increase in plasma FGF-23 levels [55]. Chronic subclinical inflammation, insulin resistance, hyperhomocysteinemia, and malnutrition-inflammation-associated dyslipidemia can also contribute to accelerated CV disease in CKD. In advanced CKD stages, cardiac fibrosis mediated by synthesis of TGF-ß, tissue inhibitor of metalloproteinase-1 (TIMP-1), and alpha-1 collagen predominated in endocardial and epicardial areas [51]. Recent evidence shows upregulation of galectin-3 (already discussed).

Box 7.10: Definition of "Worsening Renal Function" (WRF)
- The most frequently used definition:
- An increase in serum creatinine >26.4 μmol/L compared to baseline values.
- Some authors have suggested the alternative definition of a reduction in eGFR of >20% from baseline [56] (the two definitions are not interchangeable).
- The use of cystatin C does not appear to offer substantial advantages compared to the creatinine derived.

Box 7.11: Caveats with Definition of WRF in HF
- Measuring true, real-time GFR remains difficult in the setting of ADHF.
- Formulas for estimation of GFR have been validated when serum creatinine is in a steady state making all equations imprecise, particularly in ADHF.
- Serum creatinine reflects only GFR and not tubular injury directly, whereas tubular injury may help to better predict and characterize WRF.
- Serum concentration of creatinine begins to rise many hours after WRF started.

Box 7.12: How to Assess Renal Congestion
- There is no direct method to assess renal congestion.
- Natriuretic peptides are not specific for renal congestion.
- Echo/Doppler should be explored as a means to assess renal vein congestion.

7.2.3 Potential New Biomarkers

Several cardiac biomarkers indicating myocardial injury and HF (like troponin, creatinine kinase, natriuretic peptides) are established and included in regular clinical work. On contrary, nephrology is lacking of approved biomarkers of WRF, and clinicians should rely on eGFR which is imprecise and could be even misleading. Several renal biomarkers recently were found to might be of diagnostic and prognostic value for CV outcomes in CKD (Table 7.1) [57]. However, evidence from prospective studies is needed before any of these markers become regular diagnostic or prognostic tool.

Table 7.1 Potential new biomarkers of WRF in HF

Biomarker	Biology	Clinical data
NGAL or siderocalin	– Produced and secreted by neutrophils – Scavenger of cellular and pericellular labile iron, reducing its availability for bacterial growth	– Limits oxidative damage in acute and chronic disease – Increased in the plasma and urine of patients with sepsis and WRF [58]
Cystatin C	– A cysteine protease inhibitor synthesized and released into the blood by all nucleated cells – Better marker of GFR than creatinine – Not affected by age and gender	– Urinary excretion predicts the need for dialysis in acute WRF earlier than creatinine – Outperformed eGFR in the CV prediction in CVD patients [59]
KIM-1	– A transmembrane protein which is normally not detectable in urine	– Measurable after ischemic and nephrotoxic damages of proximal tubule – May be elevated before histological evidence of proximal tubule damage [60]
NAG	– A lysosomal brush border enzyme	– It was found elevated in acute WRF but also in HF, hypertension, and diabetes [61]
Interleukin-18	– A proinflammatory cytokine	– Detected in urine after acute ischemic proximal tubule damage – It was suggested to have a role in myocardial cell damage [61, 62]
L-FABP	– Binds selectively to intracellular unsaturated fatty acids and lipid peroxidation products	– It was found in urine of patients with acute WRF [63, 64]

NGAL neutrophil gelatinase-associated lipocalin; *KIM* kidney injury molecule; *NAG N*-acetyl-B-(D)-glucosaminidase; *L-FABP* liver fatty acid-binding protein

7.3 Some Issues on Pharmacotherapy Used in the Management of HF and WRF

7.3.1 *Primum nil nocere*: Diuretics—A Double-Edged Sword in Treating HF and WRF

Pharmacotherapy used in the management of HF may worsen renal function. The cornerstone of treatment for ADHF is the use of oral and intravenous loop diuretics. These agents represent a double-edged sword as they may resolve congestion but worsen renal perfusion by arterial underfilling and heightened activation of the sympathetic and RAAS leading to WRF. Higher doses of loop diuretics are also associated with elevated serum creatinine and reduced survival in the HF population, but this might just reflect the need to use higher doses in more sick patients [65]. Furosemide can increase fibrosis by its known stimulation of the renin-angiotensin-aldosterone axis. In addition to activating the RAAS, furosemide can also inhibit renal tubular 11-hydroxysteroid dehydrogenase-2, which would allow cortisone to activate the renal mineralocorticoid receptor [66]. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a fivefold increased rate of WRF [46]. However, it should be noted that despite these observations, aggressive diuresis was associated with a 69% reduction in death at 180 days. The relative balance of arterial and venous pressure, volume, and flow resulting in congestion of the kidney appears to be important in the drop in renal filtration that occurs during acute treatment of ADHF [67].

Box 7.13: Diuretic Administration in Patients with HF and WRF

- Earlier diuretic use decreases mortality in severe ADHF, but there is an overall relationship between increased loop diuretic dosing and mortality.
- Compared with normal individuals, patients with CHF need higher doses of loop diuretics to achieve similar sodium excretion, i.e., the dose-response curve shifts downward and to the right.
- Higher doses and continuous infusions of furosemide resulted in more patients developing WRF with no improvement in hospitalization or death [68].
- The use of high doses of IV loop diuretics should be discouraged in patients with HF in whom signs and symptoms are adequately controlled, and if IV loop diuretics are necessary due to the exacerbation of dyspnea or widespread edema, they should be used at the minimum efficacious dose [69].

- The risk of IV loop diuretic-related WRF may be further aggravated when an ACE inhibitor or ARB at full dose is maintained in the therapeutic schedule.
- In patients with CHF, weak response to loop diuretics is further attenuated in the case of very prolonged oral diuretic therapy (so-called braking phenomenon: diminished diuretic effectiveness secondary to postdiuretic sodium retention).
- Diuretic resistance must be suspected when a decline in natriuresis occurred, i.e., when the urine output is relatively poor (<1000 mL per day) in spite of the maximal tolerated oral dose of a loop diuretic (i.e., 250 mg of furosemide per day).
- Clinicians need better guidance on the use of loop diuretics in ADHF including the use of bioimpedance to estimate body water levels as well as novel biomarkers of tubular damage such as NGAL [70].
- Measurement of cardiac output and venous pressure may help ensure adequate and targeted diuretic therapy and allow safer navigation through the precarious situation of combined HF and WRF [71].
- The optimal dose and frequency of dosing of loop diuretics are important clinical issues: a single dose of furosemide elicits transient natriuresis, and loop diuretics may be given two or more times per day [72].
- Continuous dosing was not more effective than an optimally prescribed repeated bolus regimen, as proven in the Diuretic Optimization Strategies Evaluation (DOSE) trial (68); however, discussion is still opened.

Box 7.14: Management of Diuretic Refractoriness to Oral Diuretics

- The addition of non-loop diuretics (i.e., thiazide- or potassium-sparing diuretic) may overcome the escape phenomenon due to activation of the RAS and sympathetic system and sodium reabsorption by more distal sodium transporters [68].
- Adopt the IV method of administration for loop diuretics (to be given at the same doses or at higher doses compared to those given orally).
- Use repeated bolus regimen/continuous diuretic infusions to avoid the phenomenon of postdiuretic salt retention [73].
- Aldosterone receptor antagonists should be taken into consideration as an adjunctive treatment to resolve congestion and reduce the diuretic dose.
- If diuretic-resistant fluid overload exists despite an optimized cardiac output, removal of isotonic fluid can be achieved by the use of extracorporeal ultrafiltration [74].

7.3.2 *Periculum in mora*: Therapeutic Nihilism in Treating HF Patients Due to Fear of WRF

The proportion of individuals with CKD receiving appropriate cardiovascular risk modification treatment is lower than in the general population. This "therapeutic nihilism" [75] is based on the concern of WRF [76, 77]. If too cautiously treated, those patients develop equally life-threatening cardiovascular complications.

Box 7.15: WRF and Therapeutic Nihilism in HF

- Many medications necessary for management of complications of advanced CKD generally are considered safe with concomitant cardiac disease (phosphate binders, drugs for hyperparathyroidism, vitamins, and erythropoiesis-stimulating agents [78, 79] as well as endothelin system antagonists, adenosine and vasopressin receptor antagonists, and inflammation suppressors [80]).
- Less than 50% of patients with CKD were treated with the combination of aspirin, beta-blockers, ACE inhibitors, and statins.
- Renal failure remains a common identified reason for not prescribing ACE inhibitors or ARBs.
- Limited data is available regarding the specific use of ARBs or ACE inhibitors in patients with CKD and HF.
- Patients with HF and CKD taking ACE inhibitors had a lower risk of death at 2 years and were less likely to have hospitalizations for decompensated HF [81].
- In the Valsartan Heart Failure Trial (Val-HeFT), patients with CKD valsartan extended the time to first morbid event (death, sudden death with resuscitation, hospitalization for HF, etc.) [82].
- An increase in serum creatinine of 30% or less is not associated with long-term renal damage, and continued use of the drug in the absence of other adverse effects is allowed.
- An increase in serum creatinine greater than 30% warrants discontinuation of the drug.
- Up to a 30% increase in creatinine that stabilizes within 2 months was actually associated with long-term nephroprotection.
- These results lead to the advice that ACE inhibitors and ARBs can be cautiously used in patients with CKD, if serum creatinine does not increase beyond this amount and K remains consistently <5.6 mmol/L.
- It should be remembered that ACE inhibitors do not damage the kidney; they modify intrarenal hemodynamic reducing filtration fraction. They protect the kidney by reducing pathological hyperfiltration. Until there is no other dangerous situations (i.e., hypotension, hyperkalemia), treatment with ACE inhibitors and ARBs is feasible.

- Minimal data is available to guide clinicians on the use of aldosterone antagonists in CKD to improve CV outcomes.
- In patients with symptomatic HF, the hyperkalemia resulting from administration of aldosterone antagonists may be much more marked, particularly in patients with diabetes (hypo-renin hypoaldosteronism and type IV renal tubular acidosis)
- Patients with moderate CKD (creatinine level < 220 μmol/L) and/or potassium <5 mmol might benefit from the treatment with aldosterone antagonists with low risk for potential life-threatening hyperkalemia [83].
- WRF affects no less than 20% of patients with CHF who undergo a single course of intravenous (IV) infusions with loop diuretics.
- In at least half of the cases, the iatrogenic increase in serum creatinine is reversible within approximately 1 week after the end of the course of infusion therapy [84].

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Heart Failure and Metabolic Factors

8

Peter M. Nilsson, John Molvin, and Martin Magnusson

8.1 Introduction

The increasing prevalence of coronary heart disease (CHD) and type 2 diabetes (DM2) is partly due to the aging European population and partly due to increased prevalence of risk factors that interact to increase the risk of heart failure (HF) [1, 2]. This could be due to either a common antecedent (genetics, early life programming) or that of hypertension, a well-established risk factor for HF in itself, which is also associated with impaired glucose metabolism in many subjects and often coexists with obesity [3]. Therefore, new ways are explored to reduce the risk of HF by the use of antidiabetic drugs and lifestyle interventions to control glucometabolic status that could also improve hemodynamics and blood pressure control, as stated in European guidelines [4]. In this review we would like to provide an overview of the epidemiology and pathophysiology, as well as treatment aspects, of HF in relation to impaired metabolic control, more specifically hyperglycemia but also other metabolic abnormalities (Table 8.1).

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Table 8.1 Metabolic factors associated with increased risk of heart failure or with adverse prognosis in patients with established heart failure

• Hyperglycemia, glucotoxicity
• Insulin resistance
• Lipids abnormalities, lipotoxicity
• Free fatty acid metabolism of cardiomyocytes
• Hemochromatosis
• Hyperuricemia
• Vitamin deficiency (vitamin B1, thiamin)
• Inborn error of metabolism (i.e., glycogen storage disease)

8.2 Diabetes and Heart Failure Risk: Epidemiology

In the Framingham cohort, diabetes was associated with twofold risk of heart failure for men and a fivefold increased risk for women [5]. In women, diabetes appears to be an even stronger risk factor for heart failure than a history of coronary heart disease [6]. As stated above, both the incidence and prevalence of HF are significantly higher in the diabetic population, and it also carries a considerably worse prognosis [7]. Not only manifest diabetes poses a significant risk. The structural and functional harmful effects on the cardiovascular system induced by glucometabolic disturbances represent a continuum and are present before the actual diagnosis of diabetes is made exemplified by insulin resistance and elevated HbA_{1c} levels being associated with an increased risk of incident HF [8, 9]. The risk of heart failure also increases with age and duration of diabetes [10, 11] as well as smoking, high systolic blood pressure, and elevated body mass index (BMI). Elevated HDL cholesterol levels seem to have a protective effect, but no association has been seen for LDL cholesterol.

Already in the prediabetic range, the risk of HF is increased according to observational studies [12]. In established HF, glycemic control was a major determinant of prognosis in a multinational European study organized by the European Society of Cardiology (ESC) [13]. The authors concluded that the presence of diabetes markedly increases the risk of 1-year adverse clinical outcomes in outpatients with HF independent of a variety of common risk factors. A better control of hyperglycemia and other risk factors in these patients could lower the risk of HF, at least based on some trial evidence.

8.3 The National Diabetes Register of Sweden

Data from the National Diabetes Register (NDR) in Sweden has documented the increased risk of HF in both patients with type 1 [14] and type 2 diabetes [15]. Individuals with type 1 diabetes had a four-time increased risk of being admitted to the hospital with HF compared to population-based controls [14]. Poor glycemic control and impaired renal function substantially increased the risk of HF in type 1 diabetes [14]. For type 2 diabetes, the NDR authors stated that the risk of HF increased with age and duration of diabetes. Modifiable factors associated with increased risk of HF in these patients were smoking, high systolic blood pressure, and raised body mass index (BMI). In a subgroup of 18,281 patients (87%) from the

same study, with data for blood lipids, higher HDL cholesterol was associated with lower risk of HF, but there was no association with LDL cholesterol levels [15]. Factors of importance for these associations with HF risk are glycemic control [16] and obesity [16, 17].

8.4 Mechanisms for Heart Failure in Diabetes

Although the epidemiological association between HF and diabetes is well-established, the underlying mechanisms remain elusive. This association may be the consequence of underlying metabolic disturbances linked to insulin resistance and chronic inflammation but also to the hemodynamic burden imposed by hypertension and arterial stiffness linked to impaired glucose metabolism [18]. Hyperglycemia and changes in the metabolism could play a role [19]. The specific role of glucotoxicity on myocardial function has been studied, as well as the shift to fatty acid metabolism in cardiomyocytes during the transition to overt type 2 diabetes [20].

Subclinical heart disease (e.g., left ventricular diastolic dysfunction (LVDD) and left ventricular hypertrophy (LVH)) is heavily overrepresented in patients with diabetes [21, 22], and the existence of a specific diabetic cardiomyopathy (DCM) has been an ongoing debate over the past decades [23]. The underlying mechanisms for DCM are most probably multifactorial and to date incompletely understood. The most accepted explanation of DCM is ischemic heart disease and/or small vessel disease [24]. However another possible explanation of DCM may be a metabolic disorder within the cardiomyocyte [25, 26] causing an unfavorable substrate use in the formation of adenosine triphosphate (ATP) in mitochondria. More free fatty acids (FFA) are used as substrates instead of glucose, which affects calcium hemostasis and consequently cardiomyocyte relaxation and contractility negatively [27–29]. Interestingly, animal studies have also indicated that high plasma levels of glucose cause impaired calcium hemostasis and LVDD [30, 31], and a human study has shown that small increases in plasma glucose provide a momentary development of LVDD as measured by echocardiography examination [32]. Furthermore, the development of LVH has been shown to be partially independent of blood pressure in diabetes, implicating additional mechanisms behind LVH development in diabetes [21]. One suggested explanation is that the hyperinsulinemia caused by the peripheral insulin resistance in type 2 diabetes directly affects the cardiomyocytes by insulin anabolic effects [33].

8.5 Other Metabolic Disturbances and Heart Failure Risk

Besides hyperglycemia, other metabolic abnormalities have been linked to the risk of HF including hemochromatosis with iron deposits in the myocardium [34]. An indirect evidence for the role of hypercholesterolemia and HF is the fact that statin therapy, and thereby a reduction of LDL cholesterol, is associated with a more favorable outcome in HF patients [35]. However, these results could not be replicated in a randomized trial setting in the two major studies of statins and HF [36,

37]. Finally, both hyperuricemia [38] and some variants of inborn error of metabolism could contribute to the risk of HF in susceptible individuals [39]. The new biomarker copeptin, reflecting vasopressin and plasma volume control, has also been associated with diabetic heart disease and death [40].

8.6 Metabolomics and Heart Failure Risk

One of the most innovative methods to identify novel causes of disease is called metabolomics, e.g., liquid chromatography/mass spectrometry (LC/MS), allowing the acquisition of high-throughput profiles of the metabolic status of whole organisms providing a comprehensive assessment of molecules that are substrates and/or products of metabolic pathways [41]. HF is caused by an interaction between lifestyle and genetic factors, and a metabolomic profile can provide an integrated picture of food intake and the genetic set of metabolic regulatory enzymes. Such changes in metabolite profiles precede HF-associated disease development (e.g., cardiovascular disease (CVD) and diabetes) by years. For example, it has, through metabolomic analysis, been shown that elevated levels of three essential aromatic and branched-chained amino acids (isoleucine, phenylalanine, and tyrosine) predict future diabetes [41], as well as increased risk of future CVD development [42]. Interestingly, as for diabetes and CVD, essential amino acids also seem to play a major role in the prediction of HF. A recent study identified a combination of four metabolites (histidine, phenylalanine, spermidine, and phosphatidylcholine C34:4) to create a blood metabolite profile characteristic to HF with a discriminatory ability similar to that of B-type natriuretic peptide (BNP) alone, and also in the same study another metabolite panel, which consisted of the asymmetric methylarginine/arginine ratio, butyrylcarnitine, spermidine, and the total amount of essential amino acids, provided significant prognostic values in HF patients independent of BNP and traditional risk factors [43]. However, although metabolomic profiling in HF offers a promising new approach, with a footing in biological function, most studies done to date examine HF patients with reduced ejection fraction (HFrEF) which only accounts for approximately 50 percent of HF cases. As HF with preserved ejection (HFpEF) in itself is a mixed syndrome, most likely to be associated with a variety of metabolic anomalies [44], it is possible that future metabolomic studies including the whole range of HF patients (both HFrEF and HFpEF) could detect other HF-associated metabolomic profiles.

8.7 Intervention Studies with Anti-Obesity Drugs or Older and Newer Antidiabetic Drugs

8.7.1 Anti-Obesity Drugs

So far the results of studies on the effects of drugs lowering body weight with the aim of reducing CVD morbidity and mortality have been disappointing [45].

8.7.2 Insulin, Metformin/SU, and Glitazones

The treatment of hyperglycemia in itself could lower composite cardiovascular endpoints, as shown in studies of some newer antidiabetic drugs. On the other hand, some antidiabetic drugs, both older, i.e., glitazones, and newer, i.e., saxagliptin, were associated with an increased risk of HF [46].

8.7.3 SGLT2 Inhibitors (EMPA-REG OUTCOME, CANVAS)

These drugs promote natriuresis and lower both office and ambulatory blood pressure, in addition to reduction of hyperglycemia. Two major randomized, controlled trials have contributed data on the effects on HF, the EMPA-REG OUTCOME study [47] and the CANVAS Program (CANVAS and CANVAS-Renal) [48], in patients with type 2 diabetes and history of a previous cardiovascular event. In the EMPA-REG OUTCOME study (empagliflozin vs. placebo), the primary outcome was significantly reduced (hazard ratio, HR 0.86) (95% confidence interval, 0.74–0.99; $P = 0.04$ for superiority) but also the hospitalization for HF (35% relative risk reduction) [47]. In a separate publication, the benefits of empagliflozin treatment were extended also to patients with prevalent HF at study baseline [49]. Also in the CANVAS study (canagliflozin vs. placebo), the rate of the primary composite endpoint with active treatment was lower than with placebo, HR 0.86 (95% CI, 0.75–0.97; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority) [48]. This was also true for the risk of hospitalization for heart failure, HR 0.67 (95% CI: 0.52–0.87) [48]. The beneficial effect on HF risk in these two studies could well have been influenced by an improved control of central hemodynamics, including a lowering of blood pressure but also of reduced arterial stiffness.

The EMPEROR HF trial will evaluate the efficacy and safety of empagliflozin in patients with chronic HF, including those with and without diabetes [50].

8.7.4 DPP-4 Inhibitors (SAVOR, TECOS)

The inhibition of the enzyme DPP-4 has mostly showed no difference versus placebo for overall clinical benefits, as evident from the SAVOR-TIMI [51], EXAMINE [52], and TECOS [53] trials in patients with type 2 diabetes and a previous cardiovascular event. However, in one of the trials (SAVOR-TIMI), the risk of HF was significantly increased with the use of saxagliptin [51]. This could represent a chance finding but could also be a consequence of pharmacological differences between DPP-4 inhibitors. On the other hand, there was no increase of the composite cardiovascular endpoint in SAVOR-TIMI, proving that this drug is not influencing total cardiovascular risk versus placebo [51].

8.7.5 GLP-1 Analogues (LEADER, SUSTAIN, EXSCEL)

In three different clinical trials involving GLP-1 analogues versus placebo in patients with type 2 diabetes and a previous cardiovascular event, a favorable effect was noted for reduction of the primary composite cardiovascular endpoint, but no added benefit for HF risk as a separate endpoint. In LEADER the risk of HF was nonsignificantly lower with liraglutide versus placebo, HR 0.87 (0.73–1.05) [54], and in SUSTAIN the figures were for semaglutide vs. placebo, HR 1.11 (0.77–1.61) [55]. Finally, in the recently published EXSCEL study with exenatide once weekly vs. placebo, the HR was 0.94 (0.78–1.13) [56]. The FIGHT trial studied the clinical stability of liraglutide in patients hospitalized for acute heart failure. The result indicated that liraglutide did not provide any additional benefits in the risk of rehospitalization due to acute heart failure [57].

8.8 Conclusion

In summary, evidence suggests that patients with HF are characterized by metabolic changes and chronic inflammation that together with a hemodynamic burden will add to the risk of comorbidities and mortality. In fact, HF represents the upper end of the cardiovascular continuum, starting with elevated risk factors and increasing the risk of coronary heart disease when HF will progress as a consequence of the previous risk factor burden but also by myocardial scarring and loss of function following the ischemic events. This could also be called progressing cardiovascular aging, as reflecting similar processes as found in the large elastic arteries with advancing age. There are also other examples of metabolic factors influencing cardiac function and the risk of HF, but impaired glucose metabolism associated with insulin resistance is the most important metabolic abnormality contributing to HF. In the future, the increased exploration of metabolomics and biomarkers in HF and atherosclerotic disease could refine risk prediction [58, 59].

Among antidiabetic drugs, the new class of SGLT2 inhibitors has been shown to lower the risk of hospitalization for HF in diabetic subjects with high cardiovascular risk in large randomized, placebo-controlled studies [47–50]. This could be due to natriuresis and diuretic effects, influencing the central and peripheral hemodynamics with, for example, lowering of blood pressure. A reduction of arterial stiffness and inflammatory markers, besides the improvement of glycemic control, could add to these benefits. As mentioned before the future results from the EMPEROR HF trial will also provide information on the efficacy and safety of the SGLT2 inhibitor empagliflozin in patients with chronic HF, including those with and without diabetes [50]. On the other hand, the new incretin-active drugs (DPP-4 inhibitors and GLP-1 analogues or agonists) have not shown any special protection of HF in seven different large-scale, placebo-controlled studies [51–57].

The quest for new ways to control the metabolic abnormalities associated to HF is promising, and new drugs are under development [60–62], for example, mineralocorticoid receptor antagonists (MRA) with both hemodynamic and metabolic

effects [63]. For the moment, improved glucometabolic control could add to a more favorable prognosis in patients at high risk of HF or with already established HF. The new class of SGLT2 inhibitors seems of special importance and very promising in this respect [64, 65].

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Role of Central Blood Pressure and Arterial Stiffening

9

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The relationship between brachial blood pressure (BP), hypertension and heart failure is well established. However, two concepts have gained a growing audience these last years: the pressure amplification between central and peripheral arteries in response to arterial stiffening and pressure wave reflection and the left ventricle (LV)-arterial system coupling in heart failure (notably with preserved ejection fraction also referred to as diastolic heart failure) as arterial stiffening can result in impaired active ventricular relaxation and passive ventricular compliance. An increasing number of physiological studies, as well as pathophysiological, epidemiological and pharmacological studies, have underlined the importance of measuring not only brachial systolic and pulse pressures but also central systolic and pulse (i.e. systolic *minus* diastolic) pressures and arterial stiffness.

The aims of this chapter are (1) to detail the haemodynamic characteristics of the arterial circulation in order to explain why it is important to measure arterial stiffness and central BP in hypertensive patients, (2) to describe the various non-invasive methods currently available to measure arterial stiffness and central BP and (3) to discuss how arterial stiffness and central BP measurements can help understanding the relationship between hypertension and heart failure.

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9.1 Pathophysiology of Central Blood Pressure and Wave Reflection in Hypertension

9.1.1 Haemodynamic and Reflection of Pressure Waves

During ventricular contraction, a part of the stroke volume is forwarded directly to the peripheral tissues, while the remainder is momentarily stored in the aorta and central arteries, thereby stretching the arterial walls and raising local blood pressure (Fig. 9.1). Part of the energy produced by the heart is thus used for the distension of arteries and is transferred to the vessel walls as potential energy by passive loading of elastic elements in the wall. During diastole, the aorta recoils, and the "stored" energy is restored to the arterial system, squeezing the accumulated blood forwards into the peripheral tissues, ensuring quasi-continuous flow, especially during diastole (Fig. 9.1). Cardiac work has two components: potential energy (pressure generation-dP/dT) and kinetic energy (volumic pump, related to SEV and blood velocity). The systolic work is delivered during 1/3 of the time, i.e. any increase in pulse pressure will lead to an increase in dP/dT. In order to optimize the cardiac work during ventricular ejection, the energy spent to increase pressure (i.e. to distend arteries) should be retrieved as kinetic energy during diastole. Thus the optimum is obtained for a slow and small increase in pulse pressure, inducing large distension. The relation between increase in pulse pressure and increase in arterial volume defines arterial compliance (or its inverse arterial stiffness). Thus the efficiency of heart vessel coupling depends on the stiffness and geometry of the arteries, mainly the proximal aorta [2]. When arterial stiffness is low, arterial wall opposes low resistance to distension, and dP/dT is minimized, while high compliance is retrieved during

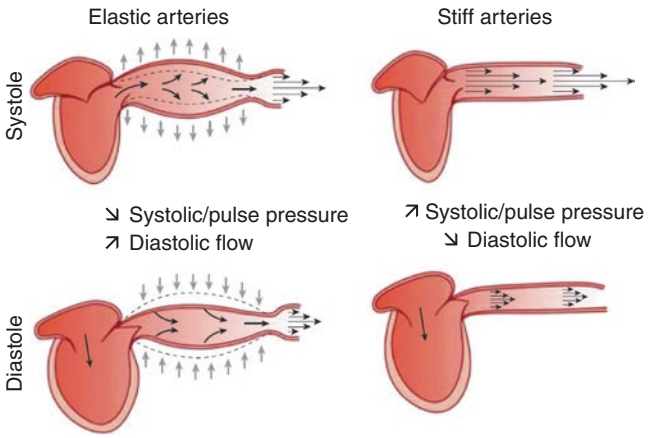

Fig. 9.1 Schematic representation of the role of arterial stiffness on assuring continuous blood flow through the peripheral circulation and how the aortic stiffening leads to increased SBP and PP. Adapted from Briet et al. [1] with permission from Elsevier

diastole. On the contrary, when the arterial system becomes rigid and distension limited, most of the stroke volume will flow through the arterial system and peripheral tissues only during systole with two consequences: intermittent high pulsatility flow and short capillary transit time with reduced metabolic exchanges.

The ejection of blood into the aorta generates a pressure wave that propagates along the aorta towards the peripheral arterial tree. The velocity of wave propagation along the aorta, i.e. pulse wave velocity (PWV), is a direct measure of arterial stiffness. The pressure waveform differs whether measured centrally close to the heart or more distally. The central arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave [1] (Fig. 9.2). Indeed, the arterial tree is not a simple tube but a complex structure that can be seen as a branched tube with a reflection site at its distal end. From the heart towards the periphery, arteries continuously decrease in diameter (i.e. geometric taper) and increase in stiffness (i.e. elastic taper, also named "arterial stiffness gradient") while also continuously branching [3]. In fact, the notion of reflection site is statistic; the sum of multiple reflection sites (bifurcations, tapering, diameter mismatch, peripheral resistances) acts as a unique site, which grossly correspond to the renal arteries (see below). The stiffness gradient, together with the geometric taper, local arterial branching and lumen narrowing, creates an impedance mismatch causing partial reflections of forward pressure waves travelling back to the central aorta (reflected wave) [3, 4] (Fig. 9.3).

The wave reflections will considerably change the pressure wave amplitude and shape along the arterial tree. Forward and reflected pressure waves overlap, and the final amplitude and shape of the pulse pressure wave are determined by the phase relationship (the timing) between these component waves. The overlap between the two waves depends on the site of pressure recording along the arterial tree. Peripheral arteries are close to reflection sites, and the reflected wave occurs at the impact of forward wave, i.e. the waves are in phase producing an additive

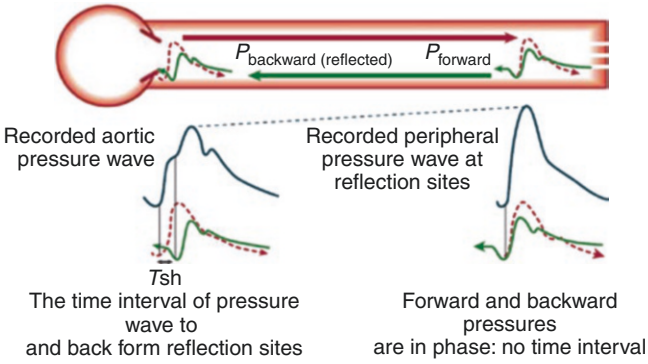

Fig. 9.2 Representation of forward and reflected pressure wave travelling and the influence of their timing and overlap on recorded aortic and peripheral pressure waves. *Tsh* time to shoulder. Adapted from Briet et al. [1] with permission from Elsevier

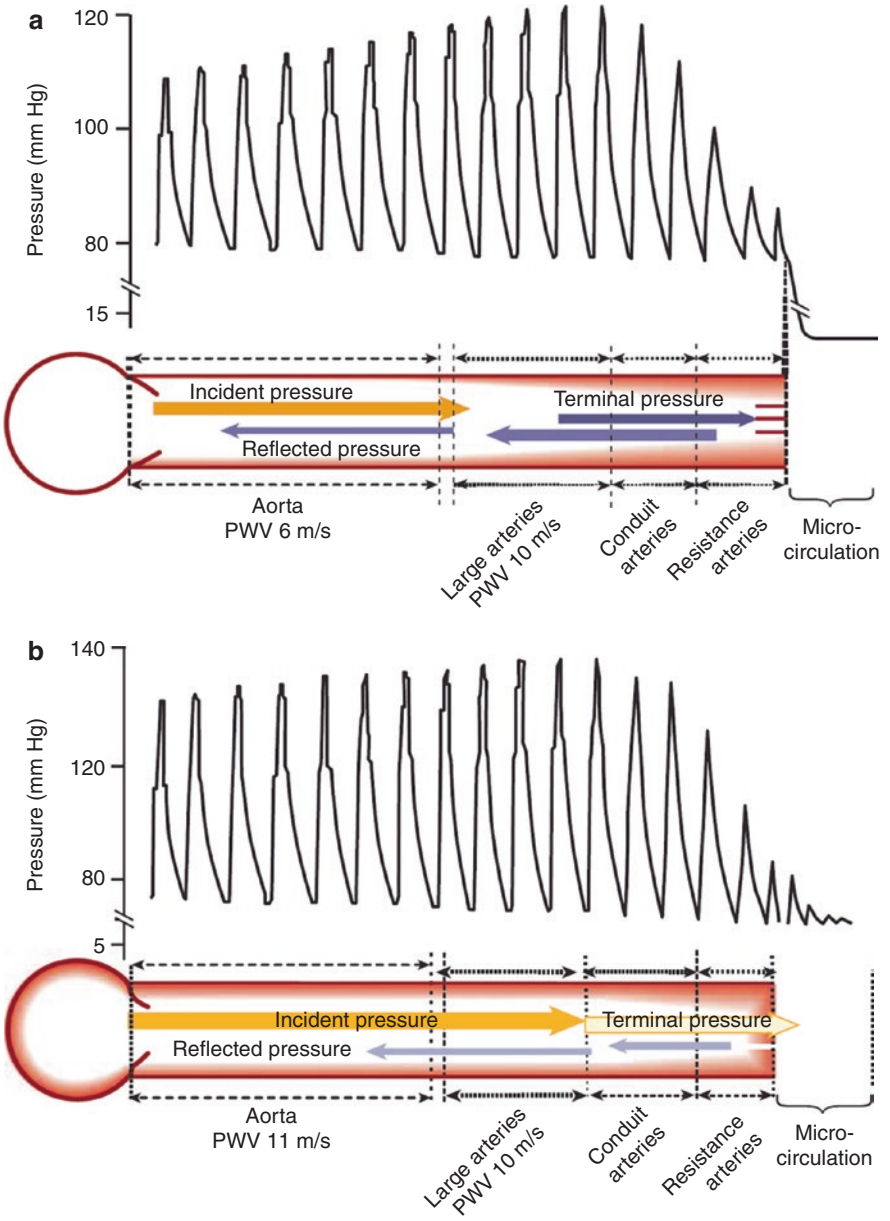

Fig. 9.3 Upper panel: in the presence of arterial stiffness gradient (aortic PWV < peripheral PWV), partial pressure wave reflection occurs distant from microcirculation and returns at low PWV to the aorta in diastole maintaining central-to-peripheral amplification. Partial pressure wave reflections limit the transmission of pulsatile pressure energy to the periphery and protect the microcirculation. Lower panel: When the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), pulsatile pressure is not sufficiently dampened and is transmitted, thus damaging the microcirculation. In parallel, the central-to-peripheral pressure amplification is attenuated. Adapted from Briet et al. [1] with permission from Elsevier

effect. The ascending aorta and central arteries are distant from reflecting sites, and the return of the reflected wave is variably delayed depending on PWV and travelling distances (Figs. 9.2 and 9.3) [1, 2]. In the aorta or central arteries, the forward and reflected waves are not in phase. In subjects with low PWV, reflected waves impact on central arteries during end systole or early diastole, increasing the aortic pressure in early diastole and not during systole. This is physiologically advantageous, since the increased diastolic pressure boosts the coronary perfusion without increasing the LV pressure load. When PWV is high, the reflected wave comes back early during systole, increases central SBP and PP and increases LV work.

Pressure waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. The reflection pattern is thus complex, but may be seen as a "net" or "effective" reflection pattern, where all the forward and backward running waves seem to add up to one single forward and backward wave, representing the global effect of all reflections present [2]. The phenomenon of wave reflection can be quantified through the augmentation index (AIx)—defined as the difference between the second (P2) and first (P1) systolic peaks (P2 – P1 = AP, i.e. augmentation pressure) expressed as a percentage of pulse pressure (AIx = AP/PP) (Fig. 9.4).

Thus, apart from a high PWV, also changes in reflection sites can influence central SBP, PP and AIx. The major determinant of central SBP and PP is, by definition, the forward pressure wave, since the reflected wave cannot physically carry more energy than the forward wave, but can be of high amplitude if reflections are coming from a major site [2]. In clinical investigation, not only DBP and height, which are related to total peripheral resistance and reflection sites, but also age and aortic PWV are the main determinants of AIx.

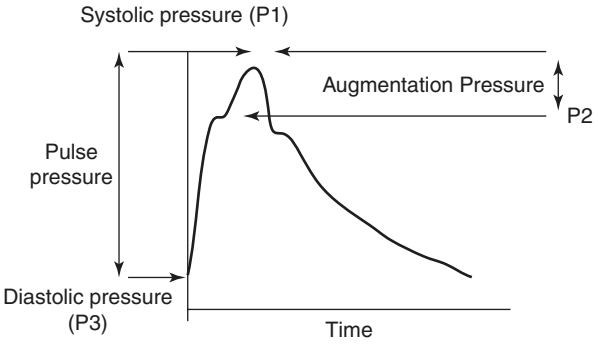

Fig. 9.4 The phenomenon of wave reflection can be quantified through the augmentation index (AIx)—defined as the difference between the second (P2) and first (P1) systolic peaks (P2 – P1 = AP, i.e. augmentation pressure) expressed as a percentage of PP: AIx = AP/PP. Adapted from Laurent et al. [5] with permission from Oxford University Press

9.1.2 Central-to-Peripheral Amplification Phenomenon

When SBP is recorded invasively and simultaneously in the aortic arch and at multiple peripheral sites, it is possible to detect an "amplification phenomenon", i.e. under resting conditions in healthy men, brachial SBP is about 10% higher than aortic SBP [6] (Fig. 9.3). Indeed, in the presence of the physiological arterial stiffness gradient (aortic PWV < peripheral PWV), partial pressure wave reflection occurs distant from microcirculation and return at low PWV to the aorta in diastole; thus reflected wave arrives back at the aortic root during late systole, whereas at the site of peripheral artery (i.e. brachial artery), the pressure wave travels rapidly, and the reflected wave (from peripheral branching sites and small arteries) arrives at the recording site very close to the forward wave, i.e. in early systole, thus rising local SBP. In average, central SBP is lower than distal SBP, leading to the so-called central-to-peripheral amplification. By contrast, when the stiffness gradient disappears or is inverted (aortic PWV > peripheral PWV), pulsatile pressure is not sufficiently dampened at the central level, and the central-to-peripheral pressure amplification is attenuated [2, 6] (Fig. 9.3).

The amplification phenomenon is attenuated by ageing and hypertension [6] because of arterial stiffening. Indeed, by favouring early wave reflections, arterial stiffening increases peak- and end-systolic pressures in the ascending aorta, increasing myocardial pressure load (left ventricular hypertrophy) and oxygen consumption and decreasing the diastolic blood pressure and subendocardial blood flow. Thus central SBP is higher in elderly subjects and hypertensive patients than in young normotensive subjects and closer to the brachial SBP value, reducing the difference. Indeed, at the site of brachial artery, arterial stiffness is not influenced by age and little by hypertension, and the timing of forward and reflected waves is similar to those in young normotensive subjects.

Central-to-peripheral amplification can be expressed either as absolute value (peripheral SBP minus central SBP; peripheral PP minus central PP) or relative value (peripheral SBP/central SBP; peripheral PP/central PP).

9.1.3 Reflection Magnitude

The time-domain analysis of the pulse waveform, called pulse waveform analysis (PWA), allows quantifying the effects of pressure wave reflection on the central arterial waveform. The determination of forward and backward waveforms requires a pressure-flow analysis in the time domain (Fig. 9.5). In early systole, prominent wave reflections are reduced; thus early systolic pressure and flow can be interpreted according to a simple model originally proposed by Westerhof et al. [8], referred as "the standard" Windkessel model for the systemic circulation: $Z_c = \Delta$ Pressure/Δ Flow, where Z_c is characteristic impedance and Δ Pressure and Δ Flow are calculated at the time point at which flow and pressure reach 95% of their peak value (Fig. 9.5). Because of the superimposition of reflected

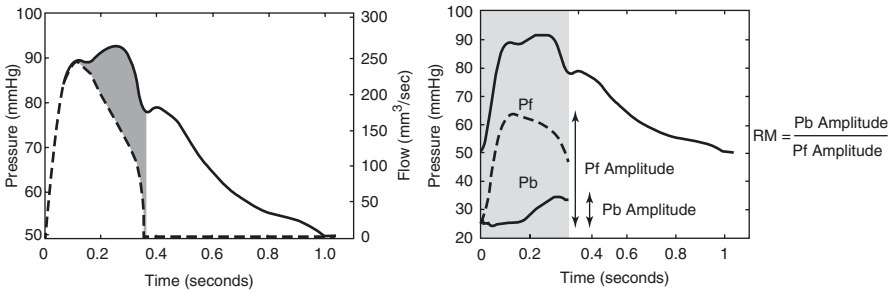

Fig. 9.5 Wave separation analysis. Once Z_c is known (see text), pressure and flow waves can be quantitatively "scaled" in the vertical axis (**a**), allowing for identification of the difference in their waveforms (grey area), which is assumed to be the result of wave reflections. Pressure can be separated into forward and backward pressure (Pf and Pb), and the amplitude ratio of Pb/Pf (reflection magnitude) can be computed (**b**). Adapted from Chirinos et al. [7] with permission from Wolters Kluwer Health

(backward) and incident (forward) waves in the early systole, measured pressure equals the sum of forward and backward pressures, and measured flow equals the sum of forward and backward flows (backward flow having a negative sign). Pressure and flow waves can be quantitatively related to each other, through Z_c. A procedure, commonly called wave separation analysis (WSA) (Fig. 9.5), can be used to decompose the pressure signal into its forward (Pf) and reflected (backward, Pb) components:

$$\mathrm{Pf} = \left(P + Q^{*} Z_{\mathrm{c}}\right) / 2$$

$$\mathrm{Pb} = \left(P + Q^{*} Z_{\mathrm{c}}\right) / 2$$

In practice, this way of calculating Pf and Pb is not very different from the one resulting from frequency analysis where each individual harmonic is studied and then adding all harmonics. The ratio of their amplitudes defines the reflection magnitude:

$$\text{Reflection magnitude, RM} = \text{Pb amplitude} / \text{Pf amplitude}$$

Interestingly, this computation of RM does not depend too much on the calibration of the flow waveform, and some authors [4] have proposed an approximated approach using pressure information only, assuming a triangular or a physiologic flow waveform. Although very appealing from a theoretical point of view, time domain or frequency domain wave magnitude determination has produced little breakthrough advances in the comprehension of heart vessel coupling.

9.2 Methods for Determining Arterial Stiffness and Central Blood Pressure

A large number of reviews have made recommendations for adequate measurements of arterial stiffness and central BP [5, 9, 10]. We will shortly review here the main methods.

9.2.1 Arterial Stiffness Measurements

Arterial stiffness can be evaluated at the systemic, regional and local levels. In contrast to systemic arterial stiffness, which can only be estimated from models of the circulation, regional and local arterial stiffness can be measured directly, and non-invasively, at various sites along the arterial tree. A major advantage of the regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters strongly linked to wall stiffness. Table 9.1 details the various methods currently used for determining arterial stiffness.

9.2.1.1 Regional Measurements of Arterial Stiffness

The aorta is a major vessel of interest when determining regional arterial stiffness for at least two reasons: the thoracic and abdominal aorta makes the largest contribution to the arterial buffering function, and aortic PWV is an independent predictor of outcome in a variety of populations.

Two-site pulse wave velocity measurements are recommended. The gold standard is the measurement of pulse wave velocity (PWV), which is considered as the most simple, non-invasive, robust and reproducible method. Carotid-femoral PWV is a direct measurement and is usually performed using the foot-to-foot velocity method from various waveforms. These are usually obtained, transcutaneously at the right common carotid artery and the right femoral artery (i.e. "carotid-femoral" PWV), and the time delay (Δt, or transit time) measured between the feet of the two waveforms (Fig. 9.6). The "foot" of the wave is defined at the end of diastole, when the steep rise of the wave front begins. The transit time is the time of travel of the "foot" of the wave over a known distance. A variety of different waveforms can be used including pressure, distension and flow (Doppler), with similar values. The distance (D) covered by the waves is usually assimilated to the surface distance between the two recording sites, i.e. the common carotid artery (CCA) and the common femoral artery (CFA). PWV is calculated as PWV = D (m)/Δt (s). However, the pressure wave splits at the origin of the brachiocephalic trunk, the one travelling forwards to the carotid bifurcation, the other travelling down the aorta to the femoral artery. Thus the descending thoracic aorta is reached by the pressure wave after another pressure wave, originating from the same cardiac contraction, arrives at the carotid site. For correcting for this uneven pathway, it has been recommended in a recent consensus paper to measure the direct distance and to apply a 0.8 coefficient, to take into account the shorter pathway of the pressure [11]. Reference values for carotid-femoral PWV have been established in 1455 healthy subjects and a larger

Table 9.1 Device and methods used for determining regional, local, and systemic arterial stiffness (Adapted from ref. 10 with permission)

Year of first publication	Device	Method	Measurement site	Predictive value for CV events (year first publication)	Ease of clinical utility	Approval by FDA
Regional stiffness						
1984[a]	Complior®	Mechanotransducer	Aorta, cf PWV[b]	Yes (1999)	++	No
1990[a]	Sphygmocor®	Tonometer	Aorta, cf PWV[b]	Yes (2011)	++	Yes
1991	WallTrack®	Echotracking	Aorta, cf PWV[b]	No	+	?
1994	QKD	ECG +	Aorta, cf PWV[b]	Yes (2005)	++	Yes
1997[a]	Cardiovasc. Eng. Inc®	Tonometer	Aorta, cf PWV[b]	Yes (2010)	+	NA
2002	Artlab®	Echotracking	Aorta, cf PWV[b]	No	++	Yes
2002	Ultrasound systems	Doppler probes	Aorta, cf PWV[b]	Yes (2002)	+	NA
2002	Omron VP-1000®	Pressure cuffs	Aorta, ba PWV[b]	Yes (2005)	+++	Yes
2007	CAVI-Vasera®	ECG + pressure cuffs	Aorta, ca PWV[b]	Yes (2014)	+++	Yes
2008	Arteriograph®	Arm pressure cuff	Aorta, aa PWV[b]	Yes (2013)	++	No
2009	MRI, ArtFun®	MRI	Aorta, aa PWV[b]	Yes (2014)	+	NA
2010	Mobil-O-Graph®	Arm pressure cuff	Aorta, cf PWV[c]	No	++	Yes
2010	Ultrafast®	Echography	Common carotid	No	–	No
2013	pOpmetre®	Photoplethysmography	Aorta, ft PWV[b]	No	+++	No
2017	Withings®	Balistocardiography	Aorta	No	+++	?
Local stiffness						
1991	WallTrack®	Echo-tracking	CCA[d], CFA, BA.	No	+	No
1992	NIUS®	Echo-tracking	RA	No	+/–	No
2002	Artlab®, Mylab®	Echo-tracking	CCA[d], CFA, BA	Yes (2014)	++	Yes
	Ultrasound systems	Echography	CCA[d], CFA, BA	No	+	?
2009	MRI, ArtFun®	Cine-MRI	AA, DA	No	+	NA

(continued)

Table 9.1 (continued)

Year of first publication	Device	Method	Measurement site		Predictive value for CV events (year first publication)	Ease of clinical utility	Approval by FDA
Systemic stiffness							
1989	Area method	Diastolic decay		45	No	+/−	NA
1995	HDI PW CR-2000®	Modif. Windkessel		46	No	+	Yes
1997[a]	Cardiovasc. Eng. Inc®	Tonometer/Doppler/ Echo		47	Yes (2010)	+/−	NA
2009	MRI, ArtFun®	Cine-MRI	AA, DA	43	No	+	NA

[a]Apparatus used in pioneering epidemiological studies showing the predictive value of aortic stiffness for CV events; *PWV* pulse wave velocity
[b]*cf* carotid-femoral, *ba* brachial-ankle, *ca* cardiac-ankle, *aa* aortic arch, *ft* finger-toe
[c]Estimated, not measured
[d]All superficial arteries, including particularly those mentioned; *Ao* aorta, *CCA* common carotid artery, *CFA* common femoral artery, *BA* brachial artery, *RA* radial artery, *AA* ascending aorta, *DA* descending aorta. FDA means agreement by FDA for the market, which is necessary for use in routine clinical practice, but is not necessary for use in research centres. NA means not applicable. All apparatus have CE agreement by the European Community

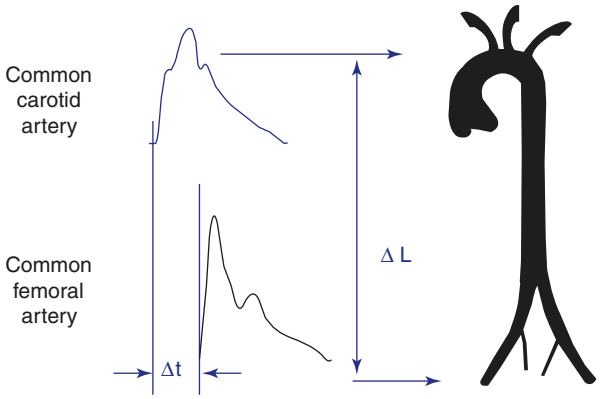

Fig. 9.6 Measurement of carotid-femoral pulse wave velocity with the foot-to-foot method. The waveforms are usually obtained transcutaneously at the right common carotid artery and the right femoral artery. The time delay (Δt, or transit time) is measured between the feet of the two waveforms. The distance (ΔL) covered by the waves is usually assimilated to the surface distance between the two recording sites, i.e. the common carotid artery and the common femoral artery. PWV is calculated as PWV = 0.8 × ΔL (m)/Δt (s). From Laurent et al. [5] with permission from Oxford University Press

population of 11,092 subjects with CV risk factors [12]. Multiple devices using pressure waveforms recorded simultaneously are validated to provide automated measurement of PWV. They are detailed in Table 9.1. They include the brachial-ankle PWV (baPWV), the cardiac-ankle PWV, and the finger-toe PWV.

Single-site pulse wave velocity measurements would simplify measurement. Several methods have challenged the reference methods described above. An increasing number of methods indeed calculate PWV over a given arterial pathway from the analysis of the brachial pressure wave. Brachial pressure wave is determined with a brachial cuff. PWV is thus referred as "single-site"- or "brachial cuff"-derived PWV and apparatus as "brachial cuff"-based devices. Importantly, PWV is estimated from various parameters, but not directly measured. These methods include the determination of the time difference between Q wave at ECG and Korotkov sounds at the brachial level (QKD) with ambulatory blood pressure measurement, the Arteriograph® system that estimates PWV from a single-site brachial-cuff oscillometric determination of the suprasystolic waveform at the brachial artery site and the Mobil-O-Graph® system that takes advantage of oscillometric recording of brachial artery pressure waveform to synthesize the central pulse wave by applying a transfer function. This latter method has phenomenological adjustments since age and blood pressure are used to refine PWV estimation.

9.2.1.2 Local Determination of Arterial Stiffness

Local arterial stiffness of superficial arteries can be directly determined using high-resolution echotracking devices. Carotid stiffness may be of particular interest, since in that artery atherosclerosis is frequent. The advantage of high-resolution

echotracking devices is their high precision for determining diameter at diastole and stroke changes in diameter, compared with classical video-image analysis. Thoracic magnetic resonance imaging (MRI) is increasingly popular since it allows combined determination of cardiac and aortic structure and function with undisputed anatomical precision, but at the cost of lower spatial and temporal resolution. However, most of pathophysiological and pharmacological studies have used echotracking techniques.

9.2.1.3 Systemic Arterial Stiffness

A methodology based on an electrical circuit using a modified Windkessel model has been developed to determine a proximal capacitive compliance and a distal oscillatory compliance. Systemic arterial compliance can also be determined using the "area method" which requires measurement of aortic blood flow (velocimeter at the suprasternal notch) and associated driving pressure by applanation tonometry over the proximal right common carotid artery. A number of theoretical, technical and practical limitations impair their widespread application in the clinical setting.

9.2.2 Central Blood Pressure Measurements

Arterial pressure waveform should be analysed at the central level, i.e. the ascending aorta, since it represents the true load imposed to the heart, the brain, the kidney and more generally the central large artery walls. Table 9.2 details the various methods currently used for determining central blood pressure. The pressure waveform can be recorded non-invasively with a pencil-type probe incorporating a high-fidelity Millar strain gauge transducer (SPT-301, Millar Instruments). The most widely used approach is to perform radial artery tonometry and then apply a transfer function (SphygmoCor, AtCor, Sydney Australia) to calculate the aortic pressure waveform from the radial waveform (Table 9.2). Indeed, the radial artery is well supported by bony tissue, making optimal applanation easier to achieve.

Aortic pressure waveform can also be estimated from the common carotid waveforms (Table 9.2). Carotid tonometry requires a higher degree of technical expertise, but a transfer function is not necessary since the arterial sites are very close and waveforms are similar. Alternatively, distension waveforms from carotid echotracking can be rescaled and used. A large number of pathophysiological and pharmacological studies have been published using these methods. Apart from methods determining the pressure waveform at the central site, novel methods have been developed, which aim at determining the discrete value of central SBP using the second systolic peak (SBP2) on the radial or brachial pressure waves (Table 9.2). Whatever the method used, an external calibration is necessary because neither tonometry nor echotracking can give access to absolute values of blood pressure. This is usually done by using brachial SBP and DBP to calibrate radial artery tonometry (at the cost of some imprecision due to brachial radial amplification) and then using the radial MBP and DBP to calibrate either aortic or carotid waveforms [5, 6].

Table 9.2 Device and methods used for estimating central blood pressure, classified through the arterial segment used for pressure wave recording (Adapted from ref 9)

Year of first publication	Device	Method	Company	Parameters
Radial artery pressure waveform				
1990	Sphygmocor®[a]	Tonometer, GTF	Atcor medical	cSBP, cPP, cAIx
1997	Cardiovasc. Eng. Inc®[a]	Tonometer, cardiac echo, impedence	Cardiovasc. Eng	cSBP, cPP, cAIx, Zc, fP, bP
2004	Pulse pen®	Tonometer, direct		cSBP, cPP, cAIx
2009	Omron HEM-9001A I®	Tonometer	Omron	cSBP, rAIx
2012	BPro	Tonometer	HealthSTATS	rAIx
Brachial artery pressure waveform				
2010	Arteriograph®	Oscillometric, add. Infl.	TensioMed	cSBP, cPP, cAIx
2010	Mobil-O-Graph®	Oscillom., ARCSolver, PVP	IEM	cSBP, cPP, cAIx, Zc, fP, bP
2010	BPLab Vasotens®	Oscillometric	BPLab	cSBP, cPP, cAIx
2012	Centron cBP301	Oscillometric	Centron	cSBP, cPP, cAIx
2012	Cardioscope II	Oscillometric, add. Infl.	Pulsecor	cSBP, cPP, cAIx
2013	Vicorder®	Oscillometric	Skidmore	cSBP, cPP, cAIx
Carotid artery pressure waveform				
1984	Millar strain gauge®[a]	Tonometer, direct	Millar	cSBP, cPP, cAIx
2004	Pulse pen®	Tonometer, direct	Diatecne	cSBP, cPP, cAIx

[a]Apparatus used in pioneering epidemiological studies showing the predictive value of central BP for CV events; *cSBP* central systolic blood pressure, *cPP* central pulse pressure, *cAIx* central augmentation index, *rAIx* radial artery augmentation index, Z_c characteristic impedance, *fP* forward pressure wave, *bP* backward pressure wave

Reference values for central BP [6] have been established in 18,183 healthy subjects and a larger population of 27,253 subjects with CV risk factors.

9.3 Arterial Stiffness, Central Blood Pressure and Systolic Dysfunction

Although the role of arterial stiffness/central BP in the pathophysiology of heart failure with reduced ejection fraction (HFrEF) is known for decades, there is less evidence from longitudinal studies in humans reporting incident HFrEF in patients with high arterial stiffness and central BP.

9.3.1 Pathophysiological Mechanisms

The mechanistic relationships between HFrEF and arterial stiffness/central BP have been analysed in several reviews and a large number of studies [2, 13–15]. We have

shown that arterial stiffness acted as "pure" pressure overload, being powerfully associated with LV concentric remodelling, whereas arterial geometry played a "pure" volume overload, being associated with LV dilatation [13]. Arterial stiffness can aggravate myocardial ischaemia, which is a major determinant of HFrEF. Indeed, arterial stiffness, through an early return of wave reflection, increases peak systolic BP and thus myocardial load, triggering left ventricular hypertrophic (LVH) remodelling and reducing diastolic coronary perfusion. The mismatch in myocardial oxygen supply-demand that is conferred by both LVH and lower central diastolic blood pressure can reduce coronary perfusion and increase subendocardial ischaemia [2, 16–18]. Aortic stiffness is higher in patients with coronary heart disease (CHD) than in non-CHD patients, as well as in HFrEF patients [14, 15], and is associated with CHD events independently of classical CV risk factors [19]. Aortic stiffness is associated with greater atherosclerotic burden [13, 15, 20], and coronary atherosclerosis may be aggravated by elevated aortic stiffness through intimal damage.

Neurohumoral activation in response to the decreased cardiac output can lead to a vicious circle. Indeed, neurohumoral-induced vasoconstriction increases resistance vessel tone to maintain mean arterial pressure but also increase vascular smooth muscle mass, tone and fibrosis, resulting in increased stiffness and central pulse pressure. A direct relationship between neurohumoral activation (activation of the sympathetic nervous system and renin-angiotensin system) and increased carotid stiffness has been seen in HFrEF [14, 15].

9.3.2 Longitudinal Studies

Several longitudinal studies have reported incident HF, but did not discriminate between HFrEF and HFpEF. In the 5960 participants in the Multiethnic Study of Atherosclerosis (MESA), free of apparent cardiovascular disease and benefiting from a 7.61-year follow-up, Chirinos et al. [7] demonstrated that reflection magnitude—RM—an index of pressure wave reflection, was strongly and independently predictive of new-onset congestive heart failure (CHF), either systolic or diastolic. In the 2602 participants to the Chronic Renal Insufficiency Cohort (CRIC), a multiethnic, multicentre prospective observational study of patients with chronic kidney disease, who were free of HF at baseline and had 3.5 years of follow-up, Chirinos et al. [21] reported that patients with cf-PWV in the middle and top tertiles had a two- to threefold higher chance of developing new-onset hospitalized HF than patients in the first tertile of cf-PWV. Brachial systolic and pulse pressure were also independently associated with incident hospitalized HF, whereas central pressures were less consistently associated with this end point. The association between cf-PWV and incident HF persisted after adjustment for systolic blood pressure.

More recent studies, which discriminated between HFrEF and HFpEF, reported variable results. Tsao et al. [22] studied 2539 participants in the Framingham Study without clinical HF at baseline and who had 10.1-year follow-up. In

multivariable-adjusted analyses, cf-PWV was associated with incident HF in a continuous and graded fashion. HFrEF and HFpEF were not defined using current guidelines but as left ventricular ejection fraction <45% and ≥45%, respectively, as defined by echocardiography or radionuclide angiography within the year of incident HF diagnosis. Cf-PWV was associated with HFrEF in age- and sex-adjusted models, which was attenuated in multivariable-adjusted models. Pandey et al. [23] studied 2290 participants to the Health ABC study (Health, Aging and Body Composition) without prevalent HF who had arterial stiffness measured as cf-PWV at baseline and a 11.4-year follow-up. In adjusted analysis, higher cf-PWV was associated with greater risk of HF after adjustment for age, sex, ethnicity, mean arterial pressure, and heart rate. However, cf-PWV was not associated with risk of HFrEF after adjustment for potential confounders. Thus, more studies are needed, with a precise determination of combined interactions between arterial stiffness and incident HF according to its category.

9.4 Arterial Stiffness, Central Blood Pressure and Diastolic Dysfunction

A common causal mechanistic pathway may be present, whereby increased aortic stiffness and central BP promote the ventricular remodelling and the development of diastolic dysfunction through delayed diastolic relaxation. Indeed, carotid-femoral PWV [12] and central BP increase with ageing [6], and their prognostic value for cardiovascular events has been demonstrated independent of traditional risk factors. In addition, the prevalence of left ventricular (LV) diastolic dysfunction increases with ageing, and LV diastolic dysfunction is a predictor of all-cause mortality [24]. Diastolic dysfunction and arterial stiffness share not only predominance in elderly subjects and hypertensives, predictive value for cardiovascular morbidity and mortality but also remodelling that includes tissue fibrosis, stiffening of cardiac myocytes and vascular smooth muscle cells and advanced glycation end-products (AGEs) deposition in type 2 diabetes.

Paulus et al. recently suggested [25] a new paradigm for HFpEF development, which identified a systemic pro-inflammatory state induced by comorbidities as the cause of myocardial structural and functional alterations, but overlooked the influence of arterial stiffness. Indeed, the systemic pro-inflammatory state in response to comorbidities such as overweight, obesity, diabetes mellitus, chronic obstructive pulmonary disease and salt-sensitive hypertension may lead not only to coronary microvascular inflammation but also to large artery inflammation. Thus, it is likely that besides coronary microvascular inflammation leading to stiff cardiomyocytes and interstitial fibrosis, and contributing to high diastolic LV stiffness and heart failure, large artery inflammation leading to increased stiffness may exaggerate diastolic dysfunction through delayed diastolic relaxation.

In addition, the role of vascular stiffness in the mechanical behaviour of the LV has not been studied properly. The large- and medium-size coronary arteries

represent a vascular scaffold which is stretched during diastole. Any increase in coronary artery stiffness might lead to improper filling of the LV because of reduced LV compliance of vascular origin. This phenomenon might explain HFpEF in diabetics and hypertensives [26].

9.4.1 Pathophysiology of the LV Loading Sequence

A pathophysiological link between arterial stiffness and LV diastolic dysfunction may involve an increased afterload (estimated by characteristic impedance—Z_c) and wave reflection (estimated by reflection magnitude, late systolic peak or aortic pulse pressure) in response to arterial stiffening, both impairing diastolic relaxation through temporal changes in myocardial wall stress, i.e. the loading sequence of the LV (Fig. 9.7). Indeed, myocardial and arterial load are time-varying phenomena, and distinct arterial phenomena determine early versus late systolic load on the heart. Specifically, arterial wave reflections generally arrive at the central aorta in mid-to-late systole, selectively increasing late systolic LV afterload and pressure. Evidence in favour of this pathophysiological link (Fig. 9.7) is summarized below.

In a case-control study including 233 subjects with normal diastolic function, mild diastolic dysfunction, and moderate or severe diastolic dysfunction, Abhayaratna et al. [27] showed that brachial pulse pressure, central pulse pressure, and PWV progressively increased according to the severity of diastolic dysfunction, independent of age and sex. Most importantly, the overall performance of PWV was superior to central pulse pressure for the detection of any diastolic dysfunction,

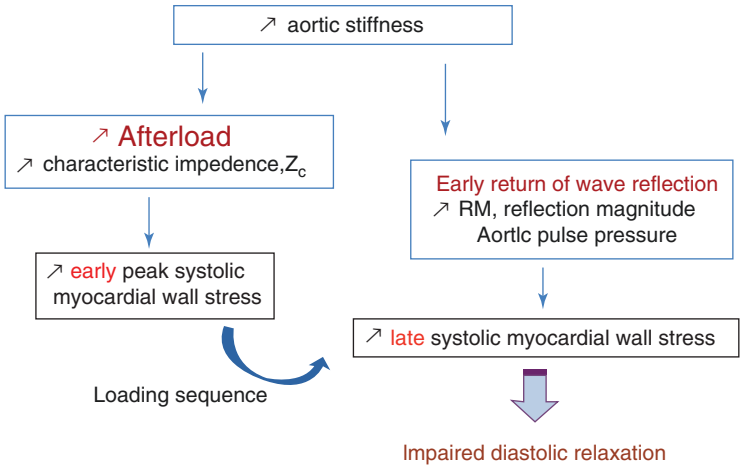

Fig. 9.7 Arterial stiffness and LV diastolic dysfunction: an increased afterload (estimated by characteristic impedance—Z_c) and wave reflection (estimated by reflection magnitude, late systolic peak or aortic pulse pressure) in response to arterial stiffening can impair diastolic relaxation through temporal changes in myocardial wall stress, i.e. delaying the loading sequence of the LV

suggesting that aortic pressure measurement may not reflect major haemodynamic determinants of diastolic dysfunction. Borlaug et al. [28] studied the impact of loading sequence on left ventricular tissue velocities in 48 subjects, using carotid characteristic impedance (Z_c) for assessing early systolic load, carotid augmentation index (cAIx) for assessing late systolic load, and tissue Doppler echocardiography (TDE) for determining LV tissue velocities. In multivariate analysis [28], Z_c, arterial compliance and cAIx were independent determinants of early diastolic mitral annular velocity (E'), suggesting an incremental influence of proximal aortic stiffness, aortic lumen, and wave reflection on early diastolic relaxation.

In the 1214 healthy volunteers of the Asklepios study who had measurements with applanation tonometry and speckle-tracking echocardiography, Chirinos et al. [29] demonstrated that proximal aortic Z_c but not reflection magnitude—RM—was a multivariate independent determinant of peak myocardial stress, whereas this was the reverse for end-systolic myocardial stress, i.e. RM but not Z_c was a multivariate independent determinant of end-systolic myocardial stress. In addition, they showed that early-ejection phase myocardial wall stress was positively associated, whereas late-ejection phase myocardial wall stress was negatively associated, with early diastolic mitral annular velocity (E') [29]. Altogether, these data indicate that reflected waves (i.e. backward travelling waves), which arrive in late systole, have little effect on peak myocardial stress, but rather on end-systolic stress [29]. Thus, by contrast to a LV early systolic load which is associated with faster relaxation, the shift in the LV loading sequence towards late systole impairs diastolic relaxation (Fig. 9.7).

These findings can be translated into the diagnosis level. Indeed, in patients who had dyspnoea as a major symptom, and in whom the diagnosis was based on invasively derived filling pressures and natriuretic peptide levels, Weber et al. [18] demonstrated that aortic PWV, aortic PP and backward wave amplitude (Pb) were effective in correctly classifying patients as HFpEF or no HFpEF and as effective as tissue Doppler echocardiography.

9.4.2 Evidence from Longitudinal Studies

By contrast to the large number of cross-sectional studies relating HFpEF to arterial stiffness, only a small number of longitudinal studies have been performed. As a proof of concept, these studies attempted to show that an increased arterial stiffness and/or a hyperpulsatile haemodynamics were associated with increased incidence of HFpEF. Unfortunately, results were mainly negative. In the Framingham Study described above, Tsao et al. [22] did not find any significant association between aortic stiffness and incident HFpEF. In the Health ABC study described above, Pandey et al. [23] showed no association between cf-PWV and risk of HFpEF after adjustment for potential confounders. The lack of significant association could have been attributable to low event rates and the relative health of the samples. More studies are needed in larger cohort, with more appropriate comorbidities, higher CV risk and longer follow-up.

9.5 Conclusion

This chapter highlighted the importance of arterial stiffness, central BP and wave reflection, for a better understanding of the relationships between hypertension and heart failure, either systolic or diastolic. We also detailed the haemodynamic characteristics of the arterial circulation and explained why it is important to measure arterial stiffness and central BP in hypertensive patients. Finally, we described the various non-invasive methods currently available to measure arterial stiffness and central BP.

9.6 Future Directions

Although a large number of cross-sectional studies are already available to decipher the various mechanisms by which increased arterial stiffness and central BP are associated with heart failure, more studies are needed, on a longitudinal approach, to determine, as a proof of concept, whether increased arterial stiffness and central BP favour incident heart failure or congestive decompensation.

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Pathophysiology of Hypertensive Heart Disease

10

Cesare Cuspidi, Carla Sala, Marijana Tadic, and Guido Grassi

10.1 Introduction

A variety of cardiac structural and functional changes, such as increased left ventricular (LV) mass, altered LV geometry, LV dysfunction, left atrial enlargement, aortic root and ascending trait dilatation, reduced coronary reserve, and prolonged ventricular repolarization, have been described in patients with long-standing arterial hypertension [1].

Subtle modifications in LV structure and geometry have been reported in the early phases of essential hypertension and even in prehypertension [2]. Among the manifestations of cardiac damage, most attention has been devoted to LV hypertrophy (LVH), a key biomarker of hypertensive heart disease, highly prevalent in current clinical practice (Fig. 10.1), and associated with systolic and diastolic dysfunction and to increased risk of heart failure and cardiovascular mortality [3].

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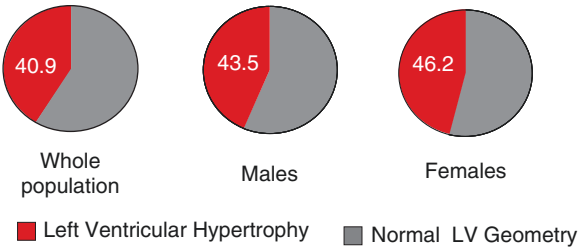

Fig. 10.1 Prevalence rates of left ventricular hypertrophy according to echocardiographic criteria in systemic hypertension (pooled data from 30 studies, 37,700 participants). Modified by Cuspidi et al. *J Hum Hypertens*. 2011; Permissions obtained from Springer Nature

Among major cardiovascular diseases, congestive heart failure is nowadays the most common cause of hospitalization in developed countries; its prevalence is progressively increasing worldwide and preceding cerebrovascular and coronary heart disease.

Congestive heart failure related to LV diastolic dysfunction is a growing clinical entity involving up to 60% of patients in clinical practice, in particular patients with systemic hypertension and LVH [4].

In this chapter the pathophysiological mechanisms involved in the progression of hypertensive heart disease will be analyzed. In particular, LVH and its subtypes, diastolic and systolic dysfunction, as assessed by imaging techniques, will be discussed in separate subsections.

10.2 Left Ventricular Hypertrophy

LVH is a cardinal manifestation of organ damage in patients with systemic arterial hypertension. Clinical and epidemiological studies have shown that LVH has a strong, independent adverse prognostic significance; identification of this condition is a fundamental step in the evaluation of hypertensive patients. LVH is an integrated marker of cardiovascular risk, reflecting cardiac effects of hemodynamic and non-hemodynamic factors operating in hypertension [5].

The rise in LV wall stress induced by increased intraventricular systolic pressure is a powerful stimulus for development of LVH, which, in turn, tends to reduce wall stress. According to Laplace's law, LV wall stress is directly related to intraventricular pressure and to radius and inversely related to wall thickness ($P = 2T\ d/r$). Increased wall thickness results from increased number of sarcomeres arranged in parallel in concentric and longitudinal in eccentric LVH, which initially develops at interventricular septum.

Hypertensive LVH has been reported to be associated with overexpression of fetal isoforms of contractile proteins such as β-myosin heavy chain, β-troponin, and skeletal α-actin. Thus, LVH may represent a regression to early stages of myocardial development rather than an overproduction of normal contractile proteins.

Both postmortem and endomyocardial biopsies have consistently shown that along with increased LV mass, the collagen fraction of the myocardium is increased in hypertensive subjects compared to normotensive counterparts. Moreover, endocardial or interstitial fibrosis and focal scars have been documented in LVH of mild degree in early phases of human hypertension [6].

In hypertensive LVH, a disproportionate accumulation of cells other than cardiomyocytes accounts for the development myocardial fibrosis [7].

These adaptive changes in LV texture initially preserve cardiac function, but in the long term, the persistent increased afterload leads to heart failure [8].

Mechanisms responsible for LVH development in its different subtypes are incompletely elucidated. Elevated BP is the major trigger; BP load, however, even when accurately defined by out-of-office measurements (i.e., home or ambulatory BP) accounts for approximately 25–30% of the observed variance of LV mass. Accumulating evidence supports the view that growth factors, cytokines and neurohormones (i.e., angiotensin II, endothelin I, catecholamines, aldosterone, insulin-like growth factor), increased aortic stiffness, myocardial ischemia due to impaired coronary microcirculation, excessive salt intake, and ethnic/genetic predisposition, overall, play a relevant role in this dynamic process (Fig. 10.2).

Several lines of evidence support a role for circulating and local renin-angiotensin-aldosterone system (RAAS) in the development of myocardial hypertrophy and fibrosis, independently of loading conditions [9]. Binding of angiotensin II to angiotensin type 1 (AT1) receptors initiates a signal transduction cascade resulting in

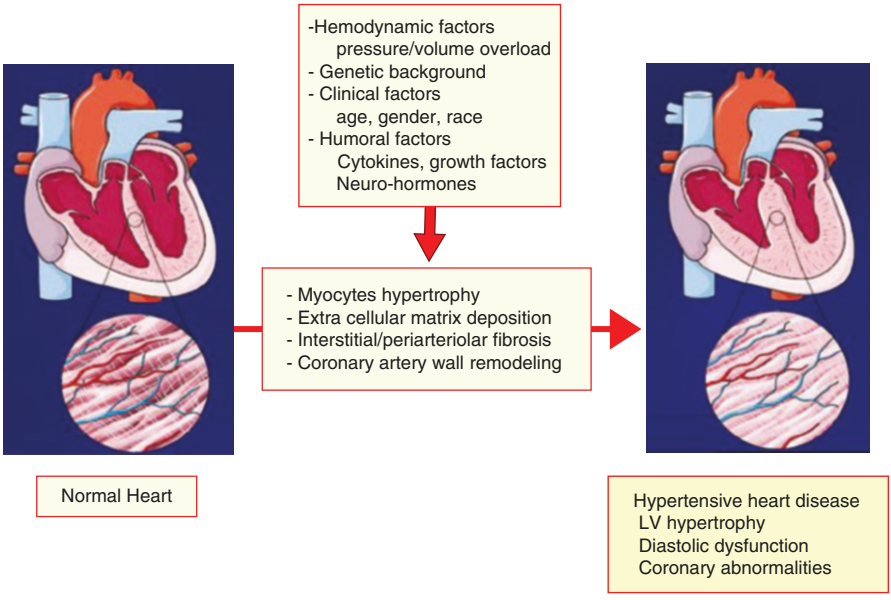

Fig. 10.2 Pathogenesis of hypertensive heart disease

enhanced collagen synthesis by cardiac fibroblasts and myocyte hypertrophy. The activity of angiotensin converting enzyme (ACE) in degradation of bradykinin and inactivation of nitric oxide may also be relevant. Aldosterone increases myocardial mass and promotes fibroblast proliferation, collagen deposition, oxidative stress, and inflammation.

Convincing evidence of the independent influence of aldosterone excess on cardiac structure has been obtained in patients with primary aldosteronism, in whom higher LV mass index, left atrial volumes, and prevalence rates of LVH compared with essential hypertensive counterparts have been documented. Furthermore, LVH regression after surgical correction of primary aldosteronism strongly supports a direct, causal role of aldosterone in LVH development [10]. Finally, genetic variations in RAAS components have been reported to influence the degree of cardiac cell growth during physiological or pathological states.

The hypothesis that sympathetic influences exert cardiotrophic effects and enhance myocardial hypertrophy has been supported by experimental studies. In the majority of animal models of cardiac hypertrophy, the rise in LV wall thickness was paralleled by increased cardiac sympathetic drive. The adverse influence of sympathetic nervous system (SNS) probably involves more complex mechanisms than activation of α- and β-adrenergic receptors on cardiac myocytes and fibroblasts: the inflammatory response driven by sympathetic overactivity has been demonstrated to be an important component of hypertension-induced cardiac remodeling. Available evidence in favor of a cause-effect relationship between adrenergic factors and cardiac hypertrophy is more controversial in humans, as no consistent association has been found between LV mass and cardiac epinephrine release or sympathetic nerve traffic in the peripheral muscle circulation in essential hypertensives [11]. New insights to support SNS role in the pathogenesis of LVH may indirectly derive from renal denervation studies reporting that a reduction of renal sympathetic afferent and efferent activity may facilitate regression of LVH. A causal role for mast cells in regulating myocardial cytokines, macrophage recruitment, and development of fibrosis in the hypertensive heart has been shown in spontaneously hypertensive rats.

Obesity and hypertension are closely linked phenotypes sharing a variety of cardiac and hemodynamic alterations. Adiposity excess affects the heart by causing hemodynamic, metabolic, and inflammatory alterations leading to epicardial and intramural fat accumulation, LV enlargement, and/or hypertrophy [12]. Pathophysiological mechanisms advocated to explain the link between obesity and LVH in both normotensive and hypertensive individuals include (1) increased intravascular volume, (2) activation of sympathetic and renin-angiotensin-aldosterone system, (3) abnormal production of myocardial growth substances from abdominal and cardiac adipose tissue, and (4) metabolic alterations that contribute to cardiac load by increasing arterial stiffness and peripheral vascular resistances.

This last mechanism plays a pivotal role also in different hypertensive subsets such as elderly, diabetes, and metabolic syndrome. The progressive stiffening of the aorta and large arteries in response to multiple risk factors and aging increases the amplitude and velocity of reflected pulse waves generated by resistance arterioles.

Arterioles, indeed, adapt to chronic arterial pressure increments through smooth muscle hypertrophy: this process tends to reduce end-arteriolar wall tension, but further increases large artery pressure and pulse wave velocity. The reflected wave, which normally reaches the central aorta after aortic valve closure, increases its velocity enough to return to the proximal aorta in late systole. This phenomenon leads to a further increase in the afterload and contributes to LVH progression/development [13].

Several data suggest a link between salt intake and LV growth in both animal and human studies. Saline overload has been consistently reported to increase LV mass; conversely, dietary salt restriction has been shown to regress cardiac hypertrophy in hypertensive rats and in salt-sensitive hypertensive patients. Although the mechanisms of cellular growth induced by sodium overload are incompletely understood, SNS activation is believed to play a role in this process. Salt intake also stimulates myocardial growth via hemodynamic mechanisms such as BP and volume overload [14] and stimulates phospholipase C activity mediated by platelet-derived growth factors.

Genetic factors related to essential hypertension also influence myocardial growth response to stimuli. Clinical observations support the view that a genetic predisposition to myocardial growth contributes up to 60% of LVH risk in essential hypertensives [15]. In particular, higher LV mass index and LVH prevalence have been reported in normotensive relatives of hypertensive patients as compared to age-matched counterparts without family history of hypertension. Moreover, LVH has been shown to develop in hypertensive patients on effective antihypertensive medications, to occur more frequently and severely in black than in white hypertensive patients. Several candidate genes responsible for LVH have been studied in different ethnic populations: the results of these studies, however, remain inconsistent.

10.3 Abnormal Left Ventricular Geometric Patterns

In the early 1990s, Ganau and coworkers proposed for the first time a comprehensive classification of LV geometry based on four echocardiographic patterns: normal LV geometry (normal LV mass and relative wall thickness, RWT), concentric remodeling (normal LV mass and increased RWT), eccentric hypertrophy (increased LV mass and normal RWT), and concentric hypertrophy (increased LV mass and RWT) [16]. In the last two decades, studies conducted in different clinical settings (i.e., general population samples, hypertensive cohorts, patients with ischemic heart disease, type 2 diabetes, and chronic heart failure) have shown that these patterns are associated with different degrees of LV systolic/diastolic function, left atrial (LA) size and function, plasma volume, peripheral resistances, clinic and ambulatory BP levels, and macro- and microvascular organ damage.

In hypertensive patients with concentric LVH, BP is characterized by increased peripheral resistances, cardiac output being slightly above normal average. In patients with eccentric hypertrophy, cardiac output is generally

increased with minimal or no elevations of peripheral resistances. Patients with concentric LV remodeling have normal or slightly reduced cardiac output and increased peripheral resistances. A progressive increase of LV preload and plasma volume has been described from LV concentric remodeling to concentric and eccentric LVH.

Available noninvasive ultrasound imaging techniques have allowed to accurately study the human cardiac and vascular structure and the impact of altered arterial properties on ventricular adaptation. Numerous studies have documented a tight association between abnormal LV geometric patterns and subclinical arterial disease. In 1074 mild to moderate untreated hypertensive patients, we found that LV mass index was positively related to systemic atherosclerosis detected by carotid ultrasound, independently of age, gender, BP, and conventional risk factors [17]. A stepwise increase in carotid intima-media thickness occurred from patients with normal LV mass and geometry to patients with LV concentric remodeling, eccentric hypertrophy, and concentric LVH. Concentric remodeling and concentric hypertrophy were cardiac phenotypes associated with higher carotid relative wall thickness compared to normal LV geometry and eccentric LVH.

The classification by Ganau et al. [16] has recently been criticized for not taking into account absolute values of LV wall thickness and internal dimensions, but only their ratio. Investigators of the Dallas Heart Study, a population-based sample of 2803 residents of Dallas County undergone to cardiac magnetic resonance imaging, have proposed a new LVH classification based on four subtypes: eccentric non-dilated and dilated LVH and concentric non-dilated and dilated LVH [18]. The authors were able to demonstrate that subjects with eccentric non-dilated LVH, at variance from other LVH subtypes, had similar levels of LV function and biomarkers of cardiac stress (i.e., brain natriuretic peptide) as their counterparts without LVH. Thereafter, Bang and coworkers tested the prognostic value of such LVH subclassification in 939 participants of Losartan Intervention for Endpoint Reduction (LIFE) echocardiographic sub-study [19] and showed that compared with patients with normal LV mass, those with eccentric dilated and both concentric non-dilated and dilated LVH had an increased risk of all-cause or cardiovascular mortality; this was not the case for patients with eccentric non-dilated LVH. Both reports documented a marginal impact of eccentric non-dilated LVH on ventricular function and cardiovascular prognosis and supported the view that the new classification of LV geometry improves the clinical/prognostic evaluation of patients with increased LV mass.

In the PAMELA study, subjects with LV geometric abnormalities, defined according to Dallas classification, were older and had higher body mass index (BMI), office and ambulatory BPs, and glucose and total cholesterol levels and lower HDL cholesterol compared to subjects with normal LV geometry [20]. Significant differences were also found among groups with abnormal LV geometry: concentric and eccentric dilated LVH exhibited higher BMI and BP levels than concentric remodeling. As for prognostic value, only concentric LVH persisted to be an independent predictor of cardiovascular morbidity and mortality after adjustment for baseline differences in LV mass index.

10.4 Diastolic Dysfunction

LV diastolic function is a complex dynamic process schematically divided into four phases, starting from aortic valve closure. The first diastolic phase refers to isovolume relaxation, which does not contribute to ventricular filling. The second early and rapid filling phase provides about 60–85% of LV ventricular filling. The third slow filling phase, defined as diastasis, contributes only 5% of total filling. The final atrial booster phase normally accounts for the remaining 5–30%, its contribution increasing with advancing age.

Diastolic LV relaxation and filling is an active process requiring Ca^{2+} reuptake from cytosol into sarcoplasmic reticulum by the calcium-handling protein Ca^{2+} ATPase in the presence of ATP [21]. LV diastolic properties are primarily affected by pathological conditions impairing the active process of calcium reuptake such as myocardial hypertrophy and myocardial ischemia. In hypertensive hearts, multiple factors including increased BP itself, structural LV changes (i.e., increased collagen matrix, disorganization of collagen fibers, abnormal collagen type I/III ratio), and impaired coronary microcirculation contribute to impair LV relaxation and to increase wall stiffness (Table 10.1). Prevalence and severity of diastolic dysfunction have been reported to be directly related to degree and type of cardiac hypertrophy, although diastolic dysfunction may also occur in the absence of LVH, as about one third of hypertensive patients without LVH fulfill echocardiographic diagnostic criteria of altered LV relaxation and filling. In animal models diastolic dysfunction has been shown to precede LVH development. Multiple factors such as insulin resistance, sleep apnea syndrome, obesity, and diabetes mellitus have been documented to contribute to diastolic dysfunction in the absence of LVH.

In the London Life Sciences Prospective Population (LOLIPOP) study including 1074 hypertensive individuals without cardiovascular disease, LV diastolic dysfunction was related to the degree of LV concentric remodeling, determined by relative wall thickness, and to the LV geometric pattern [22]. The presence of LVH was independently associated with a worse diastolic function and higher LV filling pressure when compared with subjects with normal LV geometry or non-hypertrophic concentric remodeling. Investigators of the Assessment of Prevalence Observational Study of Diastolic Dysfunction (APROS-diadys) project, a cross-sectional observational study on elderly hypertensives without systolic dysfunction ($n = 2545$) aimed

Table 10.1 Determinants of LV diastolic properties

Intrinsic factors
Completeness of ventricular relaxation (influenced by myocardial perfusion)
Passive elastic properties of the ventricle (compliance), determined by the thickness and composition of the ventricular walls
Extrinsic factors
Pressor overload
Volume overload
Strength of atrial contraction
Pericardial properties

to establish the prevalence of echocardiographic signs of diastolic dysfunction in relation to demographical and clinical characteristics, found that 1 g increase in LV mass increased the risk of diastolic dysfunction by 1.3% [23]. The prevalence of diastolic dysfunction progressively increased from normal geometry to LV concentric remodeling and eccentric and concentric LVH.

Obesity associated with hypertension enhances the risk of developing cardiac hypertrophy and diastolic dysfunction; the link between isolated obesity and diastolic dysfunction, however, remains controversial [24]. Also controversial is the association between prehypertension or mild hypertension and cardiac hypertrophy and diastolic dysfunction, when these conditions are diagnosed by conventional echocardiographic parameters. Recently developed echocardiographic techniques, such as three-dimensional echocardiography and speckle tracking imaging, provide more detailed insights into LV systolic and diastolic mechanics in three spatial directions [25]. These innovative techniques have been reported to accurately detect early LV functional alterations and to identify subtle LV mechanical abnormalities even in subjects with normal cardiac function by routine ultrasound examinations. It has been recently reported that in patients with prehypertension and white coat hypertension, the likelihood of impaired LV mechanics (longitudinal, circumferential, and radial) is higher than in counterparts with normal or optimal BP values. In conclusion, it is likely that data on prevalence and correlates of diastolic dysfunction in hypertension without apparent cardiac organ damage based on traditional echocardiographic and Doppler parameters, including tissue Doppler imaging, substantially underestimate the real, adverse impact of this condition on the heart.

The concept of isolated diastolic dysfunction in hypertensive heart disease is challenged by increasing evidence supporting an association between altered LV ventricular mechanics and deterioration of diastolic function. In patients with moderately severe hypertension, prolonged isovolumetric relaxation time, an index of impaired early diastolic LV relaxation, has been found to be associated with lower LV systolic myocardial function, as assessed by mid-wall shortening and stress-corrected mid-wall shortening.

The increase in LA size may be seen as a mechanism counterbalancing the impaired LV compliance and LV diastolic dysfunction in hypertrophied ventricles [26]. Enlargement of LA in hypertensive heart disease is regarded as a reliable marker of chronically elevated LV filling pressure and diastolic dysfunction in the absence of mitral valve diseases.

10.5 Systolic Dysfunction

Altered contractility in LVH is related to structural and functional abnormalities involving extracellular matrix and fibrous tissue, vasculature, as well as cardiomyocytes themselves [27]. In the large majority of hypertensive patients without frank

LV mass increases, LV systolic performance as traditionally assessed by LV ejection fraction (LVEF) at rest is preserved or even mildly increased.

Unfortunately, LVEF, which has been seen as the gold standard of LV systolic function for decades, does not provide a direct measure of myocardial fiber shortening, as circumferential fibers responsible for LV shortening in the short axis are located in the midportion of LV wall, between two longitudinal shells promoting long-axis shortening and twisting. In addition, two-dimensional echocardiographic evaluation of LVEF is faced with multiple limitations: foreshortening, geometry assumption, moderate accuracy, and inter-observer and intra-observer reproducibility.

Evaluation of LV systolic function as fractional shortening at mid-wall, as opposed to endocardium level, has been proposed as the most reliable method for assessing LV performance in the presence of LVH [28]. At the endocardium level, indeed, LV systolic function has been shown to be preserved or even increased in most uncomplicated hypertensives, thus losing any independent predictive value. On the contrary, subnormal LV function as assessed by mid-wall shortening has been associated with unhealthy factors at any BP level and with a marked increase in cardiac morbidity and mortality, independently of age and LV mass.

Numerous studies in hypertensive patients have reported that systolic dysfunction assessed by impaired LV mid-wall function was three- to fourfold more prevalent than systolic dysfunction assessed by conventional LV endocardial mechanics (i.e., LVEF).

Finally, in recent years LV deformation during systole has been quantified in multiple planes using speckle tracking echocardiography or magnetic resonance imaging tissue tagging. Planes of deformation have been defined in relation to myocardial fiber orientation, including longitudinal, radial, and circumferential shortening (strain). Among available strain parameters, LV global longitudinal strain appears to have more clinical relevance, as good predictor of cardiovascular and total morbidity and mortality in hypertensive population [29]. In hypertensive patients, abnormalities of this measure of LV longitudinal contractile ability have been reported even in the absence of structural and functional LV alterations as assessed by conventional echocardiography [30].

Thus, new echocardiographic techniques may significantly improve early diagnosis of functional alterations in hypertensive heart disease and identify high-risk individuals to be appropriately treated.

10.6 Future Directions

Inadequate prevention strategies such as early identification and effective treatment of hypertension, associated comorbidities, and early subclinical damage are the main factors leading to advanced LV remodeling, altered cardiac function,

perfusion, and electrical activity that adversely impact hypertensive heart disease. As a consequence, the burden of cardiovascular morbidity and mortality associated to hypertensive heart disease can be reduced by preventing LVH development and improving accuracy and cost-effectiveness of noninvasive diagnostic tools (imaging and biochemical markers) for detection of LV structural and functional alterations in the early, reversible phase of the disease.

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Part III

Diagnosis of Heart Failure in Hypertensive Patients

Role of Echocardiography

11

Silvia Iancovici and Maria Dorobantu

11.1 Introduction: Role of Echocardiography in Defining Heart Failure

Hypertensive heart disease(HHD) represents one of the etiologies of heart failure [1] (HF); the classic paradigm of progression from HHD to HF is that HHD leads to LV hypertrophy and diastolic dysfunction, followed by LV dilatation and decreasing ejection fraction (EF) [2]. Diastolic and systolic dysfunction of the left ventricle may coexist, and the sequence of appearance may differ between patients; diastolic dysfunction may occur in the absence of systolic dysfunction; however when systolic dysfunction is present, virtually there is some degree of impaired diastolic function, as well [3]. To a certain extent, it is of relevance to differentiate between a large, dilated LV with poor ejection fraction that defines systolic HF and a small, hypertrophied LV with normal EF and diastolic dysfunction, as found in diastolic HF.

The new HF guidelines redefined systolic and diastolic HF as *HF with reduced ejection fraction* (HFrEF) when EF <40% and *HF with preserved EF* (HFpEF) when EF >50% [1, 4]. For the definition of HFpEF, the European guidelines also include the presence of signs and symptoms of HF and elevated levels of natriuretic peptides and at least one of the following: relevant structural heart disease (LV hypertrophy or left atrial enlargement) or the presence of diastolic dysfunction [1].

In the case of an EF between 40 and 49%, the American guidelines describe the entity of *HFpEF borderline* [4]; meanwhile the European guidelines define the *HF*

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with midrange EF (HRmrEF) that also has to associate elevated levels of natriuretic peptides and at least one of the following: relevant structural heart disease (LV hypertrophy or left atrial enlargement) or the presence of diastolic dysfunction [1]. In addition, the American 2013 guidelines have also described the entity of *HFpEF improved* as a subset of patients with HFpEF who previously had HFrEF [4].

Therefore, in the presence of clinical signs of HF, echocardiography represents the main investigation utilized to discriminate between the different types of HF.

11.2 Evaluation of Left Ventricular (LV) Hypertrophy and Cardiac Mass

The evaluation of left ventricular hypertrophy, including LV mass measurement and assessing LV geometry, is the major role of echocardiography in hypertensive patients [5]. It is essential to determine LV mass and to establish the type of LV hypertrophy.

11.2.1 LV Measurements

Using the parasternal long-axis acoustic window at the level of the LV minor axis, the following linear measurements of LV can be obtained: left ventricular end-diastolic internal dimension (LVDd), interventricular septum (IVS), and posterior wall (PW). M-mode recordings have the best temporal resolution and may be chosen from 2D images. Sometimes, it may not be possible to align the M-mode cursor perpendicular to the long axis of the ventricle, and anatomical M-mode images can be used in these situations; the same LV dimensions can be obtained from the parasternal short-axis view using direct 2D measurements. The use of 2D-derived linear dimensions overcomes the common problem of oblique parasternal images resulting in overestimation of cavity and wall dimensions from M-mode [6]. When 2D measurements are used, the wall thickness and linear dimensions should be measured at the level of the LV minor dimension, at the mitral leaflet tip level. The upper limit of normal for LVd is smaller than the M-mode measurement [6].

The 2015 American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations for chamber quantification describe a normal left ventricular wall thickness (interventricular septal wall or posterior wall) as 0.6–1.0 in males and 0.6–0.9 in females, respectively. This is measured at the blood-tissue interface using either 2D or M-mode echocardiography, typically from the parasternal long axis [7].

Furthermore, left ventricular hypertrophy (LVH) is defined as an increase in LV mass and wall thickness due to increased cardiomyocyte size, characterized by a complex series of transcriptional, signaling, structural, electrophysiological, and functional events that affect all cardiac cell types [8]. An increased wall thickness may be suggestive of LVH; however, as an exclusive measurement, it cannot indicate LV remodeling or increased LV mass.

There are several methods that effectively calculate LV mass using M-mode echocardiography, 2DE, and 3DE. All measurements should be performed at the end of diastole (the frame before mitral valve closure or the frame in the cardiac cycle in which the ventricular dimension or volume is largest). Those that use M-mode (either blinded or 2D-guided) and 2D echocardiographic linear measurements for the LV diastolic diameter and wall thickness rely on geometric formulas to calculate the volume of the LV myocardium, while 3DE can measure it directly.

Among the different methods that have been proposed for quantifying the LV mass is the so-called M-mode method or Cube formula [9]:

$$\mathrm{LVM} = 0.8x\left\{1.04\left[\left(\mathrm{LVIDd} + \mathrm{PW} + \mathrm{IVSd}\right)3x\left(\mathrm{LVIDd}\right)3\right]\right\} + 0.6g$$

This method uses the thickness of the septum (IVSd), the posterior wall (PW), and the diameter of the left ventricle at end-diastole (LVIDd). This formula is not highly accurate, since it makes the geometric assumption that the LV is prolate ellipsoid, which is not true in all patients (Fig. 11.1) [9].

Other methods to estimate LV mass are the 2D formulas: the truncated ellipsoid and the area-length method [9]. Most studies that have compared 2D-guided M-mode measurements of LV mass with the 2D echocardiographic area-length or truncated ellipsoid methods in normally shaped ventricles have shown subtle differences, but no clear advantage of one technique over the other [10]. The majority of community-acquired prognostic evidence has been gathered with M-mode imaging [6]. The LV mass normal range for men is 49–115 g/m^2 using the linear method and 50–102 g/m^2 using the 2D formulas and for women 43–95 g/m^2 using the linear method and 44–88 g/m^2 using 2D, respectively, according to the latest chamber quantification guidelines [9].

Three-dimensional echocardiography is the best method to directly measure the LV cavity without any geometrical assumption and, therefore, is more accurate than the M-mode and 2D methods [9]. The accuracy of 3DE is reportedly similar to cardiac magnetic resonance (CMR) imaging methods for measuring LVM [6].

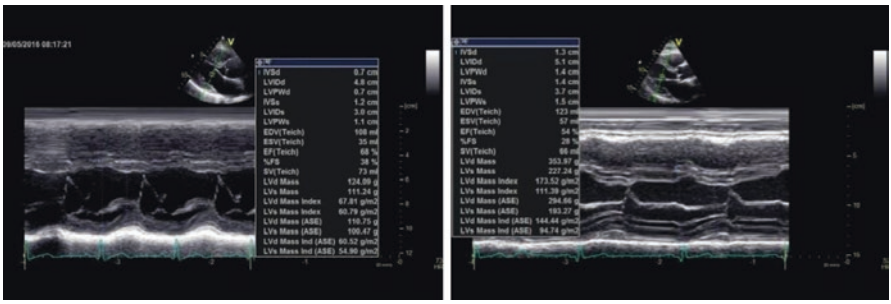

Fig. 11.1 Examples of M-mode calculation of LV mass. Normal LV mass 60 g/m^2 (left picture) and concentric hypertrophy IVS 13 mm and PW 14 mm, with increased LV mass 144 g/m^2 (right picture)

The normal range for the 3D LV mass formula is 77 (57–97) g/m^2 for a European man and 74 (58–90) g/m^2 for a European woman and 64 (40–88) g/m^2 for a Japanese man and 56 (34–78) g/m^2 for a Japanese woman [6], respectively.

11.2.2 LV Geometry

Generally, the LV geometry is better classified using two simple echocardiographic parameters: relative wall thickness (RWT), calculated as (PW × 2)/LVDd or (IVS + PW)/LVDd, and indexed LV mass. RWT can categorize the LVH as either concentric (RWT greater than 0.42) or eccentric (RWT less than 0.42) [5]. The indexing of LV mass allows for comparisons in subjects of different body size. However, whether to use height, weight, or BSA as the indexing parameter remains controversial. Studies suggest that indexing to height raised to allometric powers such as 1.7, 2.13, and 2.7 has advantages over indexing to BSA, especially when attempting to predict events in obese patients. However, most large population studies reporting LV mass have indexed to BSA [7].

Concentric LV hypertrophy developed with hypertension is characterized by uniformly increased wall thickness, normal cavity size, and increased LVM (Fig. 11.2). Concentric LV hypertrophy is an adaptive response to high systemic pressure. In addition, hypertension can be seen in other diseases such as aortic stenosis, coupled with increased peripheral resistance [6].

Eccentric hypertrophy is seen in conditions associated with volume overload (e.g., mitral regurgitation) and is caused by increased diastolic wall stress. In these cases, the echocardiographic findings are increased LV cavity size, normal LV wall thickness, and increased LVM. Patients with eccentric hypertrophy have similar modifications in diastolic function and the longitudinal and radial function as those with concentric hypertrophy [11].

Concentric remodeling refers to a late-stage response of the LV when LV cavity size is normal or small with increased LV wall thickness but with normal LV mass. Concentric LV remodeling can be caused by chronic pressure, volume overload, or coronary artery disease (Table 11.1).

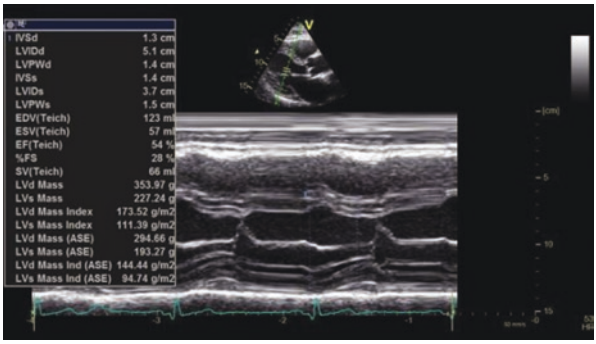

Fig. 11.2 M-mode LV study with concentric hypertrophy: IVS, 13 mm; PW, 14 mm; LVDd, 51 mm; RWT, 52 mm; LV mass, 144 g/m^2

Table 11.1 Classification of LV remodeling [6, 9]

	LV mass (g/m²)				
LV geometry	M-mode	2D	3D	RWT	Clinical situations
Normal				<0.42	
Men	≤115	≤102	≤97 (88)[a]		
Women	≤95	≤88	≤90 (78)[a]		
Concentric hypertrophy				>0.42	Pressure overload, HHD, aortic stenosis
Men	>115	>102	>97 (88)[a]		
Women	> 95	>88	>90 (78)[a]		
Eccentric hypertrophy				<0.42	Volume overload, mitral regurgitation
Men	>115	>102	>97 (88)[a]		
Women	>95 g	>88	>90 (78)[a]		
Concentric remodeling				>0.42	Pressure or volume overload, ischemic heart disease
Men	≤115	≤102	≤97 (88)[a]		
Women	≤95	≤88	≤90 (78)[a]		

[a]These values represent the cutoffs for the Japanese population [6]

Table 11.2 Differential diagnosis of LV hypertrophy [12]

Hypertrophic cardiomyopathies
• Sarcomere protein gene mutations
• Inborn errors of metabolism (glycogen storage diseases, AMP-kinase, carnitine disorders, lysosomal storage disease, Anderson-Fabry)
• Neuromuscular diseases (like Friedreich's ataxia)
• Mitochondrial diseases
• Malformation syndromes (Noonan, LEOPARD, Costello, CFC)
• Newborn of diabetic mother
• Drug-induced (tacrolimus, hydroxychloroquine, steroids)
Hypertrophy linked to intense physical training
Hypertrophy secondary to abnormal left ventricular filling conditions
Isolated basal septal hypertrophy of the elderly

11.2.3 Differential Diagnosis of LV Hypertrophy

Left ventricular hypertrophy is a common finding during echocardiography. A precise evaluation of the left ventricular wall thickness, ventricular mass, and distribution of hypertrophy is crucial for diagnostic workup, for follow-up, and for prognostic evaluation.

The differential diagnosis of left ventricular hypertrophy includes hypertrophic cardiomyopathies, hypertrophy secondary to abnormal left ventricular filling conditions, hypertrophy linked to intense physical training, and the isolated basal septal hypertrophy of the elderly [13] (see Table 11.2).

In an adult, hypertrophic cardiomyopathy is defined by a wall thickness ≥15 mm in one or more LV myocardial segments – as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging [CMR], or computed tomography [CT]) – that is not explained solely by loading conditions, and in children, the diagnosis of HCM requires an LV wall thickness

more than two standard deviations greater than the predicted mean (z-score >2, where the z-score is defined as the number of standard deviations from the population mean) [12].

Echocardiography is a reliable diagnostic tool in differentiating the physiologic hypertrophy described in athletes from the pathologic hypertrophy in HHD. In athletes, left ventricular hypertrophy often resembles comorbid conditions; therefore the differential diagnosis is crucial. The E/A evaluation to identify diastolic dysfunction is a good parameter for identifying and differentiating pathological and physiological myocardial hypertrophy [14].

11.3 Evaluation of Left Ventricular Diastolic Function

The development of LV diastolic dysfunction may precede hypertrophy in patients with hypertensive heart disease [15].

Diastolic dysfunction is usually identified during echocardiographic evaluation and may be one of the first abnormalities found in patients with hypertension [15].

A comprehensive evaluation of diastolic dysfunction should include a grading of diastolic dysfunction; nevertheless, more importantly, assessment of LV filling pressure should be included, as increased values have prognostic relevance [16]. When evaluating diastolic function, it is important to take into consideration some clinical data, such as heart rate, blood pressure, and underlying rhythm, as well as the 2D and Doppler findings with respect to LV volumes and wall thickness, EF, left atrial (LA) volume, and severity of mitral valve disease [17].

There are several parameters that have been studied in the evaluation of diastolic function. These include the mitral inflow measurements (E and A velocities, deceleration time, and isovolumic relaxation time) and tissue Doppler measurements which include early diastolic tissue velocity (e').

The most important parameter is the ratio between the transmitral E velocity and the pulsed wave tissue Doppler-derived early diastolic velocity (the E/e' ratio) [16]. The E/e' ratio is very rare over 14 in normal individuals [18]. Other parameters that can be used are the E/A ratio during the Valsalva maneuver and the difference between the duration of mitral A wave and reversal pulmonary vein flow Ar wave [17]. The Valsalva maneuver can help distinguish normal LV filling from pseudonormal filling, as a decrease in E/A ratio of >50%, not caused by E and A velocities fusion, is highly specific for increased LV filling pressures [17]. An increase in pulmonary vein Ar duration versus mitral A duration (Ar-A) is consistent with increased LVEDP and diastolic dysfunction [17]. Pulmonary artery systolic pressure can also be an indicator of increased LV filling pressures, when there is no pulmonary disease associated. The presence of LA dilatation is a reliable index of long-term increased LV pressures [19]. LV hypertrophy, when present, is usually associated with diastolic dysfunction [19].

11.3.1 Evaluation of Diastolic Dysfunction in Patients with Normal EF

This is the most common clinical situation for hypertensive patients.

According to the 2016 Echocardiography Guidelines for left ventricular diastolic function, there are four parameters used to determine the diastolic function [17]:

1. Annular *e* velocity: Septal *e* < 7 cm/s, lateral *e* < 10 cm/s
2. Average *E*/*e*′ ratio > 14
3. LA volume index >34 mL/m^2
4. Peak TR velocity > 2.8 m/s

The LV diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function [17]. LV diastolic dysfunction is present if more than half of the available parameters meet these cut-off values. The study is inconclusive if half of the parameters do not meet the cutoff values (Fig. 11.3) [17].

11.3.2 Evaluation of Diastolic Dysfunction in Patients with Reduced EF

When evaluating patients with reduced EF, mitral inflow measurements correlate with LV filling pressure, functional classes, and prognosis [20].

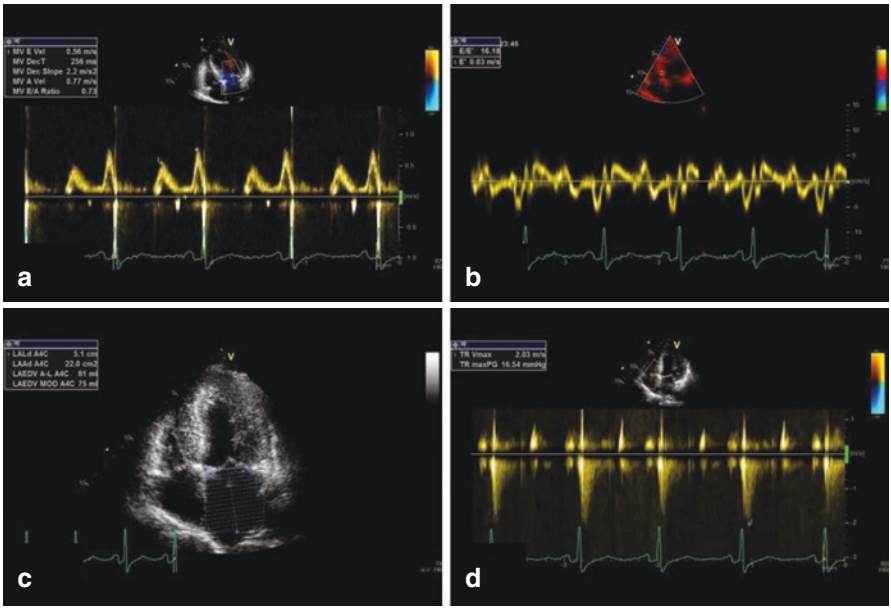

Fig. 11.3 Diastolic function evaluation. (**a**) PW mitral flow velocities; (**b**) tissue Doppler velocities, septal *e* 0.3 m/s, *E*/*e*′ = 14; (**c**) 2D tracing of LA volume; (**d**) peak TR velocity 2 m/s

The recommendations of the latest guidelines for diastolic function evaluation in patients with depressed EFs are:

- If *E*/*A* ratio is <0.8, along with a peak *E* velocity of <50 cm/s, then mean LAP is either normal or low, and the patient has grade I diastolic dysfunction.
- If *E*/*A* ratio is >2, LA mean pressure is elevated, and grade III diastolic dysfunction is present. DT is usually short in patients with HFrEF and restrictive filling pattern (<160 ms) [17].
- *E*/*A* ratio < 0.8, along with a peak *E* velocity of >50 cm/s, or an *E*/*A* ratio > 0.8 but <2, additional parameters are needed, such as the following:
  (A). Peak TR velocity > 2.8 m/s
  (B). *E*/*e* ratio > 14
  (C). LA maximum volume index>34 mL/m^2 [17].

If more than half or all of the variables meet the cutoff values, then LAP is elevated, and grade II diastolic dysfunction is present [17].

If only one of the three available variables meets the cutoff value, then LAP is normal, and grade I diastolic dysfunction is present. If there is a 50% discordance or only one variable is available, the findings to estimate LAP are considered inconclusive [17].

In patients with depressed LVEFs, the pulmonary vein S/D ratio may be used if one of the three main parameters is not available. A ratio < 1 is consistent with increased LAP [17].

In HHD, the course of the disease in general begins with a diastolic dysfunction as a primary modification [11], starting with grade I diastolic dysfunction and later followed by a more severe diastolic dysfunction and chronically increased filling pressures, leading to the development of LV hypertrophy that worsens the diastolic dysfunction further. This leads to LV remodeling with consequent LV systolic dysfunction [6].

11.4 Evaluation of the Left Atrium (LA)

The LA undergoes remodeling in response to an increase in the LV filling pressures, and, therefore, in chronic arterial hypertension, it generally dilates; LA size has been shown to have prognostic value in hypertensive patients [21]. LA dimensions can be performed in the long-axis view (anteroposterior diameter) and four-chamber view; LA is measured at ventricular end-systole when it is at its biggest size. Volume assessment is preferred over linear measurements as the volume is more accurate, especially for the remodeled LA [22]. The LA volume may be estimated by two methods: area-length method or the modified Simpson methods. The LA volume is usually scaled for BSA and expressed in mL/m^2; the normal range is up to and including 34 mL/m^2 [9]. LA enlargement is a well-known independent

determinant of stroke, cardiovascular events, and death [23]. The main reasons for increased LA volume are arterial hypertension and obesity [23].

Apart from the dimensions of LA, its function has been studied based on the assumption that the LA contraction may be altered due to long-standing increased LV filling pressures. But there are a lot of limitations when trying to evaluate the LA function by echocardiography. There are several parameters studied so far, such as the LA strain and the function of the left atrial appendage [16].

11.5 Evaluation of Left Ventricular Systolic Function

Evaluation of the left ventricular systolic function is the fundamental part of echocardiography in hypertensive patients. Although coronary artery disease is the most common cause of left ventricular systolic dysfunction, arterial hypertension is a possible cause of functional impairment of the LV [5].

Standard parameters used in everyday clinical practice for the evaluation of the left ventricular systolic function are fractional shortening, eyeballing of left ventricle function, calculation of ejection fraction using the Simpson method, calculation of stroke volume, cardiac output, cardiac index, contractility measurements using dp/dt, and the Tei index.

11.5.1 Linear Measurements

Theoretically, the LV ejection fraction can be calculated using fractional shortening by the Teichholz formula: EF = (ED volume – ES volume/ED volume) × 100.

This formula relies on the geometric assumptions; however it is not very reliable and is only applicable in patients that have a normal-sized ventricle and normal function; therefore its use in the daily practice has been discontinued [7].

11.5.2 2D Measurements

The left ventricular ejection fraction (LVEF) represents the systolic volume as a percentage of the end-diastolic volume and is calculated with the biplane modified Simpson rule [7]. The biplane method of multiple discs (Simpson's) fared well even with abnormal ventricles and is the only method recommended in the recent (2015) ASE/EACVI guidelines. According to these, LVEFs of >52% for men and > 54% for women, respectively, are suggestive of normal LV systolic function [9]. Limitations for the Simpson method are the difficulty in tracing the endocardial borders, foreshortening of the ventricle, being an approximation of the true volume (because the posterolateral and anteroseptal region is not considered), and the presence of dyssynchrony (it is difficult to time diastole and systole if the ventricle does not contract in all regions at the same time) [24].

11.5.3 3D Measurements

There are many studies that conclude that 3D echo is a superior technique for volume quantification compared to 2D echo, because it is independent of the geometric assumptions [6]. Transthoracic 3D echo provides an accurate method for estimating LV volumes and EF [6]. The main difficulty lies in contouring the endocardium, and this is usually the major pitfall when it comes to using this technology [25–27]. The 3D LV volumes correlate closely with the CMR-derived volumes [26]. Several 3D-echocardiographic techniques became available to measure LV volumes and mass. These can be conceptually divided into two techniques, offline techniques (which permit offline reconstruction from a set of 2D cross section) and online techniques, also known as real-time 3D echocardiography (which permits data acquisition using a matrix array transducer) [7]. Three-dimensional echocardiography does not only incorporate information about the wall motion, but it also provides a lot of functional information. For example, it is possible to combine the strain information with the 3D technique and obtain 3D reconstructions of the strain and notice the strain changes during the cardiac cycle.

11.5.4 Tissue Doppler Assessment of Systolic Function

Longitudinal systolic dysfunction is an independent marker of cardiovascular risk in hypertensive patients. Despite similarity in predictive accuracy, longitudinal indices are more sensitive but less specific than circumferential indices for the prediction of cardiovascular events in these subjects [28]. In patients with newly diagnosed and never-treated mild-to-moderate hypertension, early impairment in longitudinal left ventricular systolic function can be expected despite normal endocardial left ventricular function indicated by M-mode echocardiography [29].

Left ventricular contraction is the result of the complex interaction among differently oriented myocardial layers, which leads to simultaneous longitudinal and circumferential left ventricular shortening during systole. Although longitudinally directed fibers situated mainly in the subepicardium and subendocardium regions of the left and right ventricular free walls and the papillary muscles comprise only a small proportion of the total ventricular myocardial mass, they play a major role in the maintenance of normal ejection fraction and in determining atrioventricular interactions [30]. Not surprisingly, therefore, loss of longitudinal fiber function leads to characteristic disturbances. Echocardiographic determination of left atrioventricular plane displacement (AVPD) by M-mode and measurement of mitral annulus peak systolic velocity (Sm) by tissue Doppler (TD) are reliable methods for assessing the performance of the longitudinal LV fibers, which are mostly distributed within the subendocardium [30, 31].

The main parameter for systolic performance that can be extracted from tissue Doppler evaluation is the S' wave, which can be identified as a wave signal in the direction of the apex and initiated immediately after the QRS complex [6]. Peak mitral annular descent velocity by tissue Doppler imaging has the potential to

rapidly estimate the global LV function [32], and measurements at the septal and lateral side in the apical four-chamber view have proved to produce good results (s′ < 7 cm/s showing 93% sensitivity and 87% specificity to identify patients with LVEF <45%) [6]. Other authors have reported a slightly higher diagnostic power of tissue Doppler imaging with the PWD sample volume placed at the lateral mitral annulus, if an average S' from six mitral annular sites (lateral-medial, inferior, anterior, posterior, and anteroseptal) are recorded; six-site average *S′* of >5.4 cm/s correlates with an EF of >50% with 89% sensitivity and 97% specificity [33].

In the setting of hypertension, tissue Doppler measurements help differentiate physiological left ventricular hypertrophy in athletes from hypertrophic cardiomyopathy and the latter from left ventricular hypertrophy secondary to hypertension [6]. Long-axis systolic and early diastolic velocities are decreased in patients with pathologic hypertrophy, but preserved in athletes. These simple new echocardiographic parameters can differentiate between pathologic and physiologic hypertrophy with a sensitivity of 87% and specificity of 97% [34].

The main drawbacks are the limitations of PWD: angle dependency and its inability to differentiate between the velocity generated by actual myocardial contraction and that produced by translational motion by akinetic myocardial segments when they get pulled by the adjacent normally contracting myocardium [33].

Both longitudinal and circumferential systolic indices are early and sensitive markers of left ventricular systolic dysfunction in hypertensive patients, as a decrease in these indices is often observed in asymptomatic subjects with normal ejection fraction [35]. Impairment of longitudinal function always precedes the depression of LVEF in hypertensive patients and may be a guide to the presence of fibrosis [6].

In hypertensive heart disease, the tissue relaxation velocity (*e*) is reduced compared to normal, but to a much lesser degree than it is in other hypertrophic situations such as hypertrophic cardiomyopathy and infiltrative disorders such as amyloidosis [6].

11.5.5 Assessment of Myocardial Function by Strain

In newly diagnosed and never-treated mild-to-moderate hypertensive patients, early impairment in longitudinal left ventricular systolic function may be documented by strain rate imaging, which is afterload independent, at a time when the other parameters obtained from standard M-mode echocardiographic analysis remain normal [29].

The heart shortens and lengthens in the longitudinal direction, it thickens and thins in the radial direction, and it shortens and lengthens in the circumferential direction. A torsion or wringing motion is also present between the base and apex. When viewed from the apex, the apex rotates counterclockwise, and the base rotates clockwise in systole (twisting), with the opposite motion (untwisting) in diastole. Strain rate and strain are theoretically less susceptible to translational motion and

tethering artifacts and thus may be superior to tissue velocity in depicting regional or global myocardial function [36].

Strain (ε) is the ratio of the difference between the final length (L) and the initial length ($L0$) to that of the initial length after the application of the force for a time duration of Δt. That is, $\varepsilon = L - L0/L0$. The rate at which this happens is the SR, $SR = \varepsilon/\Delta t$. Now, it is obvious that if the distance between two points, moving at different velocities, is shortened, the strain will be a negative (−) value, and if it lengthens, strain will be a positive value [33].

The 2011 ASE/EACVI Expert Consensus on strain concluded that strain is a very important technique which can help transform echocardiography from a subjective to an objective diagnostic tool because we can quantify the strain much more accurately. The first conclusion of the Strain Task Force was to focus on the most important strain parameter which is the global longitudinal strain (GLS), usually assessed by speckle-tracking echocardiography and is calculated with the following formula:

$$\mathrm{GLS\%} = \left(\mathrm{MLs} - \mathrm{MLd}\right) / \mathrm{MLd},$$

where MLs is the myocardial length at end-systole and MLd is the myocardial length at end-diastole [37].

GLS measurements should be made in the three standard apical views and averaged. Measurements should begin with the apical long-axis view to visualize aortic valve closure, using opening and closing clicks of the aortic valve or aortic valve opening and closing on M-mode imaging [7]. Reported normal values of global longitudinal strain vary from −15.9 to −22.1% (mean −19.7%; 95% CI −20.4 to −18.9%) [6].

HF is a common consequence of HHD, and, in the majority of patients, it is related to impaired LV systolic function, which accounts for about half of HF cases [6]. In the beginning, the EF is normal in hypertensive patients.

As stated before, EF is used to differentiate between HFrEF when EF <50% and HFpEF when EF >50%. Two-dimensional strain has been shown to be abnormal in hypertensive patients with normal EF [6] and has prognostic value [6].

11.6 Evaluation of Associated Conditions

11.6.1 Ischemic Heart Disease

Ischemic heart disease (IHD) is frequently associated with HHD. Patients with HHD may develop ischemia even in the absence of epicardial coronary disease, due to the imbalance between coronary flow and the hypertrophied left ventricle; stress echocardiography is an important tool to detect IHD in hypertensive patients. One study run by Fragasso et al. [38] shows that, when compared, stress myocardial perfusion scintigraphy and stress echocardiography had sensitivities of 0.90 and 0.77 and specificities of 0.63 and 0.89, respectively, in detecting

coronary artery disease in hypertensive patients. Coronary flow reserve is also an important parameter to detect coronary stenosis, but in hypertensive patients, it can be modified also by the changes in microcirculation, independent of obstructive coronary disease [16]. Measuring the coronary flow reserve in the left anterior descending artery provides useful information in both hypertensive and normotensive patients; however the specificity was found to be lower in the hypertensive group [39].

11.6.2 The Aorta

Long-standing HHD may lead to enlargement of the thoracic aorta, as well as changes in wall thickness and stiffness. The aorta may be evaluated by echocardiography. By using all the views, there are several segments that can be evaluated: the ascending aorta (between the aortic valve and the pulmonary artery), the aortic arch, the proximal segment of the descending aorta, and a part of the abdominal aorta. Coarctation of the aorta has to be excluded especially in young hypertensive patients. Long-standing increased LV pressures may lead to an increased aortic root diameter, and it has been proven that aortic root dilatation can be considered a useful marker of subclinical left ventricular diastolic dysfunction [11].

11.7 Conclusions and Future Directions

Echocardiography is a diagnostic tool that should be used in all hypertensive patients. It is necessary to identify LV wall thickness and cavity size and calculate LV mass. In patients with hypertension, the type of LV remodeling (concentric remodeling, eccentric hypertrophy, and concentric hypertrophy) is predictive of the incidence of CV events [6]. In every patient with LV hypertrophy, one should consider and exclude other causes, such as hypertrophic cardiomyopathy or Fabry disease, for example.

Along with these measurements, an accurate evaluation of the LV systolic function using the classical parameters and the newer techniques to detect early systolic impairment carries prognostic value. Evaluating the longitudinal strain correlates with the degree of fibrosis and may have prognostic value, as discussed above.

In addition, the diastolic function should be thoroughly evaluated, as well, and, if present, establish the degree of diastolic dysfunction. Diastolic stress testing may be useful to reveal diastolic dysfunction in patients with hypertension and signs of heart failure.

Future directions in assessing patients with hypertension may address additional evaluation of aortic stiffness, central arterial pressure, and novel parameters for the systolic and diastolic function, such as the LV peak untwisting rate or early diastolic suction. Cardiac magnetic resonance imaging may also emerge as a useful investigation tool for hypertensive patients and may prove particularly useful in the differential diagnosis and assessment of the degree of fibrosis.

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The Additive Value of Cardiovascular Magnetic Resonance Imaging in Hypertensive Heart Disease

12

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12.1 Cardiovascular Magnetic Resonance for the Assessment of Hypertensive Heart Disease

Non-invasive imaging plays an important role in the management of the patient with arterial hypertension specifically in the identification of asymptomatic end-organ damage and complications of hypertension, screening for causes of secondary hypertension and risk stratification. The most commonly detected cardiac sequela of hypertension is left ventricular hypertrophy, often first detected on routine electrocardiogram (ECG). Echocardiography is recommended as the first-line imaging modality for the further assessment of suspected hypertensive heart disease (HHD) due to its widespread availability, safety and relatively low cost. Conventional echocardiography is able to quantify the degree of left ventricular hypertrophy (LVH), to assess the left ventricular (LV) systolic and diastolic function and to identify any coexistent valvular pathology. However, in a significant proportion of patients, the quality of imaging is limited by poor acoustic windows. Pharmacological stress echocardiography may aid in the non-invasive diagnosis of ischaemic heart disease, while exercise echocardiography is recommended for the evaluation of patients with heart failure with preserved ejection fraction (HfpEF).

Cardiovascular magnetic resonance (CMR) is an increasingly available imaging modality with several unique properties. CMR offers high-quality functional and morphological information as well as tissue characterization independently of the body habitus, without exposing the patient to ionizing radiation (Table 12.1). In patients with HHD, CMR can offer precise information regarding LV wall thickness,

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Table 12.1 Echocardiography versus cardiovascular magnetic resonance for the assessment of hypertensive heart disease

	Echocardiography	CMR
LV wall thickness measurement	++	+++
LV volumes and systolic function	++	+++
Detection of myocardial fibrosis	–	+++
Assessment of diastolic function	+++	++
Differentiation among LV hypertrophy phenotypes	+	+++[a]
Coexistent valvulopathies	+++	++
Ischaemia detection	+++[b]	+++
Detection of secondary causes of hypertension	+[c]	+++
Dependency on body habitus	+++	+[d]
Availability	+++	++

CMR cardiovascular magnetic resonance, *LV* left ventricle
[a]CMR may help distinguishing among hypertrophic cardiomyopathy, athlete's heart, cardiac amyloidosis, Anderson-Fabry disease and hypertensive heart disease
[b]With stress echocardiography, dependent on body habitus
[c]Echocardiography can diagnose aortic coarctation
[d]Very obese patients cannot fit in the CMR scanner

volumes and function. It can also detect and quantify the degree of myocardial fibrosis which can be useful in diagnosing alternative causes of LVH and aid risk stratification. CMR is recommended in European Society of Cardiology guidelines for the assessment of LV size and mass when echocardiography is technically not feasible and when the detection of fibrosis would have therapeutic consequences [1].

One of the most important indications for CMR is the differentiation of different LVH phenotypes, in particular the distinction of HHD from HCM, athlete's heart and infiltrative disease [2]. Furthermore, CMR provides information on aortic distensibility and can detect secondary causes of arterial hypertension. LGE may identify significant unexpected underlying pathology such as myocardial infarction or infiltration [3, 4]. Moreover, stress perfusion CMR has been shown to have a high diagnostic accuracy for diagnosing coronary artery disease, which frequently coexists in hypertensive patients [5].

12.2 Cardiovascular Magnetic Resonance for the Assessment of Left Ventricular Morphology and Function

Taking into account its excellent image quality, full cardiac coverage and independence of body habitus, CMR is currently considered the reference standard for the quantification of LV volumes and function with intraobserver and interobserver variability of 2.0–7.4% and 3.3–7.7%, respectively [6]. The reproducibility of volumetric assessment particularly in patients with HHD is significantly better using CMR compared to echocardiography [7].

Accurate measurement of LV wall thickness is of high prognostic relevance in the setting of suspected HHD. This can be most reliably achieved from cine CMR images, which allow confident detection of the endocardial and epicardial boundaries and exclusion of myocardial trabeculation. For LV volume assessment by CMR, breath-hold or free breathing cine data sets covering the whole heart are acquired in a stack of thin slices (8–10 mm), typically in the LV short-axis slice orientation and using steady-state free precession (SSFP) sequences. These cine images are characterized by a high spatial resolution and contrast between LV walls and blood pool, allowing for precise contouring of the endocardial and epicardial borders in both systole and diastole using either manual, semiautomated, or increasingly fully automated methods. By summation of the endocardial areas of all the slices at end diastole, the left ventricle end-diastolic volume (LVEDV) can be calculated. The same process is then repeated at end systole to calculate the end systolic volume and, by combining the two, ejection fraction. Left ventricular mass is calculated by subtracting the area of endocardial contours from the area of epicardial contours and summing the areas of all slices. The calculated volume is multiplied by 1.05 to account for the density of myocardium to calculate the LV mass (Fig. 12.1).

Using LV mass and LVEDV, the pattern of remodelling in HHD can be accurately characterized as either concentric (with normal LVEDV) or eccentric (with increased LVEDV). Each of these phenotypes is characterized microscopically by a different ratio between cellular hypertrophy and interstitial fibrosis [6] and thus may have different propensity towards development of diastolic dysfunction, heart failure and other adverse cardiovascular outcomes. Concentric and eccentric LVH are associated with significant intracellular and interstitial expansion, while concentric remodelling is associated with normal intracellular/extracellular myocardial structure [6].

12.3 Detection and Quantification of Focal and Diffuse Myocardial Fibrosis

Hypertensive heart disease is characterized by expansion of both extracellular and intracellular compartments, through interstitial fibrosis and myocardial cellular hypertrophy, respectively (Fig. 12.2). Fibrosis is associated with myocardial stiffening, diastolic followed by systolic dysfunction, heart failure and worse prognosis [8]. Detection and quantification of myocardial fibrosis may help in risk stratification of hypertensive patients and can also be evaluated in the response to therapies.

Generally, myocardial fibrosis can be focal as *replacement fibrosis* or diffuse as *interstitial fibrosis*. The latter is the most typical pattern in HHD, but replacement fibrosis has also been reported. Fibrosis leads to increased myocardial stiffness and subsequent changes in ventricular function, electrical activity and myocardial perfusion that may potentially affect prognosis [9].

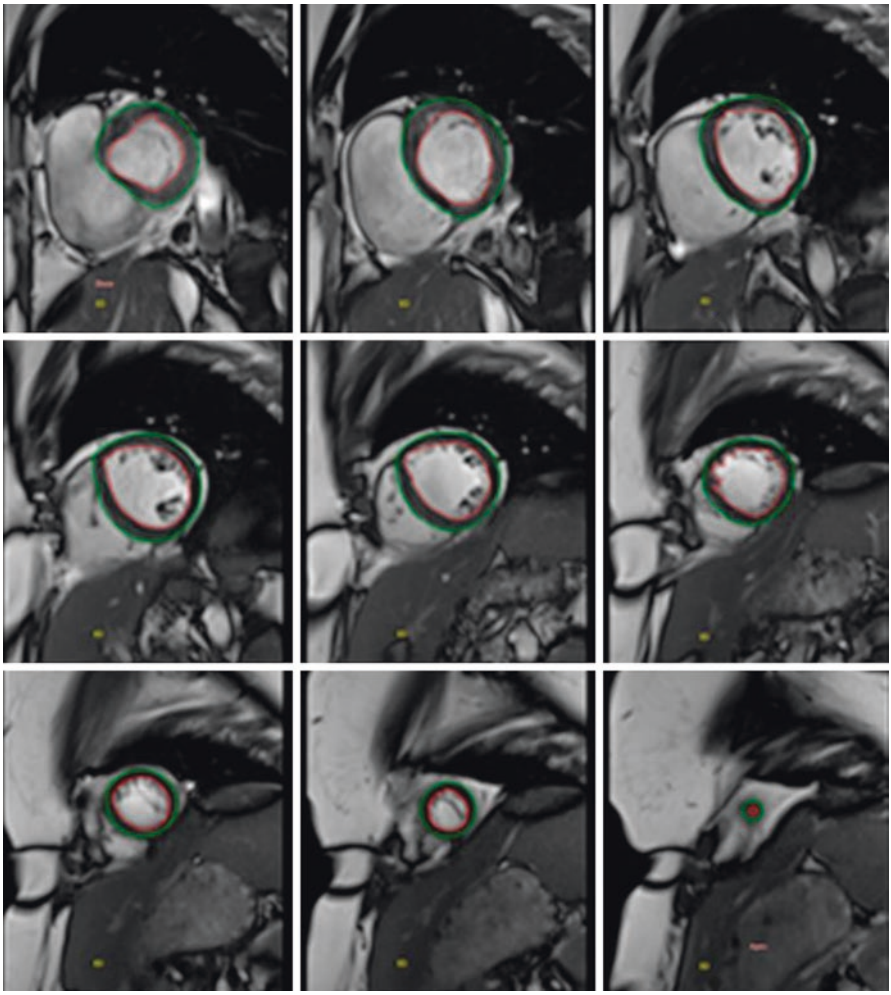

Fig. 12.1 Cardiac magnetic resonance images for left ventricular mass estimation. An example of cardiac magnetic resonance images, highlighting typical endocardial and epicardial border region-of-interest contouring from a set of study images. In this example, a total of nine slices were acquired from the base of the left ventricular myocardium (top left) to the apex (bottom right). *With permission, from* [33]

Detection and quantification of myocardial fibrosis were until recently only possible through invasive endomyocardial biopsy. CMR with gadolinium-based contrast agents allows the detection and quantification of fibrosis. Gadolinium decreases the T1 relaxation time in proportion to its concentration in tissues, meaning that tissues with high gadolinium concentrations will have shorter T1 and they will appear as bright signal intensity on T1-weighted CMR pulse sequences such as inversion recovery methods. Because most gadolinium-based contrast agents are

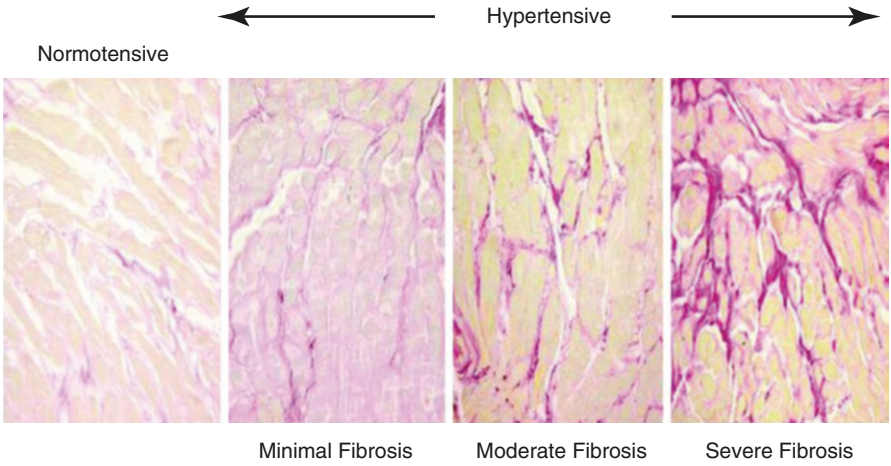

Fig. 12.2 Collagen content in the hearts of a normotensive patient and three patients with hypertensive heart disease. Patients are classified according to the degree of myocardial fibrosis: minimum (left), moderate (centre), and severe (right). Sections are stained with picrosirius red and collagen fibres appear red. *From* [14] *with permission*

extracellular, they accumulate in areas of extracellular expansion due to focal or diffuse fibrosis, increasing signal on T1-weighted images. There are two CMR modalities for assessing myocardial fibrosis: late gadolinium enhancement (LGE) imaging for detection of focal fibrosis and T1 mapping for quantification of diffuse fibrosis.

12.3.1 Late Gadolinium Enhancement

Most gadolinium-based contrast agents are exclusively extracellular and can only passively enter damaged cells with a leaky cell membrane. These contrast agents therefore accumulate in areas with damaged cells and increased extracellular space such as scar or fibrosis. LGE imaging is typically conducted 5–20 min after intravenous administration of the contrast agent, which is the most sensitive period to detect relative retention of contrast agent in areas of scar or fibrosis. Images are acquired with inversion recovery sequence and an inversion time specified to null 'normal' the signal from normal myocardium with scarred myocardium appearing as bright.

The pattern and localization of LGE have a characteristic appearance in several conditions, but in the context of HHD, LGE is patchy and non-specific, without a preferential location. LGE can therefore not be used as a sole criterion for distinguishing HHD from other LVH phenotypes. Focal fibrosis in HHD is usually mid-myocardial and may be localized in the LV free wall or interventricular septum or at the right ventricular insertion points [10]. Importantly, HHD-related focal fibrosis can be easily distinguished from an ischaemic scar, which has a typical subendocardial location, in a specific coronary territory.

Several research studies have demonstrated a high prevalence of scar on LGE CMR in patients with HHD. One study showed a prevalence of focal LGE in 50% of HHD patients, but this study included only a small number of patients [10]. Another study, which assessed the prognostic significance of LGE in hypertensive patients with known or suspected coronary artery disease, reported a prevalence of LGE of 28% [8]. This study showed that LGE was the most important independent predictor for cardiac events in this specific population [8]. However, currently there are no data regarding the prognostic significance of focal fibrosis as detected by LGE in a nonischaemic general hypertensive population.

12.3.2 T1 Mapping

T1 mapping overcomes a limitation of LGE imaging, which relies on nulling the signal from healthy myocardium and on comparing the enhancement of healthy and diseased myocardium qualitatively. When the myocardium is diffusely diseased, LGE may therefore not show any relative abnormalities. The direct measurement of the T1 relaxation time by T1 mapping, however, can be used to make a quantitative assessment of fibrosis in both focal and diffuse disease processes. In T1 mapping CMR, the T1 relaxation time is measured for each pixel of an image returning a quantitative T1 map. These maps can be acquired without contrast (native T1) or following the administration of a gadolinium-based contrast agent (post-contrast T1) [11]. Various techniques exist for quantification of T1 times including modified look-locker inversion recovery (MOLLI), shortened modified look-locker inversion recovery (ShMOLLI) and saturation recovery single-shot acquisition (SASHA) [2]. Native T1 is predominantly influenced by the relaxation of water in both the extracellular and intracellular compartments and is therefore increased in a wide range of conditions including oedema and extracellular fibrosis [12]. T1-shortening gadolinium contrast agents accumulate exclusively in the extracellular space. Therefore if the amount of extracellular space is increased, for example, due to fibrosis, infiltration or scaring, a shorter post-contrast T1 time will be measured. Post-contrast T1 mapping makes assumptions about the kinetics of gadolinium contrast agents, and the results can be influenced by renal function, haematocrit and body composition. These assumptions can be in part overcome by calculation of extracellular volume fraction (ECV), calculated from both native and post-contrast myocardial and blood pool T1, correcting for the haematocrit. ECV is histologically validated as a marker of myocardial fibrosis [13].

In HHD, T1 mapping identifies diffuse myocardial fibrosis, but in a recent report, the increases in ECV were small and only occurred in patients with LVH [4]. It was shown that patients with hypertension and LVH have higher ECV and longer native T1 when compared to hypertensive patients without LVH or control subjects. These findings can be explained by the fact that LVH in HHD is characterized by both extracellular fibrosis and myocardial cell hypertrophy [14] (Fig. 12.2). Furthermore, high native T1 values were associated with a reduction in peak systolic circumferential strain and early diastolic strain rate, a finding consistent with the expected relationship between myocardial fibrosis and function [12]. Of all remodelling

phenotypes, it has been demonstrated that patients with eccentric remodelling have the most fibrosis and greatest impairment of systolic LV function [6].

12.4 Diastolic Function Assessment

Doppler echocardiography is a well-recognized tool for characterization of diastolic function and LV filling pressures. CMR with phase-contrast imaging can also assess diastolic function using the same haemodynamic principles as Doppler echocardiography: flow interrogation across the mitral orifice and in the pulmonary veins as well as tissue velocity assessment. CMR phase-contrast imaging allows for interrogation of flow in the entire cross section of the mitral orifice and pulmonary veins, perpendicular to the major direction of flow, as opposed to pulsed-wave Doppler echocardiography in which flow is interrogated only in a single location. All haemodynamic parameters can be obtained using CMR: E and A waves, deceleration time of E wave and pulmonary diastolic S and D waves, which correlate well with Doppler-derived parameters [15]. Tissue velocities, strain, strain rate and torsion can also be obtained using CMR techniques such as tagging, feature tracking or myocardial phase-contrast imaging returning similar values as those obtained through tissue Doppler imaging (TDI). Some authors reported that diastolic function assessment by CMR can be performed in a single scan, with times ranging from 20 s to 3 min [15]. Severity of myocardial fibrosis by LGE correlates with the degree of diastolic dysfunction [16].

12.5 Detection of Myocardial Ischaemia

Current guidelines suggest that ischaemia testing, including first-pass perfusion CMR, should be considered in patients with hypertension and symptoms suggestive of myocardial ischaemia [1]. In clinical practice stress perfusion CMR can easily be combined with volumetric analysis and LGE imaging in a single scan lasting less than 1 h (Fig. 12.3). Stress perfusion CMR has a high sensitivity and specificity for the detection of significant epicardial coronary stenosis [5], including in patients with hypertension. However it should be noted that hypertension itself leads to

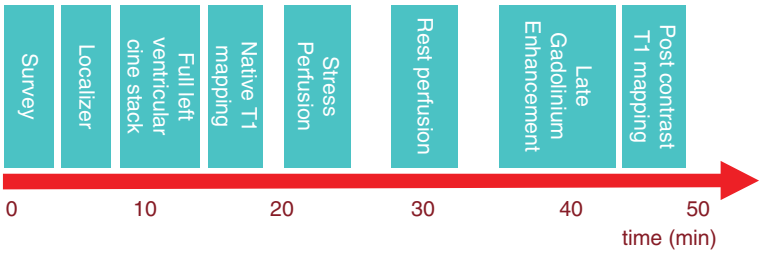

Fig. 12.3 A typical CMR examination for investigation of the patient with hypertension including stress perfusion testing for ischaemia

globally reduction in cardiac vasoreactivity which is attributed to small vessel disease [17].

12.6 Differentiation of Overlapping LVH Phenotypes

As CMR becomes more widely available, it is increasingly used to differentiate HHD from alternative causes of LV hypertrophy including HCM, amyloidosis, Anderson-Fabry disease or athlete's heart. CMR has an important role in differentiating these phenotypes as each of them has very different prognosis and treatment.

12.6.1 Hypertrophic Cardiomyopathy

According to the current guidelines, HCM is defined by the presence of increased LV wall thickness >15 mm in one or more LV segments, in the absence of abnormal loading conditions [18]. CMR is particularly useful in diagnosing HCM as it allows to accurately measure the thickness of all LV segments [19].

In clinical practice, the distinction between HCM and other overlapping LVH phenotypes such as HHD is often challenging, and the guideline criteria may be insufficient. Asymmetric HHD defined as a segmental wall thickness of ≥15 mm and >1.5-fold the opposing wall in ≥1 myocardial segments is a common condition. In a series of 129 carefully selected hypertensive subjects, asymmetric HHD occurred in 21% of cases (HCM or other causes of LVH have been excluded) [20]. In these patients, the maximal wall thickness was exclusively located in the basal or mid-interventricular septum.

It has been shown that in cases with LV wall thickness ≥15 mm, increased indexed LV mass, absence of mid-wall LGE and absence of systolic anterior motion of the mitral valve (SAM) are better CMR discriminators of HHD from HCM than EDWT ≥15 mm [3].

Both replacement and diffuse interstitial fibrosis are associated with HCM and HHD, but replacement fibrosis as identified by LGE is much more frequently encountered in HCM than in HHD patients [10, 12, 20].

Furthermore, native T1 and ECV have higher values in HCM compared to HHD patients [21]. It has been shown that a cut-off septal native T1 of 1100 ms (at 1.5T) accurately discriminates between HCM and HHD (sensitivity 96%, specificity 98%). Similarly, a cut-off ECV of 29% was able to discriminate the two conditions (sensitivity 76% and specificity 71%) [21]. In multivariate analysis, native T1 was identified as the strongest independent discriminator between HCM and HHD, also when controlling for LGE and similar magnitudes of LV wall thickness and LV mass index. Furthermore, carriers of HCM mutations but without LVH also have significantly raised native T1 compared with controls, as well as patients with mild hypertension. These findings may help in diagnosing subclinical disease as well as in distinguishing borderline HCM patients from cases with mild hypertension [21].

12.6.2 Amyloidosis

Biventricular hypertrophy with decreased LV longitudinal contraction associated with pleuropericardial effusion and thickened interatrial septum and atrioventricular valves is suggestive of cardiac amyloid deposition. LGE pattern as well as T1 characteristics may help in differentiation of the infiltrative conditions from HHD. On LGE imaging, cardiac amyloidosis has a distinctive pattern of global diffuse subendocardial hyperenhancement due to non-fibrotic expansion of interstitium, and suppression of 'normal' myocardium and blood/myocardial contrast can be poor [22]. Both native T1 and ECV have typically very high values, due to amyloid protein deposition in the extracellular space [11].

12.6.3 Anderson-Fabry Disease

Anderson-Fabry disease is characterized by an infero-lateral pattern of LGE. Since the disease is characterized by intracellular glycolipid accumulation, the extracellular space is not altered, while native T1 is shortened (T1 relaxation time of fat is short). Thus, LVH associated with short native T1 and normal ECV is highly suggestive of Anderson-Fabry disease [2, 23, 24].

12.6.4 Athlete's Heart

Physiological cardiac remodelling due to intensive physical training can be differentiated from various forms of pathological LV hypertrophy by means of geometric indices derived from CMR. One group showed that a cut-off value for diastolic wall-to-volume ratio of less than 0.15 mm × m^2 × mL(−1) can differentiate athlete's heart from all forms of pathological cardiac hypertrophy with 99% specificity [25]. Using T1 mapping techniques, it has been demonstrated that the increased LV mass in athlete's heart occurs because of an expansion of the cellular compartment, while the extracellular compartment remains relatively static [26]. Thus, ECV might be a useful tool for differentiating HCM from athlete's heart with high ECV suggesting HCM and low ECV suggesting athlete's heart [27].

12.7 Assessment of Secondary Causes of Arterial Hypertension

Magnetic resonance imaging can identify secondary causes of arterial hypertension, such as renovascular hypertension, aortic coarctation, pheochromocytoma or primary hyperaldosteronism. A screening scan for arterial hypertension typically includes imaging of the descending aorta, adrenal imaging and renal imaging and may take up to 50 min [9].

Moreover, CMR can detect subtle myocardial changes linked to pheochromocytoma. It has been shown that patients with pheochromocytoma associate myocardial anomalies which are beyond and distinct from those observed in HHD alone: global mild LV dysfunction, an increased incidence of focal myocardial fibrosis, and large areas of myocarditis. These alterations are most probably secondary to catecholaminergic stress [28].

12.8 CMR in Hypertrophy Regression Studies

CMR is a useful tool to assess LVH regression under various treatments for arterial hypertension primarily because of its excellent interstudy reproducibility. LVH regression on CMR has been reported after medical treatment, after renal denervation or after excision of an adrenal adenoma [9, 29–32]. Moreover it was shown that renal denervation significantly decreases left ventricular mass, while extracellular volume fraction remains stable, suggesting that the observed LV mass decrease was due to both a regression of myocyte hypertrophy and a proportionate decrease in the amount of extracellular matrix [30].

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Biomarkers

13

Maria Dorobantu and Miruna Mihaela Micheu

13.1 Introduction

Heart failure (HF) is a complex syndrome characterized by symptoms and signs caused by different cardiac dysfunctions leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during exercise. The term HF refers only to patients with clinical symptoms excluding the early phases with no clinical expression. The prompt recognition of the abovementioned stage is thus extremely important, enabling timely therapeutic options to be initiated. Thus, strategies to facilitate the early diagnosis are a perpetual quest. One possible key to the previous question could be circulating biomarkers, substances capable to establish the diagnosis and/or prognosis of cardiac dysfunction with high sensitivity and specificity. If in HF with reduced ejection fraction (HFrEF), echocardiography represents a diagnostic investigation at one's fingertips, for HF with preserved ejection fraction (HFpEF), the diagnosis is more challenging and relies mostly on elevated LV pressures at rest or during exercise, and consequently any new biomarker could ease diagnosis and treatment of these patients.

Among the causes of HFpEF, hypertension (HT) is one of the most frequently encountered. If there are various biomarkers for HF in general, specific ones for HF in HT are only few and not well studied. In hypertensive subjects, it is mandatory to assess the subclinical organ damage, but specific biomarkers are essential to

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facilitate the diagnosis of this preclinical phase. But not all biomarkers being evaluated in laboratory settings fulfill the required criteria to be translated into the clinics. Several prerequisites would be mandatory for a biomarker to meet: accuracy and reproducibility of the method, strong associations with the disease pinpointed after multiple studies, and the proof that biomarker-guided treatment really offers certain benefit for the patient [1]. The oncoming importance of the new emerging biomarkers is their inclusion by ACA/AHA in class IIB of recommendations for risk stratification in the management of HF [2, 3].

13.2 Biomarkers

Biomarkers with proven value in HF in HT patients—or being still under evaluation—can be classified in different categories according to the main pathophysiological mechanism which they are linked to. In view of that, these biomarkers are categorized into markers related to fibrosis, inflammation, myocyte stress, and microRNAs. A summary of the most studied biomarkers in each category can be found in Fig. 13.1.

13.2.1 Fibrosis Biomarkers

In fibrosis-related category, the most studied biomarkers are as follows: suppressor of tumorigenicity-2 (ST2), galectin-3 (Gal-3), N-terminal pro-peptide of procollagen type III (PIIINP), tissue inhibitor metalloproteinases (TIMPs), syndecan-1, homocysteine, and resistin.

13.2.1.1 Suppressor of Tumorigenicity-2

ST2 is a receptor of IL-1 family and exists in two isoforms, soluble and transmembranar, exerting its biological effects through IL-33. The attachment of IL-33 to the transmembranar receptor ST2 is cardioprotective as it impedes myocardial fibrosis and cardiomyocyte hypertrophy. Therefore, soluble ST2 exerts its effects by hindering the interaction of transmembranar ST2 to IL-33. Even if the main sources of ST2 are the cardiac fibroblasts and cardiomyocytes in response to injuries, there are also other sources such as endothelial cells that decrease the specificity of the biomarker. The most studied and well-correlated parameter with HFpEF in hypertensive patients is soluble ST2. If the prognostic value of ST2 in acute HF [4] and chronic HFrEF [5] is well established, little is known about its significance in hypertensive patients. Wang et al. showed that it is a reliable biomarker for the presence of HFpEF in hypertensive patients but cannot give additional information about the severity of HF or diastolic function [6]. The levels of ST2 rise in plasma proportionally with diastolic overload [7]. ST2 seems to depend less on age, sex, renal function, or body mass index compared with other biomarkers. Several studies showed better prognostic value of ST2 in HFpEF patients especially with HT as the main HF cause compared with those with reduced LVEF [8]. What is interesting is that

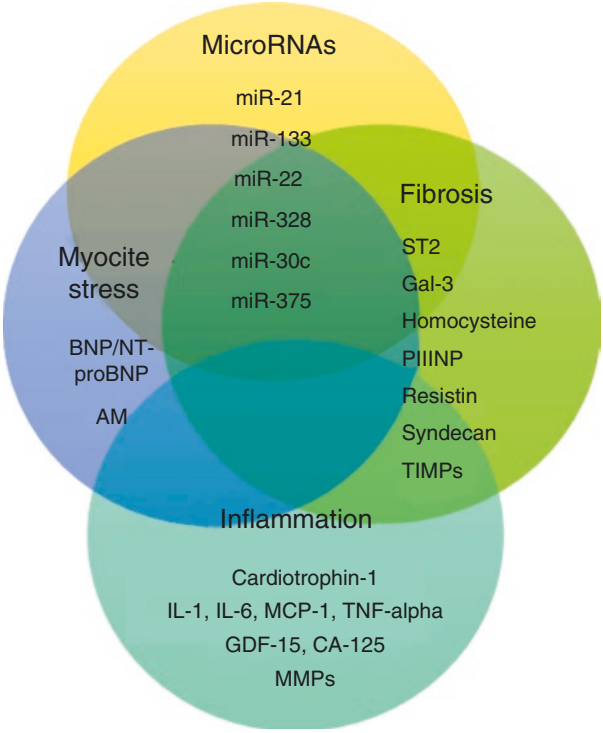

Fig. 13.1 Main pathophysiological mechanism of HF and related biomarkers. *AM* adrenomedullin, *BNP* brain-type natriuretic peptide, *NT-proBNP* N-terminal-pro-brain-type natriuretic peptide, *CA125* cancer antigen-125, *Gal-3* galectine-3, *GDF-15* growth differentiation factor 15, *IL-1* interleukin-1, *IL-6* interleukin-6, *MCP-1* monocyte chemoattractant protein-1, *MMPs* matrix metalloproteinases, *PIIINP* N-terminal pro-peptide of procollagen type III, *ST2* suppressor of tumorigenicity-2, *TIMPs* tissue inhibitor metalloproteinases, *TNF-alpha* tumor necrosis factor-alpha

ST2 was found to be comparable for the prognostic value in both HFpEF and HFrEF in one study that included all causes of HFpEF, but when only hypertensive patients with HFpEF were included, the prognostic value of ST2 improved and correlated with high pulmonary wedge pressures and increased collagen-dependent stiffness [9]. This supports the idea that ST2 is involved in HFpEF development at least by the pro-fibrotic effect in hypertensive subjects.

Evidence gathered from European or North American cohorts endorse ST2 as a cardiovascular prognostic marker in chronic HF [5]. In view of that, the addition of ST2 to a panel of validated risk factors may significantly improve the risk stratification for hospitalization and death in patients with HF. In light of the latest data, the ACA/AHA guidelines recommended the measurement of ST2 for additional risk stratification in HF patients [2, 3].

13.2.1.2 Galectin-3

Gal-3 is a member of the lectin family; these proteins are specialized in the recognition of different carbohydrates via a specific domain called CRD (carbohydrate recognition domain). Galectins are classified into three classes, depending on the number of CRDs: with one CRD (galectins 1, 2, 5, 7, 10, 11, 13–15), two CRDs (galectins 4, 6, 8, 9, and 12), and galectin-3. The latter one is called a "chimera-type galectin" as it also has a non-lectin N-terminal domain connected to CRD. Studies have shown that Gal-3 is found in various tissues such as the lung, spleen, and colon and in lower amounts in the heart, liver, and kidney [10]. A possible role of Gal-3 in myocardial fibrosis has been suggested [11]. Fibroblasts are activated after an increase in the expression of actin alpha and collagen alpha-1, both upregulated after galectin-3 activation [12]. In vitro studies proved that expression of Gal-3 in hypertrophic ventricles correlated with the development of HF [13]. On heart biopsies, Gal-3 is co-localized with activated macrophages. Gal-3 is an independent marker of outcome in HF, and it seems to be more important in patients with HFpEF [14]. It was shown to be increased in chronic HF, but interestingly it has good discrimination value also for the new-onset HF in previous healthy patients [15]. Gal-3 could be measured in asymptomatic individuals to identify fibrosis in early stages, thus allowing the prompt initiation of specific treatment. In a study conducted by van Kimmenade and colleagues, gal-3 serum levels proved to be superior to NT-proBNP in identifying HF patients at risk for short-term death or readmission for HF within 60 days. What is more, Gal-3 in conjunction with NT-proBNP further enhances the predictive value of each biomarker alone [16].

The ability of Gal-3 to predict hospitalization and death in patients with HF (along with soluble ST2 receptor and high-sensitivity cardiac troponin) has been recently acknowledged by the latest North American Guideline for the Management of HF.

13.2.1.3 N-Terminal Pro-peptide of Procollagen Type III

The pathophysiology of HFpEF is overall poorly understood. One possible explanation is an increase in fibrosis that increases ventricular stiffness which highly interferes with filling pressures. Studies show an active fibrosis process related with the installation of diastolic dysfunction and increasing proportionally with the dysfunction [17]. The predominant type of collagen in the myocardium is types I and III—both of these are important in the pathophysiology of fibrosis. Measurement of collagen pro-peptides in blood stream correlates with cardiac remodeling and fibrosis level. A marker with statistically significant values for the early diagnosis of HFpEF in HT is the N-terminal pro-peptide of procollagen type III (PIIINP). Significantly greater serum levels of PIIINP were reported in hypertensive patients having exertional symptoms and in patients with advanced HF compared to asymptomatic hypertensive patients. Within a panel of various biomarkers (NT-proBNP, CT-1, CysC, TNF-alpha, PIIINP, syndecan-4, IL-1R1, TGF-beta 1, and lipocalin-2/NGAL), PIIINP was the only one able to discriminate between control patients and symptomatic patients (either with exertional dyspnea or overt HF) [18]. Similarly, increased concentrations of PIIINP have

been proved to be correlated with LV diastolic dysfunction, LV hypertrophy, and NYHA functional class in hypertensive patients [19, 20]. All these data support the hypothesis that PIIINP might enable the diagnosis of the incipient preclinical phase HFpEF in patients with hypertension and normal resting echocardiography.

HFpEF has been associated with a significant increase in collagen I synthesis, investigated by measurement of PIP (procollagen type I) and collagen III formation, indicated by PIIINP levels (carboxy-terminal pro-peptide of procollagen type III) [21, 22]. It was also proved a rise in the degradation pathway of collagen I, ascertained by the degradation marker type I collagen telopeptide (CITP) [23, 24]. All in all, it was noted a relative increase in the collagen type III/type I ratio, showing relative higher levels of collagen III, associated with increased synthesis and unaltered or decreased degradation. Mainly chronic pressure overload but also other factors stimulate the secretion of collagen synthesis. Elevated left-sided filling pressures in hypertensive patients with normal EF are associated with circulating biomarkers of collagen I metabolism [25]. The accumulation of collagen facilitates abnormalities of cardiac diastolic function as well as contractile impairment [22, 26]. Studies showed that hypertensive patients without HF do not have an increase in passive myocardial stiffness, whereas there is a significant augmentation of myocardial stiffness when diastolic dysfunction develops [27]. There are proofs that major contributors to myocardial stiffness are collagen and titin. Certain titin structural modifications increase stiffness such as phosphorylation on region PEVK S11878 (S26) and reduction of phosphorylation on region N2B S4185 (S469).

13.2.1.4 Syndecan-1

Syndecan-1 is a new marker of fibrosis from the proteoglycan family associated with clinical outcomes in HFpEF, but not in HFrEF; noteworthy, when compared to NT-proBNP, considered the golden standard biomarker for HF at the moment, syndecan-1 showed better risk stratification [28]. It was also showed that syndecan-1 is a marker for endothelial glycocalyx disruption, a process highly implicated in atherothrombosis [29]. Apart from the cardiovascular pathology, high plasmatic syndecan-1 is also associated with renal worsening [30]. A study aiming to develop a better approach to diagnose HF in hypertensive patients showed that high level of syndecan-1 (above 2.3 ng/mL) was a strong predictor of HF [31]. The pathophysiological effect of syndecan-1 is complex and apparently influenced by the context in which it occurs. In myocardial infarction syndecan-1 synthesis is a protective factor that reduces remodeling and systolic dysfunction, whereas in hypertension it induces fibrosis. The disparate functional effect of syndecan-1 may be explained by transforming growth factor (TGF)-β activation that suppresses in the settings of a myocardial infarction, the inflammatory mechanism generated by cardiomyocyte loss, and consequently minimizes the remodeling process, whereas in HT, inflammation is less intense, and AT (angiotensin) II/TGF-β pathway increase promotes fibrosis [32].

13.2.1.5 Homocysteine

Increased levels of homocysteine are associated with an increased risk for cardiovascular diseases. The methionine-homocysteine cycle and its abnormalities are highly related with atherothrombotic events, probably by regulating the redox and methylation reactions. In chronic HF plasmatic levels of homocysteine are increased and related with adverse cardiac remodeling. There is evidence showing hyperhomocysteinemia in patients with HFpEF, but the impact of this on the pathophysiological mechanisms of HF is unknown [33]. Moreover, there is a direct correlation between plasmatic levels of homocysteine and the severity of HFpEF [34]. In hypertensive rats dietary supplementation with homocysteine increases myocardial fibrosis and impairs diastolic function [35]. Even in the absence of hypertension, hyperhomocysteinemia increases myocardial fibrosis and impairs diastolic function. All these effects were not due to hypertension as the diet with homocysteine did not change blood pressure and as modifications were reversible after antioxidant supplementation with vitamins C and E. If in vitro supplementation with antioxidants was beneficial, replicated studies in humans failed to favorably influence cardiovascular risk [36]. Studies showed a prognostic value for homocysteine in HF irrespective of ejection fraction and etiology [37].

13.2.1.6 Resistin

Adipose tissue proved to be an active organ with influences on various tissues. Among the molecules derived from this tissue, apart from lectin and adiponectin, there is a novel molecule—resistin—that is correlated with obesity and insulin resistance but also with HT and HF. Serum resistin levels increase with NYHA class and correlate with high cardiac event rates including cardiac death and progressive HF requiring rehospitalization. However, there was no correlation between the level of resistin and ejection fraction [38]. It could be an appealing marker for damasking occult hypertension in patients without many cardiovascular risk factors depicted by lower levels of adiponectin and increases in resistin [39].

13.2.2 Inflammatory Biomarkers

In the inflammatory category**,** numerous biomarkers were labelled, such as cardiotrophin-1 (CT-1), IL-6, IL-1, monocyte chemoattractant protein-1 (MCP-1), TNF-alpha, growth differentiation factor 15 (GDF-15), matrix metalloproteinases (MMPs), etc.

Uncomplicated HT is not associated with increased inflammation, but when HF symptoms were associated, CT-1, IL-6, MCP-1, GDF-15, and MMPs increased.

13.2.2.1 Cardiotrophin-1

Cardiotrophin-1 is a member of IL-6 superfamily promoting cardiomyocyte hypertrophy by enhancing the transcription of factor NF-kB DNA-binding activity and glycoprotein-130 (GP-130) degradation and further on survival pathway inhibition. In the study of Ravassa and colleagues [40], serum CT-1 was increased in

hypertensive patients compared to normotensives. The association between CT-1 and myocardial systolic function was independent of left ventricular mass even in patients with left ventricular hypertrophy (LVH) or inappropriate left ventricular mass (iLVM). Moreover, there was a significant increase in serum CT-1 in hypertensive patients with LVH or iLVM, especially in those in whom LVH or iLVM was accompanied by impaired myocardial systolic function, as compared to the remaining hypertensive and normotensive patients. One meta-analysis [41] sustains the associations between CT-1 level and HT, cardiac hypertrophy, and HF. The serum levels of CT-1 were significantly higher in patients with LVH or HF compared with controls. Subgroup analysis revealed that CT-1 levels were highest in patients with hypertension-induced hypertrophy and HF while slightly lower in patients with hypertension-induced LVH without HF. Increased plasma CT-1 levels can be a prognosis marker as it is associated with the risk of HF in hypertensive patients.

13.2.2.2 IL-6, IL-1, MCP-1, and TNF-Alpha

Data concerning inflammatory biomarkers such as IL-6 or IL-1 in HFpEF are to a certain extent heterogeneous. While some studies showed increases of IL-6 and CRP in HF regardless of EF [42], others reported lower levels in HFpEF [43]. What can be suggested is that increased inflammation is associated with transformation of asymptomatic HF to a symptomatic condition. In the same way, low-grade inflammation detected by urinary TNF-alpha proved to be correlated with LV hypertrophy in hypertensive patients [44]. Even if TNF-alpha was not extensively studied in the subgroup of hypertensive patients, it has been shown that regardless of EF, elevated TNF-alpha increases mortality [45]. Many of the inflammatory markers are likely to be induced as a response to angiotensin II which is known to be elevated in hypertensive individuals [46].

As regards IL-1, it has become particularly appealing in relation to HF especially since anakinra, a recombinant human IL-1 receptor antagonist, has been granted marketing authorization. D-HART2 (NCT02173548) is an ongoing study that questions the benefit of anakinra on patients with preserved ejection fraction, irrespective of the cause that provoked the HF.

Inflammation turns out to be apparent in the moment there is a target organ affected. High levels of IL-6, MCP-1, and IL-8 appear in the plasma of hypertensives when there are already symptoms of HF [47]. MCP-1 attracts macrophages that once hyperactivated start to release TGF-β, the primum movens in the fibrosis process and diastolic dysfunction [26, 48]. However, what can be imputed to all mentioned inflammation markers is the lack of specificity, many of the medical conditions being accompanied by an inflammatory response.

13.2.2.3 Growth Differentiation Factor 15 and Glycoprotein CA125

GDF-15, an endogenous anti-hypertrophic factor, is consistently associated with important LVH in hypertensive patients and diastolic dysfunction [49]. Glycoprotein CA125 is related with the increase of fluids in the serosal cavities but also with high pressures in the pulmonary capillaries and right atrium [50]. To be noted that glycoprotein CA125 gives information also about the diastolic function, being

inversely correlated with the deceleration time of E wave on transmitral Doppler [51].

13.2.2.4 Matrix Metalloproteinases

The inhibition of TIMPs and increase of MMPs have been associated with HT [27], generating an increase in collagen accumulation. Patients with HFpEF have significant elevations of MMP-2 and MMP-9 compared to those without signs of HF [17, 52]. In more advanced hypertension, when there is also cardiac remodeling, high MMP-9/TIMP1 ratios are signs of myocardium impairment.

Even if each individual marker is valuable in part, panels with multi-biomarkers increase diagnosis discrimination and specificity. One such panel including biomarkers related with collagen homeostasis such as MMP-2, MMP-8, TIMP-4, and PIIINP provides a good positive diagnosis for HFpEF [27]. The proof of a pro-fibrotic status on this multi-panel sustains a poor prognosis in patients where hypertension produced left ventricular hypertrophy and diastolic dysfunction.

13.2.3 Myocyte Stress

Another appealing category of biomarkers to be studied in HFpEF is that reflecting myocyte stress such as natriuretic peptides (NP) and adrenomedullin (AM).

13.2.3.1 Natriuretic Peptides

The most important natriuretic peptides are brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP), atrial natriuretic peptide (ANP), and N-terminal pro-ANP (NT-pro-ANP). ANP and NT-pro-ANP are stored in granules at the atrial level and released into circulation after atrial stretch, high left atrial pressures being the main stimulus for ANP release.

BNP (brain-type natriuretic peptide) and its N-terminal by-product (NT-pro-BNP) are synthesized after an increase in end-diastolic left ventricular pressure or volume. The initial protein, pre-pro-BNP, is cleaved to form pro-BNP. The latter one is then split into NT-pro-BNP and BNP by furin and corin [53, 54]. From these two, only BNP is biologically active. The clearance of BNP is assured by neutral endopeptidases and natriuretic peptide receptor-C, while NT-pro-BNP is removed by organs with high blood flow: the kidney and liver. If many studies investigated and proved the increase of NPs in accordance with systolic dysfunction, fewer trials investigated their potential diagnostic role in the diagnosis of diastolic dysfunction [55, 56]. Circulating levels of natriuretic peptides are elevated in HFpEF but lower in concentrations than in HFrEF. To support the diagnosis of HFpEF, partition values for diagnosis are BNP $\geq$100 pg/mL and NT-proBNP $\geq$800 pg/mL [57]. Pro-BNP is also associated with LV mass index especially with eccentric hypertrophy [58]. Unfortunately natriuretic peptides depend upon a wide range of conditions such as age, sex, obesity, kidney disease, and atrial fibrillation, which make the interpretation extremely difficult notably in elderly individuals having associated

comorbidities. In view of the multiple interfering factors that may influence plasma levels of NPs, the use of these biomarkers should be seen in conjunction with the clinical data and echocardiography, because in mild forms of diastolic dysfunction and HFpEF, NP level can be normal. Twenty years ago, Nishikimi and colleagues investigated the response of three biomarkers (BNP, ANP, and adrenomedullin) in normotensives versus hypertensives at rest but also after exercise [59]. All three biomarkers displayed elevated levels in resting conditions in hypertensive individuals compared with normal subjects. In exercise settings, ANP increased predominantly in hypertensives compared with normal subjects, while BNP level increased only in HT patients; adrenomedullin concentration did not change in either of the two groups.

13.2.3.2 Adrenomedullin

Adrenomedullin is a hormone with the main role to decrease systemic vascular resistance, and comparable with NPs, it induces natriuresis and diuresis. AM is a potent peripheral vasodilator with many pleiotropic effects: positive ionotropic effect and suppression of renin-angiotensin-aldosterone system. It is related with HT, LVH [60], heart failure [61], and AMI but also with non-cardiac conditions such as sepsis or pneumonia. Its plasmatic values increases in patients with HFpEF [62] with no correlation between ejection fraction and the levels of AM [61]. Pro-adrenomedullin produced in equimolar amounts with adrenomedullin and more suited for measurement in practice could also be a prognostic marker because in stable patients with diastolic dysfunction, increased values are associated with higher mortality [63]. This is also a marker of brachial pulse pressure, carotid plaques, and intima-media thickness [64]. It plays an important role also in congestive HF, preliminary preclinical studies showing this could be a potential therapeutic agent in congestive HF, reducing ventricular afterload and increasing cardiac contractility [65].

13.2.4 MicroRNAs

MicroRNAs are small noncoding RNAs with increasing clinical applications as these are posttranscriptional regulators of gene expression. Even if microRNAs have not been included in HF management in daily practice, some specific panels have been identified for differentiation of HFpEF or HFrEF, respectively. A number of molecules have been linked to impaired ejection fraction, such as miR-221, miR-328, miR-30c, and miR-375 [66]. On the other hand, miR-21 and miR-133 levels are higher in patients with hypertension and HFpEF, being correlated with diastolic dysfunction. It has been shown that miR-21 promotes myocardial fibrosis and hypertrophy by upregulation of Bcl-2 [67]. This gives interesting insights into the pathogenesis of HFpEF and opens new therapeutic possibilities [68].

However, the current available data as regards the majority of biomarkers are limited to resting settings. Therefore, their secretion has to be tested also under exertion conditions in order to accurately determine their potential role in making a diagnosis of early HFpEF. An overview of all biomarkers discussed in this chapter as well as their role in the diagnosis and evaluation of hypertensive HF is presented in Table 13.1.

Table 13.1 Biomarkers in hypertensive heart failure with preserved ejection fraction

Category biomarkers	Name of biomarker	Main results	References
Fibrosis biomarkers	ST2	Diagnosis	[4, 5]
		Correlation with increased LVEDP	[7]
		Prognosis marker	[2, 7, 69]
	Gal-3	Diagnosis	[15, 70]
		Prognosis marker	[14, 16]
	PIIINP	Diagnosis	[17, 25, 57]
		Mortality marker	[71]
	TIMPs	Diagnosis	[25, 72]
	Syndecan-1	Diagnosis	[31]
		Prognosis	[28, 30]
	Homocysteine	Diagnosis	[33, 34]
		Prognosis	[36, 37]
	Resistin	Occult HT detection	[39]
		Detection of high- risk patients	[38]
Inflammatory biomarkers	Cardiotrophin-1	Diagnosis	[41]
		Systolic dysfunction detection	[40]
	IL-6	Diagnosis	[42, 43]
		Detect symptomatic HF	[47]
	MCP-1	Diastolic dysfunction	[26, 48]
	TNF-alpha	Mortality risk assessment	[45]
	GDF-15	LVH and diastolic dysfunction	[49]
	CA-125	High pulmonary capillary pressure	[50]
	MMPs	Diastolic dysfunction	[51]
		Diagnostic	[17, 52]
Myocyte stress	BNP/NT-pro-BNP	Diagnostic	[57]
		Left ventricle hypertrophy	[58]
		Guide therapy	[2, 73]
	AM	Diagnosis	[62]
microRNAs	miR-21	Mortality risk assessment	[61, 63]
		Myocardial fibrosis and hypertrophy	[68]
	miR-133	Diagnosis	[67]
		Diastolic dysfunction	[67]

AM adrenomedullin, *BNP* brain-type natriuretic peptide, *NT-pro-BNP* N-terminal-pro-brain-type natriuretic peptide, *CA125* cancer antigen-125, *Gal-3* galactin-3, *GDF-15* growth differentiation factor-15, *IL-6* interleukin-16, *MCP-1* monocyte chemoattractant protein-1, *MMPs* matrix metalloproteinases, *PIIINP* N-terminal pro-peptide of procollagen type III, *ST2* suppressor of tumorigenicity-2, *TIMPs* tissue inhibitor metalloproteinases, *TNF-alpha* tumor necrosis factor-alpha

13.3 Future Directions

The current approach of precise medicine is mainly based on biomarkers able to facilitate diagnosis, prognosis, and patient-tailored management. Profound knowledge of HF pathophysiological mechanisms as depicted by specific biomarkers could provide insights to identify the correct therapeutic targets. Since the pursuit to identify the ideal biomarker to be targeted has not yet come to an end, further research in this field is needed.

Particularly, there are two key issues to be addressed by future studies:

1. Validation of emerging biomarkers by using precise and robust outcomes.
2. Use of multi-biomarker strategies to streamline the risk stratification, diagnosis, and prognosis.

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Part IV

Complications of Hypertensive Heart Disease

Atrial Fibrillation and Other Arrhythmias in Hypertensive Heart Disease

14

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14.1 Introduction

Cardiovascular disease is the leading cause of death worldwide, and arterial hypertension is the most common risk factor for cardiovascular events [1]. The prevalence of hypertension appears to be around 20–50% in the general population, with an increasing trend, directly related to the aging population [2–4]. Hypertensive heart disease is associated with a variety of cardiac arrhythmias, mostly atrial fibrillation (AF).

Arterial hypertension is the most comorbid condition in patients suffering from AF [5]. It has been indicated that arterial hypertension is present in about 60–90% of patients with established AF [6]. Even high-normal blood pressure (BP) is associated with increased incidence of AF [7]. It is estimated that hypertension raises the risk of AF by about twofold [8] and is responsible for 14% of all AF cases [9]. AF represents the most common cardiac arrhythmia affecting approximately 3% of individuals worldwide [10–11]. The prevalence increases up to 10% in the population over 75 years of age [9, 12–13]. AF is considered a major risk factor of stroke, heart failure, sudden death, and overall mortality, as it is associated with a fivefold increase in the risk of stroke, a threefold increase in the risk of heart failure (HF), and a twofold increase in the risk of mortality [14–16].

The presence of hypertension increases the incidence of stroke by threefold annually, and strokes related to AF are more severe [17–20]. The coexistence of hypertension and AF further increases the annual risk of cardiovascular events and especially stroke.

Finally, besides AF, other supraventricular arrhythmias and ventricular arrhythmias may occur in the hypertensive patients, especially in those with left ventricular hypertrophy (LVH).

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14.2 Mechanisms Underlying AF and Other Cardiac Arrhythmias in Hypertensive Heart Disease

Several different procedures may be involved in the arrhythmogenesis in hypertensive patients. There is a complex of hemodynamic changes, neuroendocrine factors, atrial and ventricular structural remodeling, and electrophysiological changes that is thought to contribute to the onset of cardiac arrhythmias [21].

14.2.1 Renin-Angiotensin-Aldosterone System (RAAS)

Hypertension is associated with activation of the renin-angiotensin-aldosterone system [22] which has a key role in the development of AF [23]. It has been demonstrated that angiotensin II induces proliferation of fibroblasts and extracellular matrix and leads to atrial myocyte hypertrophy and fibrosis that predispose to AF occurrence [24]. Also it has been stated that high angiotensin II levels may be proarrhythmic, since they are associated with increased intracellular calcium. It has been shown that angiotensin II increases the intake of extracellular calcium and also the release from the sarcoplasmic reticulum through the activation of membrane L- and T-type calcium channels [25, 26]. In addition, activation of RAAS may lead to inflammation. It has been stated that angiotensin II is related with increased synthesis of growth factors and inflammation mediators like interleukin 6 (IL-6) and therefore promotes inflammation and fibrosis [27], factors predisposing to AF. Aldosterone further exacerbates the inflammatory status, fibrosis, and oxidative stress [28–30] and contributes in atrial structural remodeling and, thus, in increased arrhythmic burden.

14.2.2 Hemodynamic Changes and Remodeling in LA

Increased afterload due to hypertension leads to increased wall thickness of the left ventricle (LV), reduced compliance of the LV, and impairment in the diastolic function. Increased end-diastolic pressure results in enlargement, remodeling, and dysfunction of the left atrium (LA), predisposing to AF. A central role in the remodeling of LA plays atrial cardiomyopathy, which includes fibroblast raise, alterations of extracellular matrix, and hypertrophy of myocytes [31]. Structural remodeling results in disorders of interconnections between muscle bundles, heterogeneity in intra-atrial conduction, unidirectional blocks, and reentry circuits. Moreover, experimental studies have indicated that the consequent distention and stretching of the atrium related to hypertension can alter atrial electrophysiological properties, including shortening of the effective refractory period and increased dispersion of refractoriness, and therefore lead to AF development [32, 33].

14.2.3 Hemodynamic Change Remodeling in LV and Electrophysiological Disturbances

Left ventricular hypertrophy (LVH) is strongly associated with the development of ventricular arrhythmias and sudden cardiac death (SCD) in hypertensive patients. It has been indicated the presence of early after depolarizations and triggered activity that may cause sustained arrhythmias in LVH conditions [34]. Furthermore prolongation and dispersion of repolarization are related to the degree of LVH and increase the risk of ventricular arrhythmias [35–37]. At cellular level, structural remodeling is associated with impaired cell-cell communication at the gap junction and increased susceptibility to ventricular arrhythmias [38]. Myocardial fibrosis in the left ventricle is also part of the structural remodeling process associated with LVH and can lead to reentry ventricular arrhythmias [39].

14.2.4 Myocardial Ischemia

Hypertension and LVH may also cause myocardial ischemia, since LVH is associated with mismatch of oxygen supply and demand. In addition, hypertension and LVH are involved in the decreased diastolic coronary blood flow and the subendocardial ischemia [40]. Moreover, microvascular dysfunction leading to myocardial ischemia has been reported in both prehypertensive and hypertensive patients even in the absence of LVH [41, 42]. The presence of myocardial ischemia may trigger ventricular arrhythmias and SCD.

14.2.5 Neuroendocrine Effects

It has been shown that arterial hypertension and LVH activate an increased adrenergic response by the sympathetic nervous system [43]. Sympathetic activation has been demonstrated that can exert a direct proarrhythmic effect and thus trigger ventricular arrhythmias and cause SCD [44, 45].

Regarding blood pressure measurement in AF patients, current guidelines recommend repeated measurements using the auscultatory method, in order to compensate for the increased beat-to-beat BP variability [46], whereas the accuracy of oscillometric BP method is regarded as questionable [46, 47].

14.3 Hypertension and the Risk of AF

14.3.1 Blood Pressure Levels and the Risk of AF

Several scientific data indicate a strong causal link between arterial hypertension and AF. Moreover, many clinical studies have indicated a direct and linear relation between BP levels and the risk of AF. A 35-year follow-up study that enrolled

healthy middle-aged men showed that baseline systolic BP (SBP) ≥140 mmHg as well as diastolic BP (DBP) ≥80 mmHg were associated with increased incidence of AF [7]. Furthermore, men with upper normal SBP (128–138 mmHg) at entry had 1.50-fold higher risk of developing AF, compared with men with SBP <128 mmHg. Other studies have also documented that high-normal blood pressure is associated with increased incidence of AF. A study that included 5311 participants from the Multi-Ethnic Study of Atherosclerosis with a median follow-up of 5.3 years showed that BP levels considered to characterize the prehypertension status (120–139/80–89 mmHg) were associated with a significant 80% higher risk of AF [48]. Similar findings were obtained from a large-scale study in which 34,221 initially healthy women were followed up for 12.4 years [49]. There was established a strong relation between systolic and diastolic BP levels and AF occurrence. In addition, it was documented that patients with BP levels in the high-normal range (130–139/85–89 mmHg) showed a 28–53% higher risk of incident AF, when compared with women with BP levels <120/65 mmHg. Moreover, it was concluded that SBP and pulse pressure (PP) were better predictors of AF incidence than DBP. This last conclusion comes to an agreement with a post hoc analysis of the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)/TRANSCEND (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) where the risk of AF significantly increased with SBP levels, whereas the impact of DBP levels was not significant [50].

Finally, sleep apnea is known to be associated with the development of AF. It is estimated that 50% of sleep apnea patients are hypertensive [51], and 30% of hypertensive patients also have sleep apnea [52, 53]. Nocturnal arrhythmias, including sinus arrest, second-degree AV block, ventricular premature beats (VPBs), and non-sustained ventricular tachycardia (NSVT), have been reported in up to 50% of sleep apnea patients.

14.3.2 Intensive BP Control and the Risk of AF

In recent years several studies in hypertensive individuals have investigated the impact of intensive BP reduction on the risk of AF. Thomas et al. [54] in a population-based, case-control study of 433 patients pharmacologically treated for hypertension stated that achieved SBP levels of 120–129 mmHg were associated with the lower risk of AF incidence. They also concluded that SBP levels <120 mmHg were associated with an increased risk of incident AF, consistent with a J-curve phenomenon (1.99-fold compared with the reference level of 120–129 mmHg). Similar findings were obtained from the Cardio-Sis trial (Studio Italiano Sugli Effetti Cardiovascolari Del Controllo Della Pressione Arteriosa Sistolica). This trial included treated hypertensive patients in sinus rhythm who were randomly separated into two groups: one with a target of SBP <140 mmHg (usual control group) and another with a target of SBP <130 mmHg (tight control group) in order to investigate any possible difference regarding the incidence of AF between the two groups. After

a median follow-up of 2 years, new AF occurred in 3.8% of patients in the usual control group and 1.8% of patients in the tight control group [55]. Moreover, it has been indicated that achieved SBP ≤130 mmHg is associated with a lower risk of new-onset AF in hypertensive patients with ECG left ventricular hypertrophy [56]. However, further studies are needed (especially in hypertensive patients without LVH) in order to confirm the hypothesis that tight BP control may be protective from new-onset AF and whether a J-curve phenomenon exists between low BP levels and AF occurrence.

14.4 Prognostic Impact of Hypertension in Patients with AF

Recently many AF trials, RELY (Randomized Evaluation of Long-Term Anticoagulation Therapy), ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes), and ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), highlighted the presence of arterial hypertension in 49–90% of individuals with AF [57–60]. Arterial hypertension is a major risk factor for stroke. Uncontrolled high blood pressure levels are associated with increased risk of ischemic stroke as well as intracranial bleeding [61–63]. Coexistence of AF further increases these risks.

In current ESC guidelines for the management of atrial fibrillation, increased BP levels represent a significant risk factor in the CHA_2DS_2-VASc (resting blood pressure >140/90 mmHg) and HAS-BLED (SBP >160 mmHg) score predisposing for thromboembolic and hemorrhagic events [64]. The SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) III and IV trials documented that stroke and systemic embolic events markedly increased at SBP levels of ≥140 in patients with AF, receiving ximelagatran (an oral thrombin inhibitor) [65]. Similarly, in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial that included 18,201 patients with AF, BP levels >140/90 mmHg at any point during the trial were independently associated with a significant higher risk of stroke or systemic embolism [66]. Moreover, a retrospective analysis of the ROCKET AF trial indicated a notable increase in risk of stroke or systemic embolism, for every 10 mmHg elevation in screening SBP [67]. Similar findings were obtained from a substudy of the RELY trial about hypertensive patients with AF, where every 10 mmHg increase in mean BP and SBP was associated with an increase by 6–7% in the risk of stroke [68].

High BP levels are also associated with increased risk of bleeding especially intracranial hemorrhage, in AF patients [69, 70]. In the BAT (Bleeding with Antithrombotic Therapy) study that included 4009 patients taking oral antithrombotic agents for cardiovascular or cerebrovascular diseases, both high SBP and DBP were related to a higher incidence of intracranial hemorrhage [66]. Moreover, in the study the optimal cutoff BP levels for prediction of intracranial hemorrhage were ≥130/81 mmHg [71], which are considered normal.

14.5 Implications of Low BP Targets in AF

It is clear that fine blood pressure regulation is imperative in the prevention of thromboembolism as well as major bleeding in patients with AF [72]. However, the excessive reduction of blood pressure may be deleterious, since it seems that a J-curve phenomenon in blood pressure exists also for patients with atrial fibrillation. A post hoc analysis of 3947 participants with AF from the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial) revealed that BP levels <110/60 mmHg were associated with increased all-cause mortality. In addition, a U-shape relationship was observed between BP levels and all-cause mortality [73]. Moreover, in the ROCKET AF trial, screening SBP levels <115 mmHg were associated with increased all-cause mortality [67].

14.6 Hypertensive Heart Disease and Supraventricular Tachycardia

LVH is a major risk factor for supraventricular arrhythmias. A meta-analysis that included 27,141 patients from several studies [74] stated the fact that in patients with LVH, supraventricular tachycardia (SVT) was significantly more frequent than in patients without LVH (11.1% vs 1.1%). Furthermore, patients with LVH have a 3.4-fold greater risk in developing SVT compared to those without LVH [74].

14.7 Hypertensive Heart Disease and Supraventricular Ectopics

Supraventricular ectopics (SVPBs) occur frequently in hypertensive patients with LVH [75]. SVPBs are also more frequent in patients with non-dipping profile [76] and during recovery from exercise [77]. Patients with excessive SVPBs and LVH are more likely to develop AF [78].

14.8 Hypertensive Heart Disease and Ventricular Arrhythmias

Several studies have shown that hypertensive patients with LVH have an increased frequency of premature ventricular ectopic beats and ventricular arrhythmias [75, 79–82]. Hypertension is a risk factor for SCD (due to ventricular tachycardia and ventricular fibrillation), particularly in the context of increased LV mass [83]. Echocardiographic evidence of LVH has been associated with ventricular arrhythmia, independently of conventional cardiovascular risk factors [79]. The LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study documented that in hypertensive patients with ECG evidence of LVH, increased LV mass index (LVMI) and LVH were associated with a prolonged QT interval and

increased QT dispersion [84]. These relations remained significant after controlling for relevant clinical variables. So, it was concluded that an increased vulnerability to repolarization-related ventricular arrhythmias might in part explain the increased risk of sudden death in hypertensive patients with increased LV mass [84]. In untreated hypertensive patients, non-sustained ventricular arrhythmias were observed in up to 5% of patients during 24-h Holter monitoring [81]. Several findings indicate a reduction in ventricular arrhythmias with optimal blood pressure regulation and regression of LVH by antihypertensive treatment [85, 86]. In addition it has been demonstrated that effective BP control and LVH regression are associated with reduced incidence of SCD [87]. In the LIFE study, absence of in-treatment ECG LV hypertrophy was associated with reduced risk of SCD independently of treatment modality, blood pressure reduction, prevalent coronary heart disease, and other cardiovascular risk factors in hypertensive patients with LVH [87].

14.9 Hypertensive Heart Disease and Bradyarrhythmias

AV conduction disturbances and sinus node dysfunction may occur in hypertensive patients with LVH. Several studies have indicated that LVH is associated with bradyarrhythmias, including complete atrioventricular block and symptomatic sick sinus syndrome [88, 89].

14.10 Conclusions

The presence of arterial hypertension predisposes for the development of various ventricular and supraventricular arrhythmias. Physicians must be alert in order to properly treat and control blood pressure levels in patients with arterial hypertension in order to decrease also the arrhythmic burden of those patients.

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Arterial Hypertension and Flash Pulmonary Edema

15

Roxana Oana Darabont

15.1 Introduction

Cardiogenic pulmonary edema (CPE), also termed hydrostatic or hemodynamic edema, is a particular form of acute heart failure (AHF) characterized by the rapid accumulation of fluid within the lung's interstitial and/or alveolar spaces as a consequence of acutely elevated cardiac filling pressures [1]. CPE occurs often in patients with underlying heart disease, but, in some situations, it can evolve even in the absence of pathologic heart conditions, like primary fluid overload. The main clinical feature of CPE is a severe, potentially fatal, acute respiratory distress.

Flash pulmonary edema (FPE) is a term to describe a dramatic form of CPE with alveolar flooding. It is attributable to an excessive permeability of the pulmonary capillaries induced, on one hand, by the abrupt increase in capillary pressure that characterizes any form of CPE and, on the other hand, by a severe endothelial dysfunction caused by the excessive activation of some neurohumoral systems [2].

There are multiple pathogenic links between arterial hypertension and CPE or FPE. First of all, hypertension is the main modifiable risk factor for heart failure in developed countries [3]. The common pathway of progression from hypertension to heart failure is the concentric left ventricular hypertrophy which can induce symptomatic heart failure with preserved ejection fraction (HFpEF). Heart failure with reduced ejection fraction (HFrEF) can occur in hypertensives through the evolution of left ventricular hypertrophy to dilated cardiac failure or as a direct complication of high blood pressures, with or without an interval myocardial infarction [4]. Both forms of heart failure represent an underlying pathologic feature for CPE or FPE occurrence.

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Moreover, arterial hypertension is an important contributor to AHF, particularly among blacks, women, and those with HFpEF [3]. It can act as a trigger or as an associated and aggravating condition as long as excess afterload is increasing metabolic demands of the heart. Data from registries have shown that 50% of patients with AHF have a systolic blood pressure >140 mmHg at admission [5–7]. In a retrospective series of patients with CPE without severe valvular disease or nonischemic cardiomyopathies, it was found that the mean initial systolic blood pressure was 198 mmHg, confirming that high blood pressure is a common feature in this setting [8].

Not least, renal artery stenosis (RAS) is an important cause of secondary hypertension. Most patients with atherosclerotic renal artery stenosis have LVH and diastolic dysfunction as a consequence of long-lasting uncontrolled hypertension [9]. Abrupt increases in systolic blood pressure, which can occur in this category of patients, can induce FPE, even more so if bilateral renal artery stenosis is present [2].

The reported prevalence of CPE among patients hospitalized for AHF in Europe can be depicted from the most recent registries: 16% in EuroHeart Failure Survey II (EHFS II) [10]; 18.5% in Acute Heart Failure Database (AHEAD) main registry, whether it was de novo AHF or decompensated chronic heart failure [11]; 13.2% in ESC Heart Failure Long-Term (ESC-HF-LT) registry [12]; and 28% in Romanian Acute Heart Failure Syndromes (RO-AHFS) registry [13]. The in-hospital mortality of patients with CPE is approximately 7% [11, 12] with most of the death occurring in day 1 of hospitalization [12].

In this chapter we will describe the mechanisms, etiology, and treatment of patients with CPE, with focus on FPE and on the implication of high blood pressure in the occurrence and evolution of patients presenting with these pathological conditions.

15.2 Pathophysiology

15.2.1 Fluid Transudation

The main pathophysiological feature of CPE is the high pulmonary wedge pressure due to acutely elevated left ventricular filling pressure and/or left atrial pressure**.** The pressure in the pulmonary capillaries is autoregulated by a sphincter that attenuates the transmission of increased pressure from pulmonary arterial vessels to the capillaries. The venous capillaries lack this protective mechanism allowing a direct impact of elevated end-diastolic ventricular pressure and/or high left atrial pressures on the pulmonary vasculature [14].

The variation of pulmonary capillaries pressure with the pressure in the left atrium is expressed by the equation:

$$P_C = \mathrm{LA_P} + \left(P_R \times \mathrm{CO}\right),$$

where:

- P_C is the capillary hydrostatic pressure—normally ~13 mmHg at the arteriolar end and ~6 mmHg at venous end.
- LA_P is the left atrial pressure.
- P_R is the pulmonary vascular resistance.
- CO represents the cardiac output [2].

This anomaly is induced mainly by left ventricular dysfunction and/or valvular diseases and more rarely only by volume overload. The "backward failure" theory was firstly hypothesized by James Hope: if a ventricle is unable to discharge its contents, blood accumulates and pressure rises in the left atrium and the related venous system [15]. It is worth noting that CPE and FPE, as clinical forms of AHF, can occur with the development of a newly arisen heart disease or as the manifestation of an acute decompensated chronic heart failure. According to the EuroHeart Failure Survey II, two-thirds of all patients admitted to a hospital with AHF already have a known history of heart failure [10]. Approximately half of all patients with AHF have preserved ejection fraction [16, 17].

Fluid balance between the interstitium and the vascular bed is dictated by the Starling equation:

$$\begin{aligned}\text{Net filtration} &= K_f \times \left(\Delta \text{hydrostatic pressure} - \Delta \text{oncotic pressure}\right) \\ &= K_f \times \left[\left(P_c - P_i\right) - \sigma\left(\Pi_c - \Pi_i\right)\right],\end{aligned}$$

where:

- K_f is the filtration coefficient = L_p (hydraulic conductivity) × S (surface area available for fluid movement).
- P_c and P_i are the capillary and interstitial hydrostatic pressures.
- Π_c and Π_i are the capillary and the interstitial fluid oncotic pressures (the interstitial oncotic pressure is derived primarily from filtered plasma protein and to a lesser degree to proteoglycans in the interstitium).
- σ is the reflection coefficient of proteins across the capillary wall [18].

In normal microvessels, there is ongoing filtration of a small amount of low protein liquid. In CPE, the increase in transcapillary filtration is generally attributed to the elevation of pulmonary capillary pressure. Mild elevations of left atrial pressure (18–25 mmHg) cause edema in the perimicrovascular and peribronchovascular interstitial spaces. With higher left atrial pressures (>25 mmHg), edema fluid invades the lung epithelium [19]. Recent years, it was more and more considered that, in some special forms of CPE, as FPE, the permeability of the capillary wall is concomitantly affected [2]. The presence of fluid in pulmonary interstitium and alveoli decreases the diffusing capacity for gas exchanges and develops

hypoventilation with consequently hypoxemia and hypercapnia. This condition is able to aggravate, in his turn, the myocardial dysfunction.

Due to the abrupt and severe pathogenic conditions that characterize CPE, compensatory mechanisms are strongly activated, particularly renin-angiotensin system and sympathetic nervous system, which can induce increased afterload through vasoconstriction and tachycardia. The augmentation of afterload and tachycardia are increasing the metabolic demands of the myocardium. In addition, tachycardia shortens the diastole, more precisely the time for left ventricular filling. Accordingly, both deleterious effects can amplify the rise of pulmonary capillary pressures (Fig. 15.1). Local tissue-based renin-angiotensin system could have an important contribution to lung injury through upregulation of sodium and water transport to the alveolar space with subsequently impaired pulmonary gas exchange and worsening hypoxemia [20, 21]. Endothelin (ET)-1 is also implicated in the pathogenesis of CPE, especially in cases without ischemia, arrhythmia, or mechanical cardiac abnormalities [22]. Endothelin is able to increase pulmonary capillary permeability and, through the activation of ET-B receptor, to impair alveolar clearance by inhibiting the amiloride-sensitive epithelial sodium channel [23, 24].

15.2.2 Role of Lymphatics

The capacity of lymphatics to remove the excess of interstitial fluid varies from patient to patient, but mostly with the duration of the disease. Patients with persistently elevated capillary wedge pressure have increased lymphatic-driven fluid clearance based on adaptive dilatation and muscularization and, therefore, do

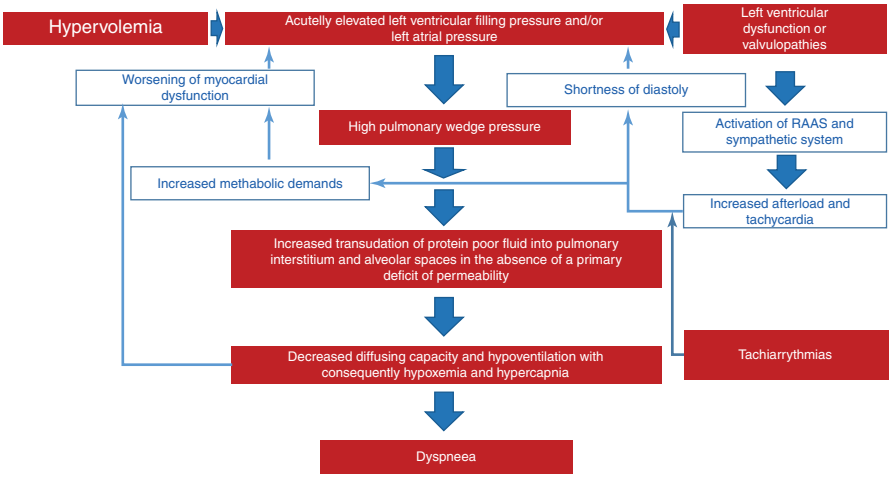

Fig. 15.1 Pathophysiology of cardiogenic pulmonary edema (*RAAS* renin-angiotensin-aldosterone system)

not develop CPE until significantly higher pulmonary capillary pressures are reached [25].

15.2.3 Pulmonary Capillary Stress Failure

Although high capillary wedge pressure is the hallmark of cardiogenic pulmonary edema in comparison with noncardiogenic pulmonary edema (increased permeability pulmonary edema, acute lung injury, or acute respiratory distress syndrome), experimental studies have indicated that severe elevation in pulmonary capillary pressure can lead to increased permeability of the capillary wall and stress failure of the blood-gas barrier. The first description of microscopic changes at the level of blood-gas barrier was based on the experimental model of West et al. [26]. It has been shown also that the breaks in endothelium and epithelium layers depend on the level of capillary pressure increase [27]. In these cases, the resulting edema fluid has a higher concentration of protein than would be expected in conventional CPE [2]. It is understandable that pulmonary capillary stress failure is a feature characteristic for de novo AHF, and it is particularly involved in the occurrence of FPE, although it has been associated also with high-altitude, neurogenic, scuba diving pulmonary edema or pulmonary edema induced by strenuous exercise [2, 28]. Moreover, the disruptions of blood-gas barrier have been proven to be rapidly reversible, in concordance with the fast recovery in FPE after the reduction of pulmonary vascular pressure [29].

Defense mechanisms consisting in alveolar fibrosis or thickening of the alveolar epithelial cell basement membrane can develop in chronically elevated pulmonary venous pressure. At the same time, intimal fibrosis and thickening of the vessel walls can be found at the capillary level [30]. The natural history of severe mitral stenosis is a typical example of pulmonary vascular adaptation in time to pulmonary venous hypertension. In line with this phenomenon is the change in clinical expression of the disease: from recurrent episodes of pulmonary edema to pulmonary hypertension and right ventricular failure [31].

15.2.4 Redistribution of the Venous Reservoir

Total blood volume is composed of *effective circulatory volume* (stressed volume) which is distributed mainly in the arterial system and nonsplanchnic venous vessels and *the venous reservoir* which is cantoned in splanchnic veins and are characterized by a higher compliance in comparison with veins of the extremities or arteries [32].

The splanchnic veins have in their media five times the numbers of α_1- and α_2-adrenergic receptors than the arteries, and, for a given sympathetic stimulus, the capacitance veins respond faster and stronger than other vascular segments [33]. Therefore, the sympathetic activation can increase the effective circulatory volume through mobilization of blood from splanchnic venous reservoir to the effective

circulatory volume, and it is estimated that up to 800 mL of blood can be translocated within seconds [34].

Burkhoff and Tyberg were the first to consider this volume shift as a possible underlying mechanism in AHF [35]. Afterward, a series of clinical trials conducted in patients with heart failure, followed up for cardiac filling pressures with implantable hemodynamic monitors, have confirmed that early stages of congestion in AHF can occur in the absence of weight gain or even precede it [36–40], and the explanation for this paradox could consist in the autonomically mediated blood drive between the venous reservoir and the effective circulatory volume [41]. Chronic heart failure evolves with an excessive sympathetic activation developed as a main compensatory mechanism and amplified by the deficit of cardiopulmonary baroreflexes.

Although this mechanisms were analyzed mostly in correlation with acute decompensation of chronic heart failure, it is hypothesized that the sympathetic activation and recruitment of blood from venous reservoir can be encountered also in CPE and FPE, with rapid and dramatic increase in effective circulatory volume, augmentation of left ventricle and left atrial filling pressures, and severe rise in pulmonary capillary pressures. This last condition may amplify, in cascade, the sympathetic drive, as long as elevations in pulmonary pressures maintain the sympatho-excitatory state through pulmonary afferents [42].

15.2.5 The Ventricular-Vascular Coupling

The main functions of a normal ventricular-vascular interaction consist in the transport of blood to different organs and the buffering of systolic blood pressure while maintaining non-pulsatile diastolic flow. Arterial stiffening is a process that affects the great vessels during vascular aging, but it can be accelerated by diabetes mellitus, renal disease, and, mostly, chronic hypertension [43]. Arterial stiffening of the elastic arteries and muscle hypertrophy in small-caliber arterioles are responsible for the decrease of vascular compliance and for the progressive rise of resistance to forward flow from the left ventricle. In order to maintain the coupling relationship and to dissipate the intramural tension, the left ventricle adapts through hypertrophic remodeling and becomes less compliant. Consequently, in this non-compliant state could occur an exaggerated pressure response to small volume increases [44]. This background is specific for patients with a long history of hypertension. The acute heart failure, including the severe manifestation with pulmonary edema, can be triggered by acute sympathetic drive: metaboreflex activation from exertion, sympathomimetic substance abuse (e.g., cocaine or amphetamine), an abrupt rebound of sympatholytic medication, or psychosocial stress [44, 45]. These conditions are inducing strong peripheral vasoconstriction with sudden rise of afterload, associated with a rapid redistribution of venous reservoir and increased preload, both effects being hardly tolerated by a non-compliant ventricular-vascular system [46].

15.2.6 The Right Ventricle

Regardless of the pathological conditions which are associated with the decrease of left ventricular stroke volume, an acute increase in pulmonary capillary pressure can only arise if an additional input of pressure energy is generated by an overstimulated right ventricle [47].

The sympathetic overdrive triggered by the failing left ventricle will stimulate also the myocardium of the right ventricle, directly and through Frank-Starling mechanism induced by the translocation of splanchnic venous reservoir. The main consequences of this process are the augmentation of pulmonary capillary with further transudation of fluid in the interstitium of the lungs and an increase of left atrial pressure. Due to the rise of interstitial hydrostatic pressure, a lot of pulmonary capillaries will collapse, and the pulmonary flow will be redistributed to the patent capillaries. Therefore, the left ventricular filling and stroke volume can decrease even more, a process partially counterbalanced by the rise of left atrial pressure in the context of an increased contractility of the right ventricle. This discrepancy between the stroke volume of the right and left ventricle is currently recognized as left-right flow mismatch [48].

15.3 Etiology: The Multifaceted Contribution of Arterial Hypertension

AHF is a syndrome, with heterogeneous etiologies and pathophysiologic conditions. Along with the understanding of this concept, the clinical classification of patients with AHF is an evolving process. Currently, the most important distinction is made between firstly occurred (de novo) AHF and acutely decompensated chronic heart failure [49, 50]. The primary cardiac dysfunction is mostly encountered in de novo AHF, while the precipitant factors are contributing more often to the aggravation of a preexisting heart failure consisting in ischemic or hypertensive heart disease, valvular diseases, or cardiomyopathies. Accordingly, we have preferred to present in this chapter the etiology proposed by Hummel et al. [51], adapted after the 2012 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [52]:

- Events with acute clinical deterioration.
  - Coronary heart disease: acute coronary syndromes and mechanical complications of acute coronary syndromes, e.g., ventricular-septal defect, acute mitral insufficiency, and right heart infarct
  - Valvular diseases
  - Myocarditis: acute myocarditis, peripartal cardiomyopathy
  - Hypertension/arrhythmia: hypertensive crisis, tachycardia, or severe bradycardia
  - Circulatory failure: acute pulmonary embolism, pericardial tamponade, aortic dissection
  - Surgical interventions and perioperative complications

- Events with delayed clinical deterioration
  - Infections, e.g., endocarditis
  - Acute exacerbation of chronic obstructive pulmonary disease/asthma
  - Anemia
  - Worsening of renal failure
  - Inadequate fluid and salt intake and non-compliance with prescribed medication
  - Drug side effects and interactions, e.g., nonsteroidal anti-inflammatory drugs and corticosteroids
  - Uncontrolled arterial hypertension
  - Hypo- or hyperthyroidism
  - Alcohol and drug abuse

A similar classification can be applied to CPE which can also occur as a first manifestation of heart failure due to an acute clinical event or as a severe deterioration of a chronic heart failure. FPE evolves with highest probability in the context of acute clinical events, despite the possibility of a previous subclinical organ damage.

The pathogenic links of arterial hypertension with CPE have been briefly described in the introduction to this chapter. Hypertension is the main modifiable risk factor for heart failure [3]. High blood pressure values are recorded in almost 50% of patients with CPE [5–8]. Not in all of these cases hypertension is the primary cause of the event but rather an associate and aggravating condition, except for "hypertensive pulmonary edema." Usually patients presenting with this condition have a long history of uncontrolled arterial hypertension, with left ventricular hypertrophy and preserved ejection fraction. The most probably precipitating factor is an abrupt and severe rise in blood pressure, with or without tachyarrhythmia. Sudden onset of atrial fibrillation can have deleterious effects not only through high ventricular rate but also due to the exclusion of left atrial pump from left ventricular filling. Other specific triggers can be strenuous exercise, hypervolemia, or even psychosocial stress. Signs of myocardial ischemia are lacking, and the clinical evolution is typical for FPE: sudden and severe flooding of pulmonary alveolar spaces, with rapid recovery after onset of treatment with vasodilators and diuretics [53]. The underling mechanisms of hypertensive pulmonary edema are synthetized in Fig. 15.2. Hypertensive cardiopathy is associated with reduced compliance and decreased myocardial strain of the left ventricle [54]. In front of a strong vasoconstriction which increases afterload, a left ventricle with previously reduced myocardial strain fails to increase stroke volume. This effect has two consequences: the stimulation of sympathetic activity and the abrupt rise in left ventricular filling pressures and in the left atrium. This severe backward rise in pulmonary capillary pressure is inducing, beyond transudation in the pulmonary interstitium, a high permeability of the blood-gas barrier (pulmonary capillary failure) with alveolar invasion of a protein-enriched fluid. The harmful effect of the hydrostatic pressure is augmented by some neurohumoral systems, the sympathetic system, the renin-angiotensin system, and the endothelin system, or by vasopressin which can increase the systemic vascular resistance, concomitantly with an antidiuretic effect [20–24,

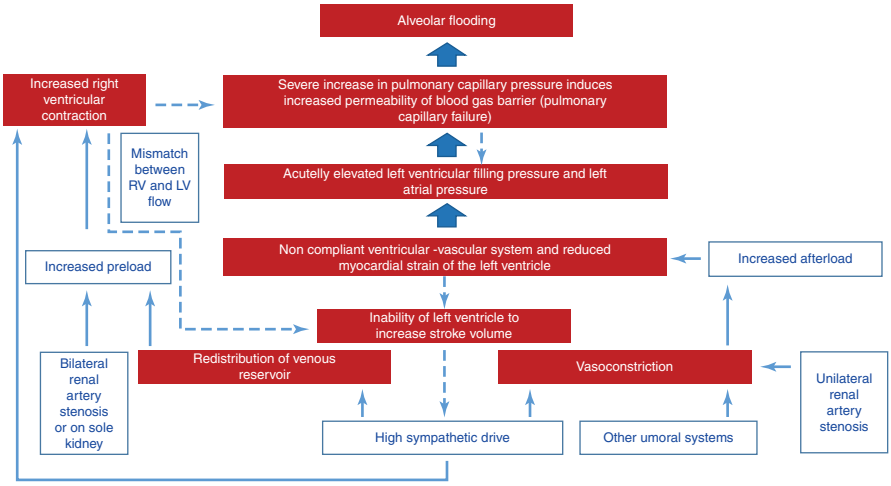

Fig. 15.2 Pathophysiology of flash pulmonary edema (*LV* left ventricle, *RV* right ventricle)

27, 55]. The sympathetic activation, driven especially to increase the myocardial contractility of the left ventricle, generates effects on the right ventricle as well. The myocardium of the right ventricle will increase its contractility through an additional Frank-Starling mechanism, favored by the overload resulted from the splanchnic reservoir translocation [47, 48]. Altogether, these adaptive processes will conduct to a mismatch between right and left ventricle stroke volume.

The evaluation of a series of patients with hypertensive pulmonary edema is sustaining the abovementioned hypothesis. Gandhi et al. have found that the ejection fraction of the left ventricle was preserved during the acute episode of pulmonary edema and similar to the one after treatment, suggesting that the edema was due to an exacerbation of the diastolic dysfunction by hypertension, not to a transient systolic dysfunction or mitral regurgitation [56]. Later on, Charoenpanichkit et al. have revealed that, in patients without inducible ischemia at dobutamine stress test, the failure to increase left ventricular stroke volume or the lack of aortic distensibility evaluated through cardiovascular magnetic resonance is associated with risk of subsequent pulmonary edema [57]. Nevertheless, Margulescu et al. have evaluated 44 consecutive patients by transthoracic echocardiography during pulmonary edema and after 48–92 h. Patients with hypertensive pulmonary edema proved to have worse ventricular-arterial coupling, longitudinal systolic function, estimated diastolic stiffness, and filling pressures compared to asymptomatic controls, indicating a decreased capacity to adapt to changes in loading [58].

One specific connection between arterial hypertension and CPE is represented by the atherosclerotic RAS (potentially significant if induces >50% reduction in lumen diameter). Hemodynamically significant RAS can critically decrease the perfusion pressure of the kidneys that triggers the activation of renin-angiotensin-aldosterone system with two possible consequences: the development of renovascular

hypertension and of the ischemic nephropathy. The association of bilateral or on sole functional kidney RAS with CPE was first reported by Pickering et al. in 1988, in hypertensive patients with azotemia in which revascularization proved to prevent CPE reoccurrence [59]. Subsequent data confirmed this initial observation, and higher rates of CPE were reported in bilateral or on sole functional kidney RAS compared with unilateral RAS [60–62]. In 2011, Messerli et al. advanced the designation of "Pickering syndrome" for FPE in patients with bilateral or on sole functional kidney RAS. In the same publication, the weighted prevalence of FPE was estimated at 14.3% for bilateral or on sole functional kidney RAS and at 3.5% for unilateral RAS [63]. Starting with the experimental model of Goldblatt, it is recognized that patients with bilateral or on sole functional kidney RAS are evolving with intravascular volume expansion due to impaired natriuresis [64]. Unilateral RAS is characterized by another hemodynamic pattern consisting in the activation of neurohumoral pathways, like renin-angiotensin system or sympathetic nervous system, able to promote severe forms of arterial hypertension with important remodeling of cardiovascular system [65–67].

Further trials should clarify an important issue: the association of hypertensive pulmonary edema with coronary artery disease which was not systematically evaluated until present. In AHEAD main registry, coronary angiography findings at discharge of patients with AHF were available only in 62.6% of cases [11]. There are no specific data about patients with CPE or FPE, except for those with Pickering syndrome for whom a rate of 58% was reported for a concomitant coronary artery disease [63].

15.4 Therapeutic Considerations

In this chapter we have focused on the pathogenic links of arterial hypertension with CPE. Therefore, we did not address the clinical presentation, the diagnostic approach, and the current recommendations for treatment of hypertensive pulmonary edema which are presented in this book in the section of hypertensive emergencies.

We are underlining here only the treatment specificities in FPE compared with CPE and the current guidelines and indications of renal revascularization in regard with FPE associated with RAS.

In patients with hypertensive pulmonary edema and clinical feature of FPE, it becomes more appropriate to rapidly set up the administration of vasodilators, as long as the treatment target must be the rapid reduction of vasoconstriction, and not of hypervolemia. Diuretics should be associated, but they are not a cornerstone in FPE treatment, like in chronic heart failure with hydrosaline retention [49].

The over debated issue of revascularization in RAS is synthetized in 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Disease in collaboration with the European Society for Vascular Surgery (ESVS). In regard to congestive heart failure and pulmonary edema, there is a class IIb recommendation (meaning that it may be considered) with C level of evidence (consensus of opinion of the expert and/or small studies, retrospective studies, registries):

balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained congestive heart failure and sudden pulmonary edema [68]. In SCAI criteria for peripheral arterial interventions, renal revascularization is considered appropriate for cardiac disturbance syndromes (flash pulmonary edema or acute coronary syndromes) in patients with hypertension and moderate RAS with a resting mean translesional gradient of ≥10 mmHg and/or severe RAS [69].

15.5 Conclusions

Arterial hypertension is a common triggering or aggravating factor for many etiologic forms of CPE as long as it is recognized that evolves frequently with important increases of blood pressure values. However, a particular feature of CPE surnamed "hypertensive pulmonary edema" can be attributed to high blood pressure as the primary cause of the event. On the one hand, it occurs in patients with a long history of uncontrolled hypertension and important remodeling of cardiovascular system conducting to a non-compliant state of the left ventricle and elastic arteries. On the other hand, it is induced usually by an abrupt and severe rise in blood pressure, mediated by neurohumoral systems. Signs of myocardial ischemia are lacking, the ejection fraction of the left ventricle is usually preserved, and the clinical evolution is typical for FPE, sudden and severe flooding of pulmonary alveolar spaces, with rapid recovery after onset of treatment. Therapeutic goals of this emergency must focus on vasodilatation and tachyarrhythmia control, in order to diminish afterload and increase the time for diastolic filling of the left ventricle. By contrast, in the so-called Pickering syndrome consisting in the occurrence of FPE in patients with bilateral or on sole functional kidney renal artery stenosis, the main pathological feature is the volume overload. Revascularization of atherosclerotic renal artery stenosis is still controversial, but current guidelines are considering that it can be considered an appropriate therapeutic solution for the prevention of FPE recurrences in patients with "Pickering syndrome."

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16 The Role of Drug Therapy in Lowering Mortality and Morbidity: From Established Heart Failure to High-Risk Hypertension

Nisha Mistry, Sverre E. Kjeldsen, and Arne Westheim

16.1 Introduction

Hypertension, untreated or insufficiently treated, is the most important cause of the development of left ventricular hypertrophy, coronary heart disease, myocardial infarction, arrhythmias, and eventually cardiac failure [1] (Fig. 16.1). Traditionally we divide heart failure into patients with reduced ejection fraction (HFrEF) and patients with preserved EF (HFpEF). In patients with HFrEF, angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), beta-blockers (β-blockers), and aldosterone antagonists now termed mineralocorticoid receptor antagonists (MRAs) are all well-established treatment with reduction of morbidity and mortality. Use of diuretics is important to reduce symptoms.

In patients with HFpEF, no treatment has specifically been shown to reduce morbidity and mortality. However, the agents used in the treatment of HFpEF, including diuretics and various calcium antagonists, may also be indicated in the treatment of patients with HFpEF due to comorbidities as hypertension, left ventricular hypertrophy, atrial fibrillation, and coronary artery disease.

Optimally, heart failure, like all other hypertensive complications, should be prevented by medical treatment, and in this aspect all the classes of antihypertensive drugs are effective. The various drug classes that may be choices for treatment or prevention of heart failure are summarized in Table 16.1 together with their mechanisms of action.

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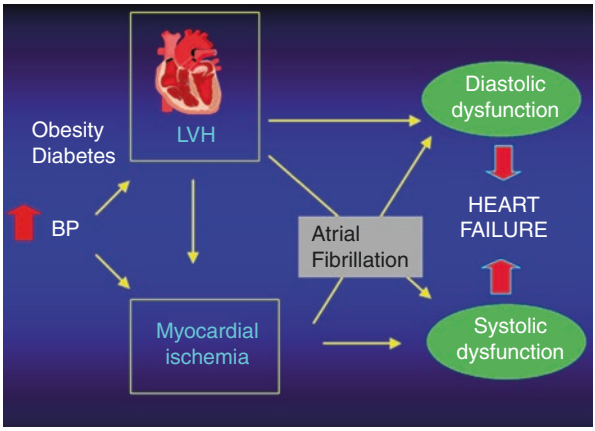

Fig. 16.1 Schematic illustration of how high blood pressure (BP) may lead to heart failure through development of left ventricular hypertrophy (LVH), myocardial ischemia, and/or arrhythmia like atrial fibrillation. Approximately half of the patients develop heart failure with preserved ejection fraction (HFpEF, diastolic dysfunction), and approximately half of the patients develop heart failure with reduced ejection fraction (HFrEF, systolic dysfunction). Structural and functional differences between HFpEF and HFrEF as well as diagnostic methods with echocardiography are explained elsewhere [55]

Table 16.1 Mechanisms for how different drug classes can improve the heart's function in HFpEF

ACE inhibitors and angiotensin receptor blockers (ARBs): Reduces or inhibits adverse effects of angiotensin II, reduces peripheral vascular resistance and arterial blood pressure, promotes regression of cardiac hypertrophy and adverse remodeling first and foremost by inhibiting of fibrosis and collagen, and increases K^+ reabsorption in renal tubules
Aldosterone antagonists (spironolactone, eplerenone): Diuretic effect by inhibiting Na^+ and water reabsorption in renal tubules, promotes regression of cardiac hypertrophy and adverse remodeling such as ACE inhibitors and ARB but by blocking mineralocorticoid (aldosterone) receptors and increases K^+ reabsorption in renal tubules and lowers arterial blood pressure
Beta-blockers: Negative chronotropic and anti-ischemic effects which reduce myocardial oxygen demands, extends the filling time of the ventricle, anti-arrhythmic via stabilized membrane potential and lowers arterial blood pressure by reducing cardiac output and inhibits renin release
Digitalis (digoxin): Negative chronotropic effects and prolongs the time of filling, but potentially unfavorable positive inotropic effects in hearts with small cavity
Calcium antagonists (dihydropyridines): Reduces peripheral vascular resistance and arterial blood pressure, promotes regression of cardiac hypertrophy and adverse remodeling first and foremost by inhibiting fibrosis and collagen. Extends the ventricular filling time and anti-ischemic effects in macro- and microvascular disease (the latter typically in hypertension and diabetes)
Diltiazem and verapamil (non-dihydropyridines): Reduces both chronotropy and inotropy and thus myocardial oxygen demands and prolongs the filling time, reduces peripheral vascular resistance and arterial blood pressure, and promotes regression cardiac hypertrophy and adverse remodeling as dihydropyridines
Loop diuretics (furosemide, bumetanide): Diuretic and symptomatic effect if salt and fluid retention with dyspnea and edema; always needed when significant renal impairment
Thiazide diuretics: Some diuretic and antihypertensive effect. Used in small doses that primarily potentiates the effect of ACE inhibitors and ARB. Must always be included if three blood pressure lowering drugs are needed and renal function is almost or completely normal

16.2 Trials and Treatment of Heart Failure with Reduced Left Ventricular Function

16.2.1 Angiotensin-Converting Enzyme (ACE) Inhibitors

Angiotensin II is cleaved from angiotensin I by the action of angiotensin-converting enzyme. Angiotensin II acts on vascular smooth muscle cells both by vasoconstriction and smooth cell proliferation [2]. In addition to this, it acts by interacting with the sympathetic nervous system both peripherally and centrally to increase vascular tone [3, 4]; it causes sodium retention and hence fluid retention [5]. These actions are inhibited by ACE inhibitors.

Based on data from major studies, such as Studies of Left Ventricular Dysfunction (SOLVD), Survival and Ventricular Enlargement (SAVE), Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), Trandolapril Cardiac Evaluation (TRACE), and Acute Infarction Ramipril Efficacy (AIRE), ACE inhibitors are recommended as a first-line treatment for the treatment of patients with HFrEF, unless it is not tolerated [6].

The SOLVD trial included 2569 patients with chronic heart failure and left ventricular ejection fraction (LVEF) ≤35%. Patients were randomized to receive placebo (n = 1284) or enalapril (n = 1285). The mortality and hospitalizations for heart failure were significantly reduced in the enalapril group [7]. The CONSENSUS was the first trial to show the beneficial effects of ACE inhibitors. It was a double-blind, randomized trial where enalapril was compared with conventional heart failure treatment, reporting a 31% reduction in 1-year mortality in the enalapril group compared to the placebo group [8]. The SAVE study was a double-blind randomized study where patients with post-myocardial infarction heart failure received placebo (n = 1116) vs. captopril (n = 1115). All-cause mortality was significantly reduced in the captopril group compared with the placebo group (20% versus 25%; p = 0.019). The captopril group also had lower risks for death from cardiovascular causes, development of severe heart failure, heart failure requiring hospitalization, and recurrent myocardial infarction [9]. The TRACE study was a randomized, double-blind, placebo-controlled study randomizing patients with an enzyme-verified acute myocardial infarction and a LVEF less or equal to 35% to receive either trandolapril or placebo. Of the total study population, 23% had been characterized having a history of hypertension. The authors concluded that ACE inhibition after acute myocardial infarction complicated with left ventricular dysfunction was of greater benefit to patients with a history of hypertension (p = 0.03) [10]. The AIRE study investigators randomized 2006 patients with post-myocardial cardiac failure to receive ramipril (n = 1014) vs. placebo (n = 992). In the group randomized to receive ramipril, mortality from all causes was 17%, whereas in the group that received placebo, it was 23% (p = 0.002). Analysis revealed a risk reduction in the secondary outcomes of composite death, severe heart failure, myocardial infarction, or stroke [11].

ACE inhibitors have, in placebo-controlled trials, shown a significant improvement in ejection fraction, symptoms, and clinical status, with a reduction in

all-cause mortality of 20–25%, and decrease of 20–25% in the combined risk of death or hospitalization [12]. The European Society of Cardiology (ESC) recommends ACE inhibitors as a first-line therapy in patients with a reduced ejection fraction (<40–45%) with or without symptoms. ESC recommends ACE inhibitors as the initial therapy in the absence of fluid retention. In patients with fluid retention, ACE inhibitors should be given together with diuretics. According to the guidelines updated in 2016, ACE inhibitors should be initiated in patients with signs or symptoms of heart failure, even if transient, after the acute phase of myocardial infarction, to improve survival, symptoms, and functional capacity and to reduce reinfarctions and hospitalizations [6].

Adverse effects of ACE inhibitors are hypotension, angioedema, hyperkalemia, renal failure, and cough. It is not recommended in bilateral renal artery stenosis and angioedema in previous ACE inhibitor therapy.

16.2.2 Angiotensin Receptor Blockers (ARBs)

The ARB competitively inhibits the angiotensin II receptors, hence antagonizing angiotensin II-induced vasoconstriction, release of catecholamine, aldosterone, fluid retention, and smooth cell proliferation [13].

As shown in Valsartan in Acute Myocardial Infarction Trial (VALIANT), the ARB valsartan reduces blood pressure as efficaciously as ACE inhibitors [14]. In addition to the antihypertensive effect, the results of Valsartan Heart Failure Trial (Val-HeFT) indicate that valsartan also has an important role in the treatment of heart failure [15–17]. The Val-HeFT compared valsartan with placebo when added to conventional therapy for patients with heart failure. In this study valsartan significantly improved left ventricular ejection fraction and reduced the combined endpoint of mortality and hospitalizations due to heart failure. Furthermore, valsartan reduced the incidence of atrial fibrillation, which is a major cause of heart failure.

The Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) investigators [18] studied patients with a left ventricular EF <40% who were not receiving ACE inhibitors due to previous intolerance [19], patients with a left ventricular EF <40% who were receiving ACE inhibitors [20], and patients with a left ventricular EF >40% [21]. Patients were randomized to receive candesartan (n = 3803) or placebo (n = 3796). Candesartan significantly reduced cardiovascular deaths and hospital admission for heart failure both in the alternative and the added group and was shown to be well tolerated. The findings in patients with diastolic dysfunction (preserved group, HFpEF) did not reach the level of statistical significance.

The effect of losartan vs. captopril was compared in the randomized double-blind study Evaluation of Losartan in the Elderly (ELITE). The patients were >65 years old and had NYHA class II–IV heart failure and a left ventricular EF <40% [22]. Both the tolerability and the increase in serum creatinine were found to be the same in both groups. Fewer patients in the losartan group discontinued

therapy, and no patients discontinued losartan due to coughing as a side effect. In this study of elderly heart failure patients, mortality associated with losartan was unexpectedly lower than that associated with captopril. The ELITE II tested whether losartan was superior to captopril in improving survival and found no significant differences in the primary or secondary endpoints between the two groups, but losartan was significantly better tolerated. In the subsequent high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL), 3846 patients with EF of 40% or lower were randomized to losartan 150 mg vs. 50 mg. The higher dose of losartan led to less hospitalization for worsening of heart failure but more renal impairment, hypotension, and hyperkalemia and without difference in mortality [23].

A recent study, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM- HF), randomized patients ($n = 8442$) in NYHA II, III, or IV class with left ventricular EF ≤40% to receive the ARB (valsartan)-neprilysin inhibitor (sacubitril) ARNI (LCZ696) or the ACE inhibitor enalapril in addition to otherwise recommended therapy. The trial was stopped early because of a significant reduction in mortality and heart failure-related admissions ($p < 0.001$ and $p = 0.001$, respectively), in favor of the ARB-neprilysin inhibitor (sacubitril/valsartan) (LCZ696). Neprilysin inhibitors are recommended by the American guidelines for further reduction of mortality and heart failure-related admissions in patients tolerating ACE inhibitors. However, further studies are recommended to investigate long-term effects of neprilysin inhibitors, and importantly neprilysin inhibitors should not be given together with ACE inhibitors or in patients with angioedema due to ACE inhibitors [24].

The ESC recommends ARBs to be used as an alternative to ACE inhibitors in symptomatic patients intolerant to ACE inhibitors, to improve morbidity and mortality and to avoid hospital admission for heart failure in patients with LV systolic dysfunction [6]. They also state that ARBs can be considered in combination with ACE inhibitors in selected patients who remain symptomatic and are unable to tolerate MRAs to reduce mortality and hospital admission for heart failure.

ARB has a tolerability profile which may improve treatment compliance in patients with heart failure, the incidence of cough was similar to placebo, and it has a lower incidence of cough compared with ACE inhibitors [25, 26].

16.2.3 Beta-Blockers

Activation of the sympathetic nervous system and plasma catecholamines cause peripheral vasoconstriction and enhanced intravascular volume leading to increased left ventricular size, heart failure, and eventually provocation of arrhythmias [27, 28]. Blocking the beta-adrenergic receptors has multiple cardiac effects such as lowering blood pressure and heart rate and reduction of left ventricular chamber size which leads to improved left ventricular structure and function, hence improved left ventricular EF [29–33].

Several, large studies have demonstrated the effect of the beta-blockers bisoprolol, carvedilol, and metoprolol succinate CR in the reduction of heart failure-associated hospital admissions and mortality. Both the European and the American guidelines recommend the use of beta-blockers in the treatment of heart failure with left ventricular EF <40% [6, 24]. ACE inhibitors and beta-blockers are considered complementary and can be started together in patients with heart failure as long as the patient is stable and not in acute cardiac failure.

Cardiac Insufficiency Bisoprolol Study II (CIBIS II) was a multicenter double-blind randomized placebo-controlled study comparing bisoprolol vs. placebo in patients in NYHA III to IV, with left ventricular EF ≤35% receiving ACE inhibitors. The trial was stopped early because of a significantly lower all-cause mortality and sudden death in the bisoprolol group [34].

Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) (metoprolol vs. placebo, n = 3991) [35], Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) (carvedilol vs. placebo, n = 2289) [36], and Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) (nebivolol vs. placebo, n = 2128) [37] were all relatively large randomized studies showing a significant reduction in all-cause mortality and all-cause hospitalization in favor of the beta-blockers used in the studies.

This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, left ventricular EF, and ischemic or nonischemic etiology. Adverse effects of beta-blockers are hypotension, bradycardia, and fatigue.

16.2.4 Mineralocorticoid Receptor Antagonists

Aldosterone, a mineralocorticoid hormone, affects sodium retention and potassium excretion mainly in the renal tubules [38]; it is also involved in sympathetic activation, parasympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage; and it impairs arterial compliance [39–42].

Randomized Aldactone Evaluation Study (RALES) was a double-blind study including patients with severe heart failure with left ventricular EF <30%, receiving treatment with traditional heart failure medications (ACE inhibitor, loop diuretic, and, in most cases, digoxin). Approximately 50% of the patients were randomized to receive spironolactone (25 mg/day); the other 50% received placebo. This trial demonstrated the importance of aldosterone antagonist in the treatment of heart failure patients, with a 30% reduction in the risk of death among the patients receiving the aldosterone antagonist. The patients receiving aldosterone antagonists also had a significant improvement in heart failure symptoms and had a 35% lower frequency of hospitalization for worsening heart failure [43].

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) investigators included patients with acute myocardial infarction complicated with heart failure to receive eplerenone (n = 3313) or placebo in addition to conventional medical therapy (3319 patients) [44]. The

death rate among the patients receiving eplerenone was significantly lower (478 versus 554 deaths; $p = 0.008$).

In Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF study) [45], patients ($n = 2337$) with NYHA class II heart failure and a left ventricular EF of <35% were randomized to receive eplerenone (up to 50 mg daily) or placebo, in addition to otherwise recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. The primary outcome occurred in 18.3% of patients in the eplerenone group vs. 25.9% in the placebo group ($p < 0.001$). Significantly lower number of patients in the eplerenone group vs. placebo (12.5 vs. 15.5%, respectively, $p = 0.008$) died, and hospitalization for heart failure was also reduced. Thus the trial was stopped prematurely. Significantly more patients in the eplerenone group vs. placebo had serum potassium level exceeding 5.5 mmol/L (11.8% vs. 7.2%, $p < 0.001$, respectively).

The ESC recommends aldosterone receptor antagonists in addition to ACE inhibitors, beta-blockers, and diuretics in heart failure with reduced EF, to reduce mortality, morbidity, and heart failure-associated admissions [6].

Adverse effects of aldosterone receptor antagonists include gynecomastia or breast pain which was reported in 10% of men treated with spironolactone vs. 1% of men in the placebo group [43]. Aldosterone receptor antagonists can cause hyperkalemia; thus treatment of patients with renal impairment or serum potassium >5 mmol/L should be exercised with caution and with close follow-up and frequent laboratory tests.

16.2.5 Diuretics

Diuretics reduce the pre- and afterload, resulting in reduced pulmonary and peripheral congestion [46, 47], and it is therefore recommended for the improvement of signs and symptoms of heart failure. Patients should be encouraged to up- and down-titrate the dosage of diuretics according to signs and symptoms of worsening heart failure. Diuretic of the thiazide type is often combined with other antihypertensive drugs for the treatment of hypertension and prevention of heart failure. Otherwise, in more severe heart failure with overt fluid retention and in particular in patients with reduced renal function, loop diuretics like furosemide and bumetanide would be indicated.

16.3 Trials and Treatment of Heart Failure in Patients with Preserved Left Ventricular Function

The prevalence of hypertension appears to be 30–55% in the general population [48], and it tends to increase with increasing age. In the Framingham study, 92% of the patients with heart failure had a history of hypertension, and approximately 50% of them developed heart failure after suffering from myocardial infarction [49].

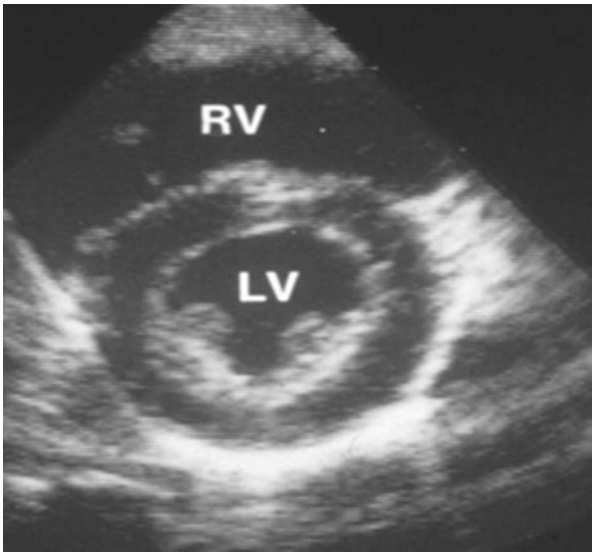

Fig. 16.2 Photo shows ultrasound short-axis visualization of left ventricle with concentric hypertrophy (thick walls, small cavity, and high wall/lumen ratio), the typical left ventricular geometry in patients with heart failure with preserved ejection fraction (HFpEF). *RV* right ventricle, *LV* left ventricle

Hypertension may lead to heart failure through the development of eccentric hypertrophy, dilatation of the left ventricle, and reduced left ventricular EF (HFrEF), or it may lead to concentric hypertrophy (Fig. 16.2) by remodeling of the myocytes, accumulation of fibrotic tissue, hence a stiff ventricle with preserved systolic function, but impaired relaxation (HFpEF).

None of the antihypertensive agents or classical heart failure medications have been shown to be superior compared with others in patients with HFpEF. Along the same lines, none of the heart failure medications have been proven to reduce mortality in placebo-controlled studies when given with conventional heart failure therapy already instituted.

Several studies comparing placebo vs. conventional heart failure medications in patients with HFpEF have been performed. In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF), perindopril (ACE inhibitor) vs. placebo was compared (n = 850) [50]; in Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM-Preserved), candesartan (ARB) vs. placebo was compared (n = 3023) [21]; in Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) [51], irbesartan (ARB) vs. placebo was compared (n = 4133); in the Digitalis Investigation Group (DIG) trial [52], digoxin vs. placebo was compared (n = 988); and in Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) [53], spironolactone was compared with placebo. None of these studies showed a significant reduction of mortality or heart failure-related hospitalizations.

Thus, there is no specific treatment for HFpEF per se; however the importance of treating accompanying symptoms or conditions, such as hypertension, diabetes, left ventricular hypertrophy, atrial fibrillation, coronary artery disease, dyspnea, congestion, or impaired renal function, is emphasized. These accompanying conditions

Table 16.2 Selection of drugs at HFpEF relative to accompanying causes and conditions

Hypertension[a]: ACE inhibitors or ARB, calcium antagonist, thiazide[b], beta-blockers, aldosterone antagonist
Hypertension and diabetes: As above as well as empagliflozin[c]
Diabetes without hypertension (rare): ACE inhibitors or ARBs, aldosterone antagonists, or empagliflozin
Left ventricular hypertrophy (almost always): ACE inhibitors or ARBs, calcium antagonists, aldosterone antagonists
Rapid atrial fibrillation: Beta-blockers, diltiazem or verapamil; the groups may be combined to avoid the use of amiodarone[d]
Normal frequency atrial fibrillation: ACE inhibitor or ARB, dihydropyridine calcium antagonist, aldosterone antagonist
Stable coronary disease[e]: ACE inhibitors or ARBs, beta-blockers, calcium antagonists, aldosterone antagonists
Impaired renal function[f]: ARB, beta-blockers, calcium antagonist, aldosterone antagonist with monitoring of serum K^+
Overhydration, dyspnea, edema: Furosemide (loop diuretics) which is titrated down to maintenance dose

[a]Drugs from different groups can be combined to achieve target BT <130/80 mmHg (<140/90 in elderly)
[b]Many patients with normal renal function manage with thiazide without loop diuretics typically in combination with ACE inhibitors or ARB
[c]Diuretic effects, lowers blood pressure and weight as well as life-prolonging effect in diabetes
[d]Toxic medication which may be indicated when rapid atrial fibrillation and cardiac failure with reduced EF
[e]Unstable angina, NSTEMI and STEMI are not mentioned in this overview; usually indication of immediate coronary angiography
[f]Consider using K^+ lowering resin if se-K^+ is >5.0 mmol/L

and the choices of treatment are summarized in Table 16.2. Beyond the medication well established in patients with HFrEF, calcium antagonists can safely be used in patients with HFpEF. The dihydropyridine calcium antagonist amlodipine has specifically been investigated [54], and the non-dihydropyridine calcium antagonists verapamil and diltiazem can be effective in patients with HFpEF with rapid atrial fibrillation and a background with hypertension, usually with left ventricular hypertrophy. The non-dihydropyridine calcium antagonists can also be combined with β-blocker in many of these patients in order to avoid the toxic amiodarone. A prerequisite for combining non-dihydropyridine calcium antagonists with β-blocker is usually diagnostic work-up with echocardiography findings of preserved EF indicating HFpEF as explained in detail [55] (Fig. 16.3).

16.4 Prevention of Heart Failure in Randomized Studies of High-Risk Hypertensive Patients

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [56], the main objective was to determine whether a calcium antagonist amlodipine or the ACE inhibitor lisinopril was more effective in preventing coronary heart disease than the diuretic chlorthalidone [56]. Despite a slightly

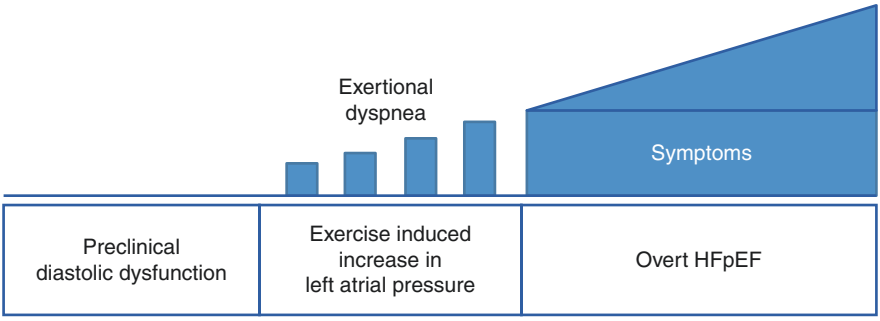

Fig. 16.3 Schematic illustration of the development from early subclinical diastolic dysfunction to more severe diastolic dysfunction associated with functional dyspnea and established heart failure with preserved ejection fraction (HFpEF) with continuous symptoms. Subclinical diastolic dysfunction is a typical finding in people with mild-to-moderate hypertension; diagnostic procedures are explained in detail by Smiseth [55]

but significantly greater reduction in blood pressure with chlorthalidone than with the calcium antagonist and the ACE inhibitor, there was no difference between treatments in the primary outcome or in all-cause mortality, but the risk of heart failure, as a component of a tertiary endpoint, was increased by 38% in the amlodipine-treated patients and by 19% in the lisinopril-treated group when compared to the diuretic-treated group. Even taking into consideration the limitations of the ALLHAT [57], these data suggest that diuretics are effective in reducing the risk of hospitalizations associated with heart failure. However, previous medication was discontinued in the ALLHAT participants at randomization, and it is likely that the lack of diuretic treatment in hypertensive patients with very high risk of developing heart failure explained the differences between the treatment groups.

In Hypertension in the Very Elderly Trial (HYVET) [58] with all patients older than 80 years, enrolled patients were randomly assigned to receive either the diuretic indapamide or matching placebo. The ACE inhibitor perindopril, or matching placebo, was added if necessary to achieve the target blood pressure of <150/80 mmHg. Besides the significant 30% reduction in fatal or nonfatal stroke and 21% decrease in death from any cause, the most striking finding was the 64% reduction in heart failure. Although only 25% of patients on active treatment were on indapamide alone at the end of the study, these data once again emphasize the potential clinical benefits of diuretics in preventing heart failure when prescribed alone or in combination with a blocker of the renin-angiotensin system.

The Systolic Blood Pressure Intervention Trial (SPRINT) [59] was designed to assess the most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality in hypertensive patients with a high risk for cardiovascular events but without diabetes. At enrollment patients had a systolic blood pressure >130 mmHg. They were randomly allocated to a target systolic blood pressure of <120 or <140 mmHg. To achieve these targets, physicians could use diuretics, calcium antagonists, ACE inhibitors, or ARBs. The protocol encouraged the use of drug classes such as thiazide-type diuretics (chlorthalidone was encouraged as the first-line

agent), loop diuretics (for participants with chronic kidney disease), and beta-adrenergic blockers (for those with coronary artery disease). In order to reach the predefined targets, diuretic therapy might have been withheld to obtain a systolic blood pressure close to 140 mmHg in some patients and intensified in those patients who were allocated to the <120 mmHg target. Thus in the low target group, the prescription of diuretics increased by 24%. In comparison, the prescription of calcium antagonist, beta-blockers, and blockers of the renin-angiotensin system (RAS) increased by 21.5, 10, and 22%, respectively. In the latest visit, 76% of patients received a RAS blocker, 67% a diuretic, 57% a calcium antagonist, and 41% a beta-blocker in the intensive treated group. In the control, numbers were 55.2% for RAS blockers, 42.9% for diuretics, 35.4% for calcium antagonist, and 30.8% for beta-blockers. The results of the trial showed significantly reduced primary events in patients of the intensive-treatment group. However, 50% of the primary endpoints were due to incident heart failure. Although the majority of patients included in the intensive-treatment group of the protocol were treated simultaneously with a diuretic and a RAS blocker, one may wonder how determinant was the increase in the intensity of diuretic and other drug therapy in reducing heart failure and mortality. With the lesson from ALLHAT in mind [56, 57], the difference in heart failure could be predicted from the difference in medication between the two arms in these high-risk hypertensive patients.

The recent Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes Outcome Trial (EMPA-REG Outcome Trial) [60] aimed at examining the effects of the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin on cardiovascular morbidity and mortality as compared with placebo, in patients with type 2 diabetes at high risk for cardiovascular events. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. This trial demonstrated for the first time a significant reduction in the risk of death from any cause and death from cardiovascular causes (hazard ratio of 0.62 and 0.68, respectively, $P < 0.001$) in patients with type 2 diabetes. However, empagliflozin had no effect on stroke, myocardial infarction, or coronary events. The reduction in mortality was independent of the presence or absence of antihypertensive therapy, of the prescription of diuretics or RAS blockers (80% of patients were on a RAS blocker and 42% on a diuretic), and of diabetes control. The reduction in the risk of hospitalization for heart failure was the prominent feature of the study, the majority of cardiovascular events in this trial being due to heart failure.

SGLT2 inhibitors are not considered as classic diuretics, but they do have an impact on renal function causing an osmotic diuresis. The decrease in glucose reabsorption in the proximal tubule of the nephron and the resulting persistent glucosuria lead to an increase in urinary volume and probably also in urinary sodium excretion, though this latter has not been formerly demonstrated. In any case, administration of SGLT2 inhibitors was associated with a 4.8–5% increase in hematocrit in EMPA-REG suggesting hemoconcentration and in a decrease in both systolic and diastolic BP. The empagliflozin effects on blood pressure, diuresis, and natriuresis may have contributed to the reduction in heart failure hospitalizations via an intensification of diuretic therapy. Other metabolic hypotheses have also been

proposed to explain the benefits of SGLT2 inhibitors in heart failure, which need to be tested [61]. The CVD-REAL survey included more than 150,000 patients treated with SGLT2 inhibitors and as many patients not treated with an SGLT2 inhibitor. The results confirmed the major impact of this antidiabetic class on the prevention of heart failure hospitalizations (−39%) and all-cause death (−51%). The survey also demonstrated that this is a class effect [62].

These data obtained in various populations with a high risk of incident heart failure suggest that diuretics may play an important role in the prevention of death and hospitalizations due to heart failure (Fig. 16.3); however, the European heart failure guidelines [6] recommend diuretics only to reduce the signs and symptoms of congestion. In their last heart failure guidelines, the ESC has introduced the possibility to use empagliflozin in patients with type 2 diabetes "to prevent or delay the onset of heart failure and to prolong life" [6]. Thus, the role of diuretics in preventing heart failure and its complications should be reassessed in the light of most recent trials in high cardiovascular risk patients.

While HYVET [58] and EMPA-REG [61] were double blinded and placebo controlled, ALLHAT [56] and SPRINT [59] were open in design which could explain outcomes as discussed above. Other double-blind randomized trials comparing head to head different antihypertensive drugs in high-risk patients were the Losartan Intervention for Endpoint Reduction (LIFE) in hypertension study [63] and the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial [64] with incident heart failure detected as a secondary endpoint or as a component of the primary endpoint, respectively, and no major differences could be seen between ARBs, β-blocker, and calcium antagonist (losartan, atenolol, valsartan, and amlodipine).

In summary, heart failure is prevented in patients with high-risk hypertension by a combination of various antihypertensive drugs including diuretics and achieving target blood pressures <140/90 mmHg or possibly slightly lower.

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Part V

Prevention of Heart Failure in Hypertension

Non-pharmacological Treatment

17

Cornelia Bala

17.1 Introduction

Hypertensive men have a twofold and hypertensive women have threefold higher risk of heart failure (HF) compared with their normotensive counterparts [1], and hypertension (HTN) plays an important role in the development of heart failure in subjects with and without a history of myocardial infarction [2]. It is well-demonstrated that optimal blood pressure (BP) control is associated with an average 50% decrease in incident HF [3] and thus underlying the importance of BP-lowering strategies to prevent HF. Non-pharmacological interventions were proven to be effective in lowering BP and are recommended by current guidelines either alone for prevention of HTN and in low-grade low-risk HTN or, more often, as a complement to drug therapy [4, 5]. The interventions with the best level of evidence for lowering BP are (1) weight loss in patients who are overweight or obese, (2) adherence to a healthy dietary pattern, (3) sodium reduction, (4) potassium supplementation, (5) increased physical activity level, and (6) moderation of alcohol consumption, but whether these interventions can prevent occurrence of HF in individuals with HTN is less clear. Other non-pharmacological interventions (e.g., protein or fiber intake, probiotics, calcium and magnesium supplementation, stress management, and behavioral therapies) and their role in BP control is still a matter of debate. Smoking, although not having demonstrated chronic effects on BP levels [6], is an important risk factor for cardiovascular disease, and quitting smoking should be recommended to all patients with hypertension.

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17.2 Weight Loss, BP Control, and Risk of HF

Total and abdominal adiposity is shown to be correlated with risk of hypertension [7–9]. Numerous studies demonstrate that weight loss is associated with a decrease in BP values in both hypertensive and normotensive individuals. In a meta-analysis of 25 randomized controlled trials (RCTs) using as interventions energy restriction, increased physical activity, or both and having a mean duration of intervention of 66 weeks, it was shown that in the overall population, for each 1 kg of weight loss, a decrease of approximately 1 mmHg is obtained for systolic and diastolic BP [10]. The effect of weight loss on both systolic BP (SBP) and diastolic BP (DBP) was larger in subgroups treated with antihypertensive medication than in untreated populations (−7.00 mmHg vs. −3.77 mmHg and −5.49 mmHg vs. −2.97 mmHg, respectively). When subgroups with a baseline BP <140/90 mmHg vs. ≥140/90 mmHg were compared, only DBP decreased more in the subgroup with BP ≥140/90 mmHg although the difference was not statistically significant. In another meta-analysis including trials on weight-reducing diets in people with hypertension and with duration of 6–36 months, a decrease of 4.49 mmHg in SBP and of 3.19 mmHg in DBP corresponding to a mean weight loss of 3.98 kg was seen in the intervention group [11]. Only one study reported cardiovascular outcomes evaluated as self-reported hospitalizations for cardiovascular events or procedures, and no difference was found between intervention and usual care groups [12].

Anti-obesity drugs and bariatric surgical procedures are recommended by current obesity guidelines for patients not achieving weight goals by lifestyle interventions alone [13–15]. In a meta-analysis of RCTs in hypertensive adults having at least 24 weeks' duration and in which pharmacologic interventions were compared with placebo, it was shown that orlistat reduced SBP as compared to placebo by −2.5 mmHg and DBP by −1.9 mmHg and sibutramine increased DBP compared to placebo by +3.2 mmHg, and in one trial that investigated phentermine/topiramate, it was suggested that it lowered blood pressure [16]. No relevant long-term studies were identified with rimonabant, liraglutide, lorcaserin, or naltrexone/bupropion. Due to safety concerns, sibutramine and rimonabant were withdrawn from the market in 2010 and 2009, respectively. Phentermine/topiramate and lorcaserin are not approved in Europe. Bariatric surgery is an effective method for obesity control, reporting an overall 50% loss of the excessive weight. Roux-en-Y gastric bypass and sleeve gastrectomy seemed to have similar outcomes on weight loss, and both of these procedures were superior to adjustable gastric banding [17]. In the recently published GATEWAY Randomized Trial (Gastric Bypass to Treat Obese Patients With Steady Hypertension), Roux-en-Y gastric bypass plus medical therapy was compared with medical therapy alone in 100 hypertensive patients with a BMI of 30.0–39.9 kg/m^2 followed for 12 months [18]. A reduction of ≥30% of the total number of antihypertensive medications occurred in 83.7% of patients from the gastric bypass group compared with 12.8% from the control group, and remission of hypertension occurred in 51% of patients randomized to gastric bypass compared with no patient free of antihypertensive drugs in the medical therapy group.

Table 17.1 Weight management recommendations (modified after [14])

Intervention	Indications
Lifestyle intervention (diet and physical activity)	All patients with BMI ≥25 kg/m^2, irrespective of WC values and presence/absence of comorbidities
Drug therapy[a]	BMI 25–29.9 kg/m^2 and comorbidities
	BMI 30–34.9 kg/m^2 and WC men ≥94, women ≥ 80 cm with/without comorbidities
	All patients with BMI ≥35 kg/m^2 irrespective of WC values and presence/absence of comorbidities
Surgery	BMI 30–34.9 kg/m^2 and diabetes (on individual basis)
	BMI 35.0–39.9 kg/m^2 and comorbidities
	All patients with BMI ≥40 kg/m^2

BMI body mass index, *WC* waist circumference, *FDA* Food and Drug Administration, *EMA* European Medicinal Agency

[a]Approved weight-loss drugs are orlistat, bupropion/naltrexone, and liraglutide (FDA and EMA approved); lorcaserin and phentermine/topiramate (FDA approved). In patients with existing hypertension, orlistat, lorcaserin, phentermine/topiramate, and liraglutide 3 mg are preferred weight-loss medications [13]

No prospective studies specifically addressed or reported the effects of weight-loss interventions on risk of HF in the general population or in individuals with HTN. Nevertheless, weight loss was proven to be associated with several beneficial effects on heart function and structure that are plausible to decrease the risk of HF (decreasing left ventricular mass, arterial blood pressure, filling pressures, and improvement in indexes of diastolic and systolic cardiac function) and should be attempted in all hypertensive patients with overweight or obesity [19].

Current hypertension guidelines recommend maintenance of a healthy body weight (BMI of about 25 kg/m^2) and waist circumference (<102 cm for men and <88 cm for women) for non-hypertensive individuals to prevent hypertension and for hypertensive patients to reduce BP. In hypertensive subjects with overweight/obesity, any degree of weight loss is desirable and may reduce BP levels [4, 5]. Weight management strategies according to current obesity guidelines [13, 14] and applicable to hypertensive individuals are presented in Table 17.1.

17.3 Dietary Patterns, BP Control, and Risk of HF

The effects of individual nutrients or of individual foods (e.g., sodium and potassium intake, fruit and vegetables, dairy product, eggs, meat, nuts, fats and oils) on BP were assessed in numerous studies yielding conflicting results with the exception of low-sodium and high-potassium intake which were shown to lead to a reduction of BP. Dietary patterns are considered to better reflect food intake and multiple interactions between various foods consumed over a period of time, and recent nutrition research and guidelines addressed the relationship between dietary patterns and various health outcomes [20].

Dietary approaches to stop hypertension (DASH) diet is the most extensively studied dietary pattern in relation with BP control. DASH diet is a diet rich in fruits,

vegetables, and low-fat dairy products and with reduced saturated and total fat which was shown to reduce SBP and DBP in hypertensive patients with 11.4 and 5.5 mmHg more, respectively, than the control diet [21]. Both DASH and control diets had a sodium intake of about 3000 mg/day, but DASH diet had a higher content of fiber, potassium, magnesium, and calcium. In hypertensive participants, when the DASH diet was combined with a low-sodium intake (50 mmol or 1150 mg/day), a 11.5 mmHg difference in SBP was obtained when compared with those following the conventional diet with high-sodium intake (150 mmol or 3450 mg/day) [22].

Mediterranean diet is characterized by high intake of olive oil, nuts, fruit, vegetables, and cereals, with a moderate intake of fish and poultry and a low intake of dairy products, red and processed meat, and sweets; wine is consumed with moderation and with meals [23]. In the PREDIMED study which was a primary prevention RCT, Mediterranean diet supplemented with extra-virgin olive oil or nuts was shown to reduce the incidence of cardiovascular events with 30 and 28%, respectively, compared with a control low-fat diet group [24]. Diastolic blood pressure decreased more in the two groups with Mediterranean diet at the end of 4-year follow-up (−1.53 mmHg and −0.65 mmHg, respectively) compared with the control group, while systolic blood pressure was similar in the three groups [25]. No data were reported for individuals with hypertension, but number of antihypertensive medication increased with no significant between-group differences.

In individuals with metabolic syndrome, an isocaloric healthy Nordic diet rich in whole grains, rapeseed oil, berries, fruits, vegetables, fish, nuts, and low-fat dairy products of Nordic origin was shown to reduce ambulatory diastolic BP with −4.4 mm Hg compared with a control diet, with no significant differences of SBP between groups [26].

In a meta-analysis including 17 RCTs of DASH, Nordic, and Mediterranean dietary patterns, the overall effect on BP was a decrease in systolic and diastolic BP of 4.26 mmHg and 2.38 mmHg, respectively. Other interventions such as sodium restriction, physical exercise, and weight loss used in some of the included studies also led to significant BP reductions, and the relative efficacy of each intervention remains a matter of study [27].

Vegetarian dietary patterns are based on consumption of foods of plant origin, particularly vegetables, grains, legumes, and fruits and exclude consumption of meat. Some of vegetarian diets also include dairy products, eggs, and fish. In a meta-analysis of seven RCTs, SBP and DBP were significantly lower (−4.8 mmHg and −2.2 mmHg, respectively) in the overall vegetarian diet groups vs. omnivorous diet group [28]. According to baseline BP, individuals with stage 1 hypertension did not achieve a statistically significant difference in systolic and diastolic BP, while those with normal BP and prehypertension did. Subjects with stage 2 or 3 hypertension were not included in any of the RCTs. Significantly lower systolic and diastolic BP were demonstrated in a meta-analysis of 32 observational studies [28] comparing vegetarian to omnivorous diets (−6.9 mmHg and −4.7 mmHg, respectively), and the differences were statistically significant in subgroups with normal BP, prehypertension, and stage 1 hypertension at baseline.

Recent hypertension guidelines recommend a heart-healthy diet, such as DASH diet, to be followed by individuals with hypertension [5], but whether adherence to such diet may prevent HF was not specifically addressed in individuals with hypertension. Nevertheless, few studies reported that healthy dietary patterns are associated with lower rates of HF and/or HF events.

The Swedish Mammography Cohort was a prospective observational study which included 36,019 women aged 48–83 years and without baseline HF, diabetes mellitus, or myocardial infarction. After a period of 7 years of follow-up, those in the third quartile of the DASH diet score had a 37% lower rate of HF after multivariate adjustment including the presence of hypertension [29]. Subgroups with and without hypertension have similar decrease in HF rates. In the Cohort of Swedish Men which included 38,987 male participants aged 45–79 years, those in the highest quartile of the DASH component score had a 22% decrease of HF rate compared with those in the lowest quartile. The effect in patients with HTN appeared to be higher than in those without HTN but without statistical difference [30].

In the PREDIMED study, plasma N-terminal pro-brain natriuretic peptide levels were significantly lower after 1 year of intervention in both Mediterranean diet groups compared with the control diet group, thus suggesting a possible protective effect of this dietary pattern against the occurrence of HF. No analysis was performed according to the presence or absence of HTN, but around 80% of study population had a history of HTN at baseline [31]. A very recent analysis showed no significant difference in HF incidence between intervention groups and control in participants without prevalent HF during a follow-up period of 4.8 years, but this pre-specified secondary analysis may have been underpowered to detect possible benefits on prevention of HF with Mediterranean diet [32]. Another randomized study testing the effects of a Mediterranean diet vs. a prudent Western-type diet in patients following a first myocardial infarction was Lyon Heart Study [33]. A composite endpoint including cardiac death, nonfatal myocardial infarction, unstable angina, stroke, heart failure, and pulmonary or peripheral embolism was found to be significantly decreased in the Mediterranean diet group over a mean follow-up of 46 months. Numerically, HF was less frequent in the experimental group (6/219 vs. 11/204).

Vegetarian diet was shown to be associated with a 32% lower risk of ischemic heart disease compared with nonvegetarians in a cohort of 44,561 men and women enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Oxford study, of whom 34% consumed a vegetarian diet at baseline and were followed for over 11 years [34]. No data is available on vegetarian diets and risk of HF.

Nordic diet was proven to have beneficial effects on several cardiovascular risk factors including hypertension, but data from the prospective Swedish Women's Lifestyle and Health cohort of 43,310 women did not confirm an association between a healthy Nordic food index and risk of cardiovascular disease. No data were collected regarding HF incidence [35].

17.4 Sodium Reduction, BP Control, and Risk of HF

The relationship between sodium intake and levels of BP is well-established [36, 37], and current hypertension guidelines either give a general recommendation to reduce sodium consumption [5, 38] or set a target of less than 5–6 g of salt intake/day in patients with hypertension [4, 39]. Even lower intake, reaching 1500 mg (66 mmol) of sodium is recommended by the AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk [40]. Sodium consumption can be expressed as mg/day or mmol/day of sodium or as mg or g/day of salt (sodium chloride). 100 mmol of sodium correspond to 2300 mg of sodium and 5800 mg (5.8 g) of salt.

In a recent meta-analysis of 185 RCTs in which participants were randomized to a low-sodium or to a high-sodium diet, the mean difference (MD) of SBP was −5.51 mmHg, and MD of DBP was 2.88 mmHg ($p < 0.00001$ for both) in white participants with hypertension [41]. In black and Asian subjects with hypertension, the effect was larger: SBP −6.64 and −7.75 mmHg, respectively, and DBP −2.91 and −2.68 mmHg, respectively. Overall, the average sodium intake was reduced from 201 to 66 mmol/day in the intervention groups. TONE trial demonstrated that a decrease in sodium consumption of 0.9 g/day in older patients already treated with a single antihypertensive drug was able to facilitate discontinuation of drug treatment while maintaining BP <150/90 mmHg, remaining free of medication and with no cardiovascular event in 38% of subjects included in the intervention group vs. 24% in those in the control group [42]. The effects were more pronounced in those also assigned to weight-loss intervention. Adherence to low-sodium intake was a significant predictor for successful discontinuation of antihypertensive medication of up to 36 months follow-up [43]. In subjects with resistant hypertension, an important reduction of 22.7 and 9.1 mmHg for SBP and DBP, respectively, was obtained following a low-sodium (50 mmol/day) compared with a high-sodium (250 mmol/day) diet [44].

The response of BP to sodium loading or restriction is different among members of a population, and this phenomenon was called salt sensitivity of blood pressure (SSBP). Salt-sensitive (SS) individuals will respond with increases in BP following salt loading and decreases in BP with salt depletion, whereas the salt-resistant (SR) individuals will not [45]. SS individuals are more likely to be of female gender, of older age, and of African American or Asian race, to have hypertension, diabetes mellitus, metabolic syndrome, or chronic kidney disease. Genetic factors also play a role in salt sensitivity. Currently, protocols to determine salt sensitivity require complicated and time-consuming procedures and are not applicable for routine clinical practice [45].

High-sodium intake is associated with increased risk of stroke and total cardiovascular disease, with a pooled relative risk of 1.23 for stroke and 1.14 for cardiovascular disease when comparing high- vs. low-sodium intake [46]. The extent of the association is greater for larger differences in sodium intake and longer follow-up. In a recent analysis of 133,118 individuals from 49 countries in four large prospective studies, it was demonstrated that in hypertensive population, increased sodium excretion (>7 g/day) compared with moderate sodium excretion (4–5 g/day) was significantly associated with increased risk of death and major cardiovascular events (hazard ratio 1.23), while in normotensive population, it was not. In contrast,

low-sodium excretion (<3 g/day) was associated with greater risk in both hypertensive and normotensive individuals [47].

The relationship between sodium intake and risk of HF is less clear. An analysis from the Cardiovascular Health Study which included 4490 participants ≥65 years of age followed for 21.5 years demonstrated that participants in the highest quintile of sodium intake have a 19% increased risk of incident HF than those in the lowest quintile and that those diagnosed with diabetes have the largest influence on mitigating the sodium–HF association. The association between dietary sodium and incident HF was stronger for those without coronary heart disease at baseline [48]. The relationship between sodium intake evaluated with 24-h sodium urinary excretion and risk of HF was confirmed in a Finnish cohort of younger participants. Gradually increasing hazard ratios for HF were found from second to fifth quintile of sodium intake compared with first quintile (1.13, 1.45, 1.56, and 1.75, p for the trend 0.009) after adjustment for age, sex, study year and area, systolic blood pressure, total cholesterol, and body mass index [49].

No interventional studies reported effects of sodium-reduction interventions for the prevention of HF in the general population or in hypertensive subjects.

In the Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2015, the World Health Organization (WHO) sets a target of 30% relative reduction in mean population intake of salt/sodium, with the aim of achieving less than 5 g per day (approximately 2 g sodium) by 2025 [50]. In 2010, mean sodium intake at global level was 3.95 g/day (equivalent to 10.06 g/day of salt) with higher intakes in East Asia, Central Asia, and Eastern Europe (mean >4.2 g/day) and in Central Europe and Middle East/North Africa (3.9–4.2 g/day). In North America, Western Europe, and Australia/New Zealand, sodium intake was lower, ranging from 3.4 to 3.8 g/day, and the lowest intake was found in sub-Saharan Africa and Latin America [51]. The main sources of dietary sodium in 450 adults recruited from 3 geographic locations in the United States were sodium added to food outside the home (70.9%), followed by sodium inherent to food (14.2%), salt added in home food preparation (5.6%), and salt added to food at the table (4.9%) [52]. In another study from France [53], the food groups that contributed most to sodium intake were breads (24%), soups (18%), cooked pork meats (14%), convenience foods (10%), cheeses (9%), and fast foods (7%). This data suggest that differences exist between countries in term of sodium sources and that interventions should be tailored to dietary habits of different populations.

The WHO recommends several global strategies that are able to decrease sodium consumption and potentially prevent health problems related to high-sodium intake. These strategies are included in the SHAKE technical package for salt reduction [54]. SHAKE acronym is based on five key areas of intervention:

- **S**urveillance: measure and monitor salt use.
- **H**arness industry: promote the reformulation of foods and meals to contain less salt.
- **A**dopt standards for labeling and marketing: implement standards for effective and accurate labeling and marketing of food.

- **K**nowledge: educate and communicate to empower individuals to eat less salt.
- **E**nvironment: support settings to promote healthy eating.

A large number of clinical studies using various interventions to decrease sodium intake are published annually [55], demonstrating that such interventions can lead to significant results. At individual level, choice of fresh foods, choice of foods based on sodium-labeling content, avoidance of food groups known to have a high-sodium content, use of low-sodium flavoring or of low-sodium salt substitutes, and avoidance of adding salt at table are useful methods to decrease sodium intake. Initiatives to decrease sodium content in food industry or in restaurants and fast food are also helpful, and benefits are independent of changing individual behaviors [56, 57].

Successful reduction of sodium intake was reported in several countries [58] ranging from 36% in Finland, 29% in China, and 18% in Lithuania to more modest results in Denmark (7%), Iceland (6%), or France (5%).

17.5 Potassium Supplementation, BP Control, and Risk of HF

The inverse relationship between dietary potassium intake and BP or hypertension is well-demonstrated in cross-sectional and prospective studies [59–61]. The deficit in cellular potassium was shown to trigger cells to gain sodium, and dietary potassium has been shown to exert a powerful, dose-dependent inhibitory effect on sodium sensitivity which is considered a precursor of hypertension. Other mechanisms involve an increase in distal tubule Na^+-Cl^- cotransporter activity when dietary potassium intake is low with subsequent sodium retention [62]. In the INTERSALT study, a decrease in potassium excretion by 50 mmol/day was associated with an increase in SBP and DBP of 3.4 mmHg and 1.9 mmHg, respectively. The urinary potassium/sodium ratio was found to have a stronger statistical relationship to blood pressure than did either sodium or potassium excretion alone [63].

The benefits of potassium on BP lowering were demonstrated for both oral and dietary supplementations and seem to be increased in populations with concurrent high-sodium intake and in African Americans [64, 65]. The administration of 60 mmol (1380 mg) of potassium chloride decreased BP with 2 mmHg in participants with normotension and with 4–5 mmHg in those with hypertension. GenSalt study [66] was a feeding trial with repeated evaluation after 4.5 years after the original dietary intervention which confirmed that a dietary supplementation of 60 mmol/day of potassium in individuals with a high-sodium (307.8 mmol/day) diet was associated with a significant reduction of BP values (−4 mmHg for SBP and −2 mmHg DBP). Current guidelines recommend that potassium supplementation should be obtained from dietary sources rather than oral supplementation. The target for potassium intake, according to WHO, is at least 90 mmol (3510 mg)/day [67], while the US Department of Agriculture recommends a target of at least 4700 mg/day [20]. Foods rich in potassium are also heart-healthy foods such as

fruits and vegetables, nuts, dairy products, fish and meats, and soya products, and healthy dietary patterns such as DASH or Mediterranean diets are also rich in potassium.

Interventions to increase dietary potassium intake were also found to result in lower risk of stroke and of cardiovascular morbidity and mortality [68, 69], but no intervention studies examined whether potassium supplementation can prevent HF.

17.6 Physical Activity, BP Control, and HF Prevention

The beneficial effects of physical activity on BP control were proven by numerous interventional studies. Different types of physical exercise may differ in the magnitude of BP changes and should be taken into account when recommending the type and duration of physical activity in patients with hypertension.

A meta-analysis of 93 RCTs lasting ≥4 weeks and including over 5000 participants found that SBP and DBP were reduced with 10.9 mmHg and 6.2 mmHg after isometric resistance, with 3.5 mmHg and 2.5 mmHg after endurance, and with 1.8 mmHg and −3.2 mmHg after dynamic resistance training, while combined training had no significant effect on SBP and decreased DBP with 2.2 mmHg. BP reductions after endurance training were greater in hypertensive subjects (8.3/5.2 mmHg) compared with normotensive subjects (0.75/1.1), whereas dynamic resistance training had the largest effect in prehypertensive participants compared with hypertensive or normotensive subgroups [70].

Dynamic aerobic endurance exercise is defined as a physical activity which involves large muscle groups in dynamic repetitive activities leading to increases in heart rate and energy expenditure. Resistance training is an activity performed against an opposing force leading to the increase in muscular strength, power, and/or endurance; it can be either “dynamic” or “isometric” according to characteristics of opposing force [71]. Traditionally, endurance exercise was considered better suitable for hypertensive patients as in earlier studies isometric resistance exercise had been associated with exaggerated hypertensive responses, but newer data demonstrate that isometric handgrip exercise of at least 4-week duration resulted in 10% lower SBP and DBP compared with no intervention [72].

In cohort studies, higher levels of physical activity were demonstrated to be associated with lower risk of HF [73, 74], and a dose-response relationship was found between physical activity level and risk of heart failure [75]. The hazard ratios for HF decreased from 0.9 to 0.81 and 0.65 for participants engaged in physical activity of 500, 1000, and 2000 MET-min/week, respectively, compared with participants reporting no leisure time physical activity.

European guidelines of hypertension recommend at least 30 min/day of moderate dynamic exercise on 5–7 days/week and resistance exercises on 2–3 days/week can be advised [4], Canadian guidelines recommend 30–60 min/day of moderate dynamic exercise on 4–7 days/week [39], while the American Heart Association/American College of Cardiology guidelines recommend an increased physical activity with a structured exercise program [5].

Table 17.2 Types and examples of physical exercise [76–79]

Type	Examples
Dynamic aerobic (endurance) exercise	*Moderate (3–6 METS)*: brisk walking, dancing, gardening, housework, involving in games with children, walking domestic animals, building tasks (roofing, painting), carrying/moving moderate loads (<20 kg)
	Vigorous (>6 METS): running, climbing briskly up to a hill, fast cycling, aerobic, fast swimming, competitive sports and games (football, volleyball, hockey, basketball), carrying/moving moderate loads (>20 kg)
Dynamic resistance exercise	Weight lifting, circuit training using equipment (resistance-training machines)
Isometric resistance exercise	Handgrip exercise

METS metabolic equivalents

Before recommending physical activity to patients with hypertension, several precautions should be taken into account for individuals who intend to engage in more vigorous physical activity or sports [76]. Exercise testing is recommended in patients with stage 2 hypertension or in those with cardiovascular risk factors if planning moderate-vigorous intensity physical exercise (3–6 METS) and in all patients with documented cardiovascular disease for all levels of physical exercise. Absolute contraindications to aerobic and resistance training programs include recent myocardial infarction or electrocardiography changes, complete heart block, acute congestive heart failure, unstable angina, and uncontrolled severe hypertension (BP ≥180/110 mmHg) [76].

Types and examples of physical exercise are presented in Table 17.2.

17.7 Alcohol Consumption, BP Control, and Risk of HF

The relationship between alcohol consumption and cardiovascular risk factors and cardiovascular disease is complex and dose-dependent. In observational studies, alcohol consumption is positively associated with BP values, especially above an intake of three standard drinks per day [80–82]. A meta-analysis published in 2001 which included 15 RCTs and 2234 participants demonstrated that an intervention to decrease alcohol consumption compared with no intervention led to a mean reduction of 3.31 mmHg and 2.04 mmHg for SBP and DBP, respectively [83]. A significant correlation was found between percentage of alcohol reduction and reduction of BP. Individuals with hypertension at baseline and those treated with antihypertensive drugs have higher decrease in BP values following intervention. The results were confirmed in a recent meta-analysis which included 36 RCTs [84]. In people drinking <2 drinks/day, no effect was seen on BP values, whereas in those consuming ≥2 drinks/day, a reduction in alcohol intake was associated with blood pressure reduction. The most pronounced reduction was seen in participants drinking ≥6 drinks/day if they reduced their intake by about 50% (5.50 mmHg and 3.97 mmHg for SBP and DBP, respectively). In all subgroups stratified according to gender, hypertension status, or cardiovascular risk, the same relationship between alcohol reduction and lower BP was found.

In contrast with the negative effects on BP, alcohol has positive effects on increasing HDL-cholesterol and on other markers of cardiovascular risk such as apolipoprotein A1 and adiponectin or decreasing fibrinogen levels [85, 86] as well as on cardiovascular mortality [87, 88], but this protective effect was only seen in light and moderate drinkers.

The relationship between alcohol consumption and risk of HF was examined in the Framingham study cohort, and the results showed that in men the risk for congestive HF was lower at all levels of alcohol consumption compared with men who consumed less than 1 drink/week and that in women the lowest risk was in those consuming 3–7 drinks/week [89]. In a cohort of 5153 hypertensive male physicians [90], it was found that the risk of HF over a period of 18 years was decreased in light and moderate drinkers compared to those consuming<1 drink/week. No conclusion could be drawn for heavy drinkers who represented only 4% of enrolled participants. Nevertheless, toxic cardiomyopathy induced by excessive alcohol consumption remains one of the causes of HF [91], and alcoholic patients who consume >90 g of alcohol a day for >5 years are at risk for alcoholic cardiomyopathy which represents 21–36% of all cases of nonischemic dilated cardiomyopathy in Western Society and is associated with high mortality [92].

In the view of available data, current recommendation for hypertensive patients is to limit the alcohol intake to ≤20–30 g of ethanol/day in men and ≤10–20 g in women or to ≤2 drinks/day in men and ≤1 drink/day in women [4, 5].

17.8 Smoking and BP

Smoking can acutely increase BP and heart rate which persist more than 15 min after smoking a cigarette as demonstrated in an experimental study on normotensive subjects [93], and the mechanism responsible is the sympathetic activation induced by smoking at the central level and at the neuroeffector junctions [94]. Very limited data is available regarding the chronic effect of smoking on BP. In a cohort of 33,860 adults from the Health Survey for England, it was concluded that an independent chronic effect of smoking on BP was small and that complex interrelations exist among smoking, alcohol intake, and BMI [6]. Few studies examined BP values using ambulatory blood pressure measurement (ABPM) in normotensive and hypertensive smokers [95–98] and confirmed that the daytime mean values of SBP and DBP were higher in smokers irrespective of antihypertensive treatment, while office and nighttime BP values were similar. These findings raise the question whether hypertensive smokers are not undertreated if BP control is only evaluated with office measurements.

Besides its effects on BP, smoking is a major risk factor for cardiovascular disease and for increased mortality of other causes, including cancer [99].

Hypertensive patients are already at higher risk for cardiovascular disease, and the status of tobacco use should be checked at each patient visit. The advice to quit smoking should be given to all hypertensive smokers [4].

Various strategies have been shown to be effective for smoking cessation [100]. The US Public Health Service Clinical Practice Guidelines suggest the “5 As”

strategy to be used in clinical settings [101], and this strategy was embraced by many professional societies: **A**sk about tobacco use, **A**dvise to quit smoking, **A**ssess willingness to quit, **A**ssist in quitting through behavioral interventions or pharmacotherapy, and **A**rrange for follow-up contact to prevent relapse.

Unassisted smoking cessation has a very low rate of success, and only 3–5% of self-quitters maintain abstinence for 6–12 months after a quit attempt [102]. Physician advice further increase the chance of quitting smoking [103], and Internet-based intervention was also found to have a significant effect [104]. Other behavioral interventions such as motivational interview, individual therapy (counseling), or group therapy can be used to facilitate smoking cessation [100, 105]. Pharmacological therapy includes nicotine replacement therapy (NRT) formulated as chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets, and two non-nicotine medications, bupropion, an antidepressant, and varenicline, a partial nicotine receptor agonist [100]. All pharmacological therapies were found to have a superior effect over placebo in achieving long-term (>6months) smoking cessation, with an OR of 1.84 for NRT vs. placebo, 1.82 for bupropion vs. placebo, and 2.88 for varenicline vs. placebo, and the safety profile did not raise any concerns.

Electronic cigarette (e-cigarette) delivers nicotine but avoids most of the tobacco chemicals. A non-statistically significant trend toward smoking cessation was found in a recent meta-analysis [106], but long-term safety of e-cigarette is still to be proven [107].

17.9 Other Non-pharmacological Interventions for BP Lowering

Several other non-pharmacological interventions were examined in relation with blood pressure control, but evidence is not yet convincing to be incorporated in hypertension guidelines.

17.9.1 Dietary Proteins

Two meta-analysis of RCTs found modest but statistically significant differences in SBP and DBP between dietary protein groups (in which protein intake was increased either by supplementation or through diet modification) and carbohydrate groups (conventional diet) of approximately 2 mmHg with no difference between vegetable and animal protein [108, 109]. A weak negative association was also found between protein intake and lower BP levels in cross-sectional but not in prospective studies; intake of vegetal protein was negatively, but nonsignificantly, associated with SBP, but animal proteins were not [109]. In a cross-sectional analysis involving 125,287 participants from 18 countries from almost all geographical areas in the world and included in the Prospective Urban Rural Epidemiology (PURE) study, higher protein intake was associated with lower BP, whereas higher intakes of total fat,

saturated fatty acids, and carbohydrates were associated with higher BP [110]. These findings suggest that a partial replacement of dietary carbohydrates with proteins might lead to a decrease of BP levels. No specific data is available for hypertensive individuals.

17.9.2 Dietary Fibers

Two meta-analyses of RCTs demonstrated beneficial effects of high dietary fiber intake on BP levels in patients with hypertension, but the magnitude of the effect differed between the two reports [111, 112]. Both meta-analyses found that the decrease of BP was larger in hypertensive compared to normotensive participants and in older vs. younger subjects. It was also observed that the effect was larger in trials with a duration of intervention > or = 8 weeks [111] and that mixtures of soluble and insoluble fibers seemed to decrease blood pressure more than either fibers alone. Insoluble fibers were associated with only small changes in blood pressure [112]. Soluble fibers are B-glucans, gums (e.g., guar gum), wheat dextrin, psyllium, pectin, and inulin and are mostly found in oatmeal, nuts, beans, apples, blueberries, carrots, barley, and psyllium; insoluble fibers are cellulose, lignin, some pectins, and some hemicelluloses which are found in whole-grain cereals, seeds, and skins of fruit [113]. The recommended dietary fiber intake is 14 g/1000 kcal [20].

17.9.3 Probiotics

Fermented milk products were shown to contain biologically active peptides with an angiotensin-converting enzyme (ACE)-inhibiting properties [114] and BP-lowering effects that were first demonstrated in animal models of hypertension [115]. Later, the studies which tested the effect of probiotics on BP in humans yielded conflicting results. In a meta-analysis of nine RCTs, it was found that probiotics consumption was associated with a significant reduction of SBP and DBP (−3.56 mmHg and −2.38 mmHg, respectively) and that the effect on DBP was more pronounced in individuals with BP ≥130/85 mmHg compared with <130/85 mmHg. Greater reduction of BP was seen with multiple as compared with single species of probiotics and in interventions >8 weeks [116]. Probiotic consumption could therefore play a role in BP control.

17.9.4 Calcium and Magnesium Supplementation

Calcium has been shown to play a role in hypertension especially in high-salt intake environment [117]. In an older meta-analysis of RCTs using calcium supplementation (mean daily dose, 1200 mg), no statistically significant effect was found on SBP or DBP in the overall population, and only SBP significantly decreased with

−2.63 mmHg in the subgroup with low (<800 mg/day) dietary calcium intake [118]. A more recent meta-analysis which only included RCTs in normotensive populations found a slight decrease of BP levels especially in younger individuals (<35 years), and the decrease was dose-dependent [119].

Magnesium has been implicated in several mechanisms linked to hypertension and BP control [120], and a meta-analysis of 22 RCTs using magnesium supplementation (mean daily dose 410 mg) demonstrated a decrease in SBP of 3–4 mm Hg and DBP of 2–3 mm Hg, which further increased with an intake >370 mg/day [121]. The favorable effects of magnesium were confirmed in more recent meta-analysis demonstrating that a median dose of 368 mg/d for a median duration of 3 months significantly reduced SBP by 2.00 mmHg and DBP by 1.78 mmHg [122].

17.9.5 Other Dietary Components

Other dietary components were found to have some positive effects on BP in hypertensive patients such as flaxseed [123], fish oil [124], dark chocolate [125], and tea [126]. Coffee can acutely increase BP, but a meta-analysis examining the effect of chronic coffee consumption did not show any statistically significant effect on BP or the risk of hypertension [127]. Increased fruit and vegetable consumption was associated with lower risk of hypertension, by 1.9% for each serving per day of fruit consumption and 1.2% for each serving per day of total fruit and vegetable consumption [128], but the effect on BP in individuals with hypertension is unclear.

17.10 Alternative Approaches to Lowering Blood Pressure

A recent scientific statement from the American Heart Association examined the evidence for alternative approaches, other than medication and diet, for lowering BP [77]. The conclusions were that among behavioral therapies, Transcendental Meditation modestly lowered BP and could be used in hypertensive patients, other meditation techniques (including Mindfulness-Based Stress Reduction) showed negative or mixed results, and yoga demonstrated no benefit. Other relaxation therapies and biofeedback approaches have modest, mixed, or no consistent evidence demonstrating their efficacy. Between the noninvasive procedures and devices, device-guided breathing had greater support than acupuncture which did not demonstrate benefits.

17.11 Multifactorial Interventions

Very few studies examined the effect of multifactorial interventions on BP control and long-term cardiovascular benefits. The PREMIER trial [129] included 810 participants with prehypertension or stage 1 hypertension randomized to 3

interventions: long-established recommendations (weight loss, physical activity, sodium intake<100 mmol/day, and alcohol <2 drinks/day in men and <1 drink/day in women), long-established recommendations and DASH diet, and advice-only group. In the first two groups, an intensive behavioral therapy was applied with 14 group sessions and 4 individual sessions during the first 6 months and then monthly group sessions supplemented with 3 individual counseling sessions for the rest of the study. After 18 months of interventions, the ORs for hypertension were 0.83 for the established group and 0.77 for the established plus DASH group compared with advice only. The effects on clinical cardiovascular events could not be established due to short-duration and sample size population.

The Look AHEAD (Action for Health in Diabetes) trial enrolled 5145 patients with type 2 diabetes of whom 75.3% were using antihypertensive medicines, randomized to intensive lifestyle intervention or to diabetes support and education (DSE). The intensive intervention group received weekly group and individual counseling sessions for the first 6 months with decreasing frequency thereafter and having as objective the achievement and then maintenance of a weight loss of at least 7% through diet and physical activity. BP levels significantly decreased at 1 year (SBP −6.8 vs. −2.8 mmHg and DBP −3.0 vs. −1.8 in intervention vs. DSE group), as well as all other measured cardiovascular risk factors, but the between-group difference diminished over time. The most sustained differences on long term were seen for glycated hemoglobin and SBP [130, 131].

At a median follow-up of almost 10 years, no significant differences between the two groups were obtained for cardiovascular morbidity and mortality. The primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina occurred at a rate of 1.83 and 1.92 events per 100 person-years in the intensive intervention vs. DSE groups [131]. One of the explanations for the lack of cardiovascular benefits is that the amount of weight loss obtained in the intervention group (8.6% at the end of first year, which was not fully maintained throughout the follow-up, with a mean of 6%) was not enough to be associated with benefits on hard endpoints. Lower cardiovascular event rate than those projected at trial start (0.7%/year vs. 3.125%/year) could have also contributed to nonsignificant difference between groups [132].

In conclusion, a whole range of non-pharmacological interventions are proven to have benefits or have been tested for the BP control in patients with hypertension, but not all are sufficiently sustained by available evidence to be recommended as routine strategies. Moreover, to establish the influence of non-pharmacological interventions on the clinical course of hypertension, including risk of HF, still needs more studies with longer duration and better methodology.

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18 Blood Pressure-Lowering Treatment and the Prevention of Heart Failure: Differences and Similarities of Antihypertensive Drug Classes

Costas Thomopoulos and Alberto Zanchetti†

18.1 Antihypertensive Treatment and Heart Failure: Prevention of Recurrences or Prevention of New-Onset Heart Failure?

Moser and Hebert were the first to call attention to the finding that blood pressure (BP)-lowering treatment did not only reduce risk of fatal and nonfatal stroke and fatal and nonfatal coronary heart disease (CHD) events but also risk of heart failure [1]. They reviewed data from 12 placebo (or no treatment)-controlled randomized trials (RCTs) including 13,837 hypertensive patients and calculated heart failure risk was reduced by 51% (risk ratio [RR] and 95% confidence interval [CI] 0.48 [0.38–0.59]). They also remarked that most of the positive RCTs they had considered had used a diuretic as BP-lowering drug [1].

In a very large meta-analysis updated to end 2013 and including 68 RCTs on as many as 245,885 participants, we extended Moser and Herbert's early analysis and we demonstrated that heart failure risk was significantly reduced by a standardized systolic BP/diastolic BP reduction of 10/5 mmHg and that heart failure reduction was even numerically greater than that of stroke (−43% vs. −38%) and much greater than the albeit significant reductions of CHD events and cardiovascular and all-cause mortality [2]. A more stringent comparison was subsequently done by our group by restricting meta-analyses to only those 35 BP-lowering RCTs (146,810 individuals) measuring all major cause-specific events (stroke, CHD, heart failure, cardiovascular

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mortality) [3], and we reported that heart failure and stroke were by far the outcomes most extensively reduced by BP lowering (RR stroke 0.58 [0.49–0.68]; heart failure 0.63 [0.52–0.75]), without a significant difference between the two reductions. We also calculated a meta-regression to compare the relationships between the relative risk reductions of the various outcomes with the extent of BP reduction [3] and found the steepest slopes for the relationships with heart failure and stroke with no significant differences between these slopes (p = 0.69, 0.78, and 0.67 for systolic BP, diastolic BP, and pulse pressure reductions, respectively). On the other hand, the slopes of heart failure reduction were significantly greater than those of all-cause mortality reduction (p = 0.022, 0.024 for systolic BP and pulse pressure reductions), although decreased mortality (both cardiovascular and all-cause) was also a significant effect. In no one of our meta-regression analyses was coronary heart disease reduction significantly related to the extent of blood pressure reduction (Fig. 18.1).

A further important question is whether BP-lowering treatment really prevents "new-onset" heart failure or mostly reduces recurring or worsening of preexisting heart failure. A correct analysis implied meta-analysis of only those BP-lowering

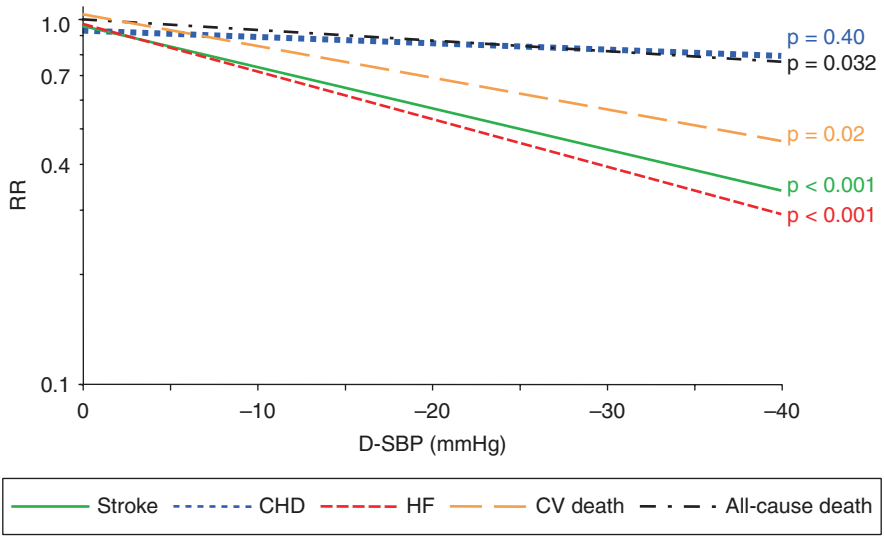

Fig. 18.1 Relationships of outcome reductions to the extent of BP reductions, in the 35 blood pressure-lowering trials in which all the listed outcomes were measured. Meta-regressions of risk ratios (RR) on absolute systolic blood pressure (SBP) differences (D) (active treatment minus placebo or less active treatment). Stroke is the green continuous line, coronary heart disease (CHD) the blue square line, heart failure (HF) the red short dashed line, cardiovascular (CV) death the orange long dashed line, and all-cause death the black dashed and dotted line. *P*-values indicate statistical significance of the slope of each outcome (colors as above to identify outcomes) on BP difference. Note the ordinates are on a ln scale. Modified from Thomopoulos et al. [3], by courtesy of *Journal of Hypertension*

RCTs explicitly excluding patients with history or current evidence of heart failure. Of the 35 BP-lowering RCTs measuring heart failure as an outcome, our search identified 18 in which baseline history of HF was explicitly listed as an exclusion criterion [4–31] and, therefore, suitable to be meta-analyzed to estimate the BP-lowering preventive effect on "new-onset" heart failure. Our search also identified other ten RCTs in which only patients with mild heart failure could have been included; added to the 18 RCTs with no baseline HF, they were used for a secondary meta-analysis (Table 18.1).

Even with the more stringent criteria of including RCTs with no baseline heart failure (Fig. 18.2), there was a large and highly significant reduction of "new-onset" heart failure, the extent of which (relative risk reduction −42%, absolute reduction −21 heart failure cases per 1000 patients treated 5 years) is very similar to that in the entire set of RCTs measuring heart failure as an outcome (relative risk reduction −37%, absolute risk reduction −19 heart failure cases). Also the secondary meta-analysis using looser criteria in selection of RCTs did not substantially change the quantitative assessment of the effectiveness of BP-lowering treatment in the prevention of development of new HF (Fig. 18.2).

Table 18.1 Blood pressure-lowering trials evaluating new-onset heart failure

Baseline HF excluded	Mild baseline HF allowed	Drug class
ACTION [4]	ADVANCE [22]	Diuretics
AUSTRALIAN-Mild [5]	FEVER [23]	AUSTRALIAN-Mild [11]
CAMELOT [6]	SHEP pilot [24]	EWPHE [13]
EWPHE [7]	SHEP [25]	HYVET [17]
HEP [8]	STOP [26]	OSLO [18]
HSCSG [9]	Cardio-Sys [27]	Beta-blockers
HYVET [10]	IDNT [28]	HEP [15]
OSLO [11]	NAVIGATOR [29]	UKPDS 38 [32]
Syst-China [12]	ORIENT [30]	Calcium antagonists
Syst-Eur [13]	PEACE [31]	ACTION [9]
USPHS [14]		CAMELOT [12]
JATOS [15]		Syst-China [22]
UKPDS 38 [16]		Syst-Eur [23]
DIABHYCAR [17]		ACE inhibitors
DREAM [18]		CAMELOT [12]
HOPE [19]		UKPDS 38 [32]
RENAAL [20]		DIABHYCAR [34]
TRANSCEND [21]		DREAM [35]
		HOPE [36]
		ARBs
		RENAAL [43]
		TRANSCEND [44]

Trials indicated by their acronyms or first author. Full titles can be found in the references. Other abbreviations: *ACE* angiotensin-converting enzyme, *ARBs* angiotensin receptor blockers, *HF* heart failure

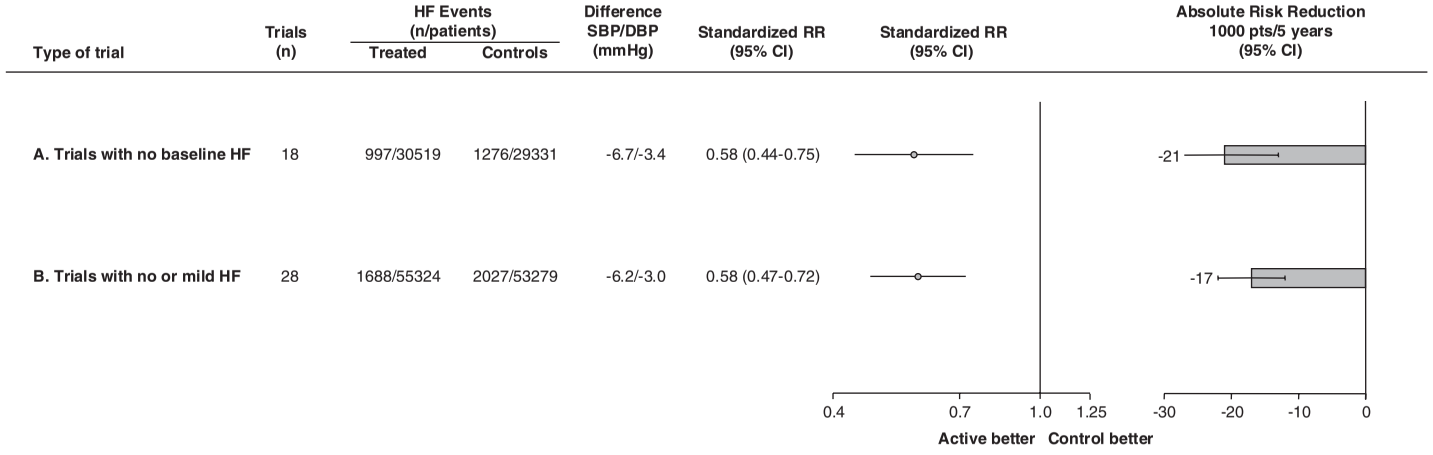

Fig. 18.2 Relative and absolute risk reduction of heart failure in blood pressure lowering in trials with no baseline heart failure (*A*) and with no or mild baseline heart failure (*B*). Each column from left to right indicates numbers (*n*) of trials considered, the number of heart failure (HF) events observed and the number of patients followed up, the difference in systolic and diastolic blood pressure (SBP/DBP) achieved between actively treated patients (treated) and controls, the risk ratio (RR) and its 95% confidence interval (CI) standardized by a 10/5 mmHg difference, the standardized risk ratio as forest plot, and the absolute risk reduction as number and 95% CI of events prevented every 1000 patients treated for 5 years. Modified from Thomopoulos et al. [3], by courtesy of *Journal of Hypertension*

18.2 Are the Various Classes of Antihypertensive Drugs Equally Effective in Preventing "New-Onset" Heart Failure?

Other clinically relevant questions are: Are all classes of BP-lowering drugs capable of significantly reducing "new-onset" heart failure, and, when directly (head-to-head) compared, are classes equally effective? A correct answer to these questions again required analyses limited to RCTs excluding baseline heart failure.

The first part of this question (i.e., the ability of each drug class to reduce new-onset heart failure) was approached by meta-analyzing placebo-controlled BP-lowering trials stratified by the class of the active drug compared with placebo. Among the BP-lowering RCTs that had rigorously excluded patients with baseline heart failure, four had BP lowering induced or initiated by a diuretic, two by a beta-blocker, four by a calcium antagonist, five by an ACE inhibitor, and two by an angiotensin receptor blocker (Table 18.1, column "Drug class"). In meta-analyses restricted to RCTs with no baseline heart failure (Fig. 18.3a), BP lowering by diuretics, beta-blockers, calcium antagonists, and ACE inhibitors significantly reduced the risk of new heart failure. Inability to find a significant heart failure reduction with angiotensin receptor blockers is likely to depend on insufficient statistical power (only two RCTs) associated with a small systolic BP/diastolic BP difference.

The second part of the question (i.e., the relative effectiveness of the various drug classes) was explored by using a second set of meta-analyses, focused on direct head-to-head comparisons of different active BP-lowering drugs, the only correct way of evaluating the relative effectiveness of two interventions. To investigate the more general question of the comparative effectiveness of various drug classes on cardiovascular outcomes, we had previously identified 50 RCTs with 58 two-drug comparisons, but of these trials, only 34 with 40 comparisons measured heart failure in addition to other outcomes. Among these head-to-head comparison trials, 18 RCTs had excluded baseline heart failure from recruitment, and seven had only allowed mild heart failure [6, 28, 33–55]. These trials allowed studying the relative effectiveness of the various drug classes in the prevention of "new-onset" heart failure (Table 18.2). Figure 18.3b shows that, even when only RCTs explicitly excluding baseline heart failure were considered, calcium antagonists were found to be significantly inferior to all other drugs in preventing "new-onset" heart failure. No significant differences were found in all other comparisons, except for some superiority of diuretics vs. all other drugs together. Separate secondary meta-analyses including also RCTs allowing inclusion of mild heart failure gave results overlapping with those of the primary analyses shown in Fig. 18.3b.

	Comparison	Trial comparisons (n)	Difference SBP/DBP (mmHg)	HF Events (n/patients) 1st Drug	HF Events (n/patients) Control	RR (95% CI)
A.	D vs PL	4	-15.1/-5.9	44/ 4476	84/ 4421	0.53 (0.37-0.75)*
	BB vs PL	2	-14.8/-8.7	31/ 777	60/ 855	0.57 (0.35-0.91)
	CA vs PL	4	-6.7/-3.9	161/ 8139	220/ 7933	0.73 (0.59-0.89)
	ACEI vs PL	5	-4.1/-1.8	530/10784	670/10812	0.79 (0.71-0.88)*
	ARB vs PL	2	-4.2/-2.0	223/ 3705	256/ 3734	0.86 (0.59-1.26)
B.	D vs All Others	10	-0.92/0.14	1067/29197	1527/33116	0.84 (0.73-0.98)
	BB vs All Others	5	1.91/0.99	334/15653	310/16848	1.05 (0.91-1.22)†
	CA vs All Others	13	-0.25/-0.87	1190/45887	1940/61353	1.16 (1.01-1.32)
	ACEI vs All Others	7	1.36/0.62	1060/22569	2072/37733	0.93 (0.80-1.11)†
	ARB vs All Others	6	-0.54/-0.07	583/16680	559/17768	1.05 (0.94-1.18)
	RASB vs All Others	11	1.05/0.57	895/23131	1883/38383	0.97 (0.84-1.13)

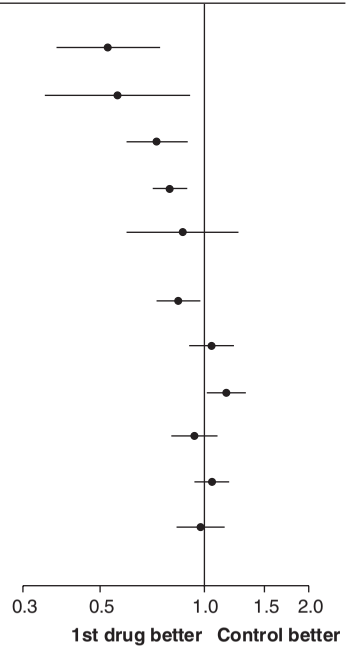

Fig. 18.3 Effects of blood pressure lowering by each of five major classes of drugs compared with placebo (*A*) and with different classes of drugs (head-to-head comparisons) (*B*) on new-onset heart failure (trials with no baseline heart failure). Columns from left to right are numbers (*n*) of comparisons, the difference in systolic and diastolic blood pressure (SBP/DBP) achieved between treatment groups (negative numbers indicate lower BP with the first drug and positive numbers lower BP with the control), the number of heart failure (HF) events observed and the number of patients followed up, the risk ratio (RR) with 95% confidence intervals (CI) calculated with the observed SBP/DBP difference, and the risk ratio represented as forest plot. *ACEI* angiotensin-converting enzyme inhibitors; *ARB* angiotensin receptor blockers, *BB* beta-blockers, *CA* calcium antagonists, *D* diuretics, *PL* placebo, *RASB* renin-angiotensin system blockers, vs. versus. The asterisks indicate RR calculated with the fixed effect model and the crosses RR values adjusted for the SBP/DBP difference. Modified from Thomopoulos et al. [3], by courtesy of *Journal of Hypertension*

Table 18.2 Trials comparing head-to-head different classes of BP-lowering drugs[a]

Diuretics vs. all	BBs vs. all	CAs vs. all	ACEIs vs. all	ARBs vs. all
ACCOMPLISH [33]	ASCOT-BPA [42]	CAMELOT [6]	CAMELOT [6]	CASE-J [45]
ALLHAT [34]	COPE [36]	ACCOMPLISH [33]	ALLHAT [34]	COPE [36]
ANBP-2 [35]	LIFE [43]	ALLHAT [34]	ANBP-2 [35]	E-COST-R [55]
COPE [36]	UKPDS 39 [44]	ASCOT-BPA [42]	JMIC-B [47]	LIFE [43]
INSIGHT [37]	(HAPPHY) [41]	CASE-J [45]	ONTARGET [53]	ONTARGET [53]
MIDAS [38]		CONVINCE [46]	UKPDS 39 [44]	(IDNT) [28]
NICS-EH [39]		INSIGHT [37]	(ABCD-H) [49]	(MOSES) [50]
VHAS [40]		JMIC-B [47]	(CAPPP) [54]	(NAGOYA) [51]
(HAPPHY) [41]		MIDAS [38]		(VALUE) [52]
		NICS-EH [39]		
		NORDIL [48]		
		VHAS [40]		
		(ABCD-H) [49]		
		(IDNT) [28]		
		(MOSES) [50]		
		(NAGOYA) [51]		
		(VALUE) [52]		

ACEIs angiotensin-converting enzyme inhibitor, *ARBs* angiotensin receptor blockers, *BBs* beta-blockers, *CAs* calcium antagonists, *HF* heart failure

[a]Trials excluding baseline HF and, between parentheses, trials allowing mild baseline HF

18.3 Does the Apparent Inferiority of Calcium Antagonists in Preventing New Onset of Heart Failure Depend on Their Pharmacological Properties or on the Design of the Trials?

An additional important question is whether the reported statistically significant inferiority of calcium antagonists in HF risk prevention [8] really depends on pharmacological properties of this drug class or rather results from the design of many trials forbidding the concomitant use of drugs known to be active in HF treatment in the calcium antagonist group but not in the other one.

Of the 13 comparisons of calcium antagonists with other classes of BP-lowering drugs in 12 RCTs excluding preexisting heart failure at baseline, four were in RCTs whose design allowed the concomitant use of diuretics, beta-blockers, or renin-angiotensin system blockers in the calcium antagonist group:

- In ACCOMPLISH [33], patients were randomized either to the association of benazepril-amlodipine or benazepril-hydrochlorothiazide; therefore both treatment groups equally received the ACE inhibitor benazepril.
- In the ASCOT-BPA trial [43], patients randomized to the calcium antagonist amlodipine could receive as second drug the ACE inhibitor perindopril (mean 58.5% throughout the time), and in the control group, patients initially

randomized to the beta-blocker atenolol could receive as second drug a thiazide diuretic (mean 65.7% throughout the trial).
- In CAMELOT [6], background therapy with a diuretic was given to 32% of patients randomized to amlodipine and to 27% of those randomized to enalapril, and a beta-blocker was given to 74% and 75% of the patients randomized, respectively, to the calcium antagonist and the ACE inhibitor.
- In CASE-J [45], patients randomized to amlodipine and those to the angiotensin receptor blocker candesartan could additionally receive a diuretic (14% in the amlodipine group and 25% in the candesartan group) and a beta-blocker (17% and 22%, respectively).

On the other hand, in eight RCTs (nine comparisons), the trial design prevented the use of all or part of drugs active in the treatment of heart failure:

- In ALLHAT [34], patients receiving a calcium antagonist could not receive diuretics and renin-angiotensin system blockers (but only beta-blockers, reserpine, or clonidine) as second drugs.
- In INSIGHT [37], all patients in the control group received a diuretic, which could not be administered in the calcium antagonist group, whereas only a minority of patients in both the groups concomitantly received either a beta-blocker or an ACE inhibitor.
- In JMIC-B [47], control patients received an ACE inhibitor, which could not be prescribed in the calcium antagonist group, with less than 25% of patients in either group concomitantly receiving a beta-blocker.
- In MIDAS [38], administration of a diuretic was reserved to the control group and prohibited to the calcium antagonist group, with 25–28% of patients in either group concomitantly receiving the ACE inhibitor enalapril.
- In NICS-EH [39], a thiazide diuretic was given to all patients in the control group and prohibited in the patients randomized to the calcium antagonist nicardipine.
- In CONVINCE [46], diuretics were used in only 26% of the verapamil patients and in 44% of control patients, and beta-blockers could not be prescribed to verapamil patients, but they were prescribed to 43% of patients in the control group.
- In NORDIL [48], diuretics were used in 17% of the diltiazem patients and in 43% of the control patients and beta-blockers in 13% and 66% of the diltiazem and control patients, respectively.
- In VHAS [40], diuretics were used only in the control arm and were forbidden in the verapamil arm, with only one patient out of the four receiving an ACE inhibitor in both arms.

Separate meta-analyses of the two sets of RCTs are summarized in Fig. 18.4. In those RCTs in which some of the drug classes effective in heart failure treatment could be administered in both the calcium antagonist and the control group, no significant difference occurred in the risk of "new-onset" heart failure between the two treatment groups (RR 0.96 [0.81–1.12]) (Fig. 18.4b), whereas a higher heart

Trial		Difference SBP/DBP (mmHg)	HF Events (n/patients) CA	HF Events (n/patients) Control	RR (95% CI)	P Heterogeneity
A. Trials forbidding use of D, BB, RASB in the CA group						
ALLHAT [34]	(CA vs D)	1.1/-0.7	706/ 9048	870/15255	1.37 (1.24-1.51)	
ALLHAT [34]	(CA vs ACEI)	-1.3/-1	706/ 9048	612/ 9054	1.15 (1.04-1.28)	
CONVINCE [46]	(CA vs D/BB)	-0.1/-0.7	126/ 8179	100/ 8297	1.28 (0.98-1.66)	
INSIGHT [37]	(CA vs D)	0/0	26/ 3157	12/ 3164	2.17 (1.10-4.30)	
JMIC-B [47]	(CA vs ACEI)	-2/-2	12/ 828	9/ 822	1.32 (0.56-3.12)	
MIDAS [38]	(CA vs D)	-4.5/0.5	2/ 442	0/ 441	4.99 (0.24-103.61)	
NICS-EH [39]	(CA vs D)	0.5/-0.4	0/ 204	3/ 210	0.15 (0.01-2.83)	
NORDIL [48]	(CA vs D/BB)	3.2/-0.1	63/ 5410	53/ 5471	1.20 (0.84-1.73)	
VHAS [40]	(CA vs D)	2.8/0.2	2/ 224	2/ 232	1.04 (0.15-7.29)	
Total		***0.6/-0.6***	***937/27492***	***1661/42946***	***1.27 (1.14-1.42)***	***0.21***
B. Trials allowing use of D, BB, RASB also in the CA group						
ACCOMPLISH [33]	(CA vs D)	-0.9/-1.1	100/ 5744	96/ 5762	1.04 (0.79-1.38)	
ASCOT [42]	(CA vs BB)	-2.7/-1.9	134/ 9639	159/ 9618	0.84 (0.67-1.06)	
CAMELOT [6]	(CA vs ACEI)	0.7/0.4	3/ 663	4/ 673	0.76 (0.17-3.39)	
CASE-J [45]	(CA vs ARB)	-1.7/-0.6	16/ 2349	20/ 2354	0.80 (0.42-1.54)	
Total		***-1.9/-1.4***	***253/18395***	***279/18407***	***0.96 (0.81-1.12)†***	***0.66***

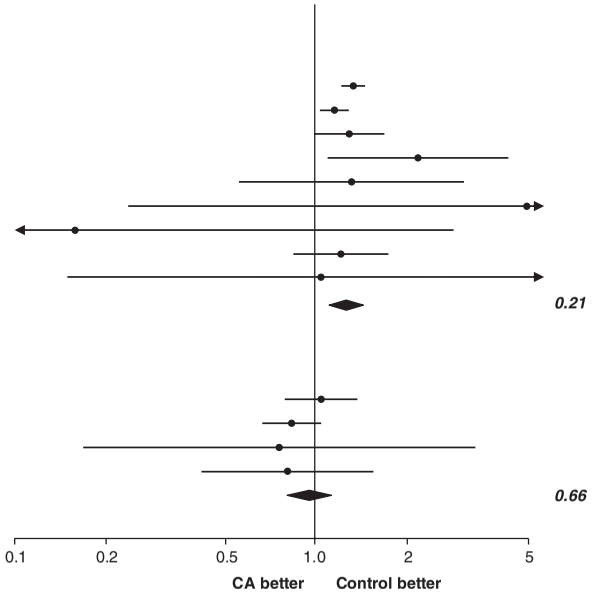

Fig. 18.4 Separate meta-analyses of trials comparing calcium antagonists with other blood pressure-lowering drugs according to trial design: (*A*) forbidding concomitant use of diuretics, beta-blockers, and renin-angiotensin system blockers in the calcium antagonist treatment group and (*B*) allowing concomitant use of diuretics, beta-blockers, and renin-angiotensin system blockers also in the calcium antagonist treatment group. Trials with no baseline heart failure. Each row reports data from single trials (indicated by acronym and drug comparison). Columns from left to right: between group systolic/diastolic blood pressure (SBP/DBP) differences, number (*n*) of heart failure (HF) events and number of patients in each treatment group, risk ratio (RR) with 95% confidence intervals (CI), RR forest plots, and *P*-value for heterogeneity for the two meta-analyses. *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *BB* beta-blockers, *CA* calcium antagonists, *D* diuretics, *PL* placebo, vs. versus. *P*-value for differences between RR in meta-analysis A and RR in meta-analysis B is 0.002. The symbol † indicates RR value adjusted for the SBP/DBP difference. From Thomopoulos et al. [3], by courtesy of *Journal of Hypertension*

failure risk occurred in those RCTs, the design of which prevented addition of drugs effective in heart failure treatment to the patients randomized to calcium antagonists (RR 1.27 [1.14–1.42]) (Fig. 18.4a). The difference between the RRs of the two groups is statistically significant ($p = 0.002$).

18.4 Conclusions

1. Heart failure is with stroke one of the two cardiovascular outcomes that are reduced by BP-lowering treatment to the greatest extent, without a clear preference for either outcome.
2. Meta-analysis of only those RCTs that specifically excluded baseline heart failure allows the conclusion that heart failure risk reduction mostly consists of prevention of the clinical manifestations of "new-onset" heart failure, at least as clinically diagnosed by hospital physicians.
3. BP lowering by any of the five major classes of BP-lowering drugs (diuretics, beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers) can significantly reduce the risk of "new-onset" heart failure. This means that, when the possibility of recurrence or worsening of preexisting heart failure is avoided, the preventing effect of BP lowering by calcium antagonists on heart failure also achieves statistical significance.
4. When RCTs head-to-head comparing different classes of agents have been used in order to appropriately explore whether all antihypertensive drug classes are equally effective in preventing new heart failure, calcium antagonists have been found significantly less effective than the other drug classes in the prevention of new-onset heart failure.
5. However, we have found that inferiority of calcium antagonists in heart failure prevention occurs only in those RCTs whose design forbade or limited the use of diuretics, beta-blockers, or renin-angiotensin system blockers as accompanying drugs in the calcium antagonist arm but not in the control arm. On the other hand, the calcium antagonist inferiority did not occur in the RCTs allowing the use of the abovementioned drugs also in the calcium antagonist arm. These findings support the hypothesis that the inferiority of calcium antagonists as far as new heart failure is concerned may depend, at least to a large extent, on an unequal use of accompanying drugs in such a way that the larger use of drugs known to reduce heart failure symptoms (diuretics, beta-blockers, and renin-angiotensin system blockers) in the control arms may mask onset of heart failure symptoms to a greater extent in control patients and create an imbalance against calcium antagonists. This interpretation supports the concept that, as for most outcomes, also the preventive effect of BP lowering on new heart failure basically depends on the lowering of BP independently of the drugs by which BP is reduced and suggests the clinical value of the association of calcium antagonists with any of the agents known to alleviate heart failure symptoms.

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Regression Under Treatment of Left Ventricular Hypertrophy and Other Structural Alterations

19

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19.1 Introduction

Hypertension-induced mortality and morbidity are produced through the impact of increased blood pressure (BP) on the heart and other target organs. Evaluation of early damage (TOD) in these target organs is an important step in a risk stratification strategy to reduce cardiovascular and renal events.

The ESH-ESC Guidelines 2013 [1] encouraged the convenience of assessing target organ damage for global risk stratification and of repeating TOD assessment during the follow-up. Among a panel of TOD included in the 2013 guidelines and based on availability, cost, and clinical significance, the evaluation of left ventricular hypertrophy (LVH) by electrocardiography and, possibly, the assessment of left ventricular (LV) mass by echocardiography are among the minimal recommended, in addition to urinary albumin excretion and glomerular filtration rate. Maladaptation of the heart in response to chronic hypertension is often associated with deleterious disorders, including cardiac fibrosis, chronic inflammatory response, and cardiac dysfunction, leading to heart failure, which remains to be a leading cause of mortality and morbidity around the world.

Several studies have shown that the regression of asymptomatic TOD occurring during treatment reflects the treatment-induced reduction of morbid and fatal CV events, thereby offering valuable information on whether patients are more or less effectively protected by the target BP achieved and the treatment strategies adopted. In the future precise targets to treat pathologic cardiac hypertrophy and heart failure more effectively are warranted.

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19.2 Electrocardiography LVH

Electrocardiographic (ECG) LVH is a powerful marker of cardiovascular (CV) morbidity/mortality in the general population as well as in different clinical settings [2]. In hypertensive patients, LVH may predict the occurrence of CV events, including myocardial infarction, stroke, sudden death, and heart failure [3, 4]. The incidence of cardiac arrhythmias [5], in particular of atrial fibrillation [6] and of renal events, such as creatinine doubling, estimated glomerular filtration rate <30 mL/min/1.73 m^2, or the need for dialysis, is also higher in the presence of LVH [7].

When the predictive value for incident heart failure of either ECG or echocardiographic LVH was evaluated in the Cardiovascular Health Study, the ability of the Framingham Heart Failure Risk Score to predict new occurrence of heart failure was similar when ECG LVH (C-index, 0.772; 95% confidence intervals, 0.726–0.815) and echocardiographic LVH (C-index, 0.772; 95% confidence intervals, 0.727–0.814) were included into the statistical model separately [8]. The results suggest an "interchangeability" between ECG LVH and echo LVH for heart failure prediction.

Several ECG diagnostic criteria for LVH are associated with an increased incidence of CV events, although their predictive value may differ according to body size [9], suggesting that in obese patients, criteria based on electrocardiographic precordial lead voltages may be less informative. Recent data also suggest that the amount of myocardial fibrosis may influence the amplitude of ECG voltages, thereby obscuring the ECG manifestations of increased LVM and limiting the sensitivity of the ECG for detecting increased LVM or changes of LV mass during treatment [10].

For these reasons the most valuable information on risk stratification may be obtained by combining different criteria, based on both voltages and QRS duration [11].

Regression of ECG LVH assessed by voltage, voltage-QRS duration, and strain criteria may be induced by treatment [12–19]. In the LIFE study, where LVH was defined by ECG and LV mass was measured by echocardiography, changes in ECG voltage and QRS duration criteria were shown to reflect changes in LV mass, measured by echocardiography [20].

BP lowering is an important determinant of ECG LVH regression as shown by the Cardiosys study, including 1111 nondiabetic hypertensive patients and showing a significantly greater decrease in the prevalence of LVH in those patients randomized to tight BP control (less than 130 mmHg) [21]. Soliman et al. demonstrated that more intensive BP reduction was associated with greater ECG LVH regression and lower rates of developing new LVH among patients with hypertension and diabetes mellitus in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study [22] and in hypertensive patients without diabetes mellitus in SPRINT (Systolic Blood Pressure Intervention Trial) [23].

In other studies, a high residual risk associated with persistence or development of ECG LVH has been observed, despite having average on-treatment systolic BP

≤130 mmHg [24], raising the possibility that additional BP lowering in patients who do not adequately regress LVH may not improve prognosis.

Few studies have compared the effect of different classes of antihypertensive drugs on changes in ECG LVH criteria. One of the largest studies was the LIFE (Losartan Intervention for Endpoint reduction in Hypertension) study, showing the superiority of losartan as compared to atenolol in reducing ECG LVH criteria (Sokolow-Lyon and Cornell product) [16]. The analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) data, in order to determine the changes in ECG LVH through 2 and 4 years of follow-up, has shown that overall change in ECG Cornell voltage was similar in patients randomized to chlortalidone, amlodipine, or lisinopril; trends in the regression of LVH in those with LVH at baseline and incidence of new ECG LVH were also similar between patients receiving chlortalidone and those treated with amlodipine or lisinopril [25].

19.3 Echocardiographic LVH

Echocardiography is recommended during diagnostic evaluation for more precise stratification of overall cardiovascular risk, since it is more sensitive for the identification of an increase in cardiac mass; furthermore it can be easily repeated for checking the status of organ damage during follow-up visits. A large number of clinical and experimental studies have shown that long-term antihypertensive treatment may be associated with a regression of echocardiographic LVH. Important determinants of LVH reduction are represented by the extent of BP decrease and by the duration of treatment. The results of the SAMPLE study [26] have demonstrated that changes in LV mass during antihypertensive treatment with an ACE inhibitor are not significantly related with changes of office measurements of blood pressure, while they resulted significantly associated with the degree of mean 24-h BP change. More recently, it has been shown that not only the extent of 24-h BP reduction but also the homogeneity, i.e., less variability in daily BP fluctuations (smoothness index), may be important for LVH reversal [27]. In the Japan Morning Surge-Target Organ Protection (J-TOP) [28], both clinic and central aortic BP were measured at baseline and during antihypertensive treatment. The results of the study show that, at multiple regression analyses, the decrease in central systolic BP was associated with those of log-transformed urinary albumin/creatinine ratio (UACR) ($\beta = 0.24$, $P < 0.01$) and LVMI ($\beta = 0.23$, $P = 0.04$), independently of the decrease in both clinic and home systolic BP, suggesting that the change in central BP could be an important therapeutic target during antihypertensive treatment, in addition to peripheral clinic and home BP [29].

Because of the tight relationship between LV mass and body size, non-pharmacological intervention may be useful in inducing LV mass decrease; in particular, body weight reduction in hypertensive obese patients was found associated with a reduction of LV mass, even independent from BP changes. Conversely, obesity

represents an independent predictor of the lack of LV mass reduction, as observed in the Strong Heart Study [30].

Insufficient evidence supports the direct effect of dietary sodium or alcohol restriction on LV mass, independent from BP reduction [31].

The development and the regression of LVH in hypertension do not depend exclusively on the level of BP but may also be modulated by several neurohumoral factors and by the aortic properties. Therefore it has been suggested that different classes of antihypertensive drugs do not have the same effect in reducing LV mass, probably because, beyond BP control, they may differently interfere with some non-hemodynamic factors, including the renin-angiotensin system and the sympathetic nervous system. In order to extract the maximal amount of information from previous studies, several meta-analyses of reversal of echocardiographic LVH obtained with the use of different antihypertensive drugs have been performed. Dahlof et al. [32] have calculated that LV mass reduction for the same decrease of BP is greater during antihypertensive treatment with ACE inhibitors, in comparison with all other classes of antihypertensive drugs, and similar conclusions have been reached by Cruickshank et al. [33]. In 1995, Fagard [34] reviewed the prospective randomized comparative studies performed at that time, in order to assess whether some classes of drugs would be more effective than others in reducing LV mass. The meta-analysis of such studies, comparing diuretics, beta-blockers, calcium channel blockers, and/or angiotensin-converting enzyme inhibitors, showed that the reduction of LV mass with each of these classes was similar to the reduction obtained with the other three classes statistically combined and, in addition, that the effect was similar for the direct comparison of angiotensin-converting enzyme inhibitors and calcium channel blockers. Two more meta-analyses by Jennings [35] and by Schmieder [36] have included only randomized, double-blind parallel-group comparisons and have indicated that the degree of BP reduction and the baseline value of LV mass represent the main determinants of LVH regression; however they have also observed that ACE inhibitors, angiotensin II receptor blockers, and calcium antagonists may be more effective than beta-blockers (mainly atenolol) and diuretics in reducing cardiac hypertrophy, for similar BP reduction [37], as shown by Fagard et al. in the last meta-analysis in 2009.

One possible explanation for these results may be the different effect of non-vasodilating beta-blockers, such as atenolol, but not vasodilating beta-blockers (such as nebivolol), on central systolic BP. In fact a lower reduction in central aortic systolic BP than in peripheral systolic BP was demonstrated with non-vasodilating beta-blockers by Pucci et al. [38].

Most of the studies included in the meta-analyses were relatively small and of short duration, usually 6 months or less, often non-comparative, without a reliable quality control of echocardiograms, providing poor information on LVH regression rates or changes in LV geometrical patterns and few data on changes of BP or on target BP achieved during treatment; in addition some studies included only patients with LVH while others patients with or without an increased LV mass [39]. To this regard, it should be underlined that the magnitude of the decrease of cardiac hypertrophy is related to the baseline LVM, and according to variability in LVM

measurements by echocardiography, only changes >10–15% can be considered of biological relevance.

Some large, randomized, blinded studies comparing the effect of two or more different antihypertensive drugs have given further information, for example, on the time course of LV mass changes. It has been thought that the length of antihypertensive treatment was associated with a progressive decrease of LV mass, thereby potentially reducing possible differences among classes of drugs. However, according to the LIFE trial, the significant difference found after 6 months between angiotensin receptor blocker-based therapy opposed to beta-blocker-based therapy was maintained throughout the whole follow-up period (up to 6 years), with differences of similar magnitude at yearly examinations [40]. Of note, BP was similarly reduced throughout the whole follow-up period hereby suggesting that antihypertensive agents have long-lasting disparate effects of LVM reduction.

In addition, BP control may be difficult in hypertensive patients with target organ damage and requires the use of antihypertensive agents in combination. To this regard, it should be emphasized that major intervention trials comparing the effects of single antihypertensive drugs on LV mass were, actually in large part, comparisons of different combination therapies, since the majority of patients in the study took more than one drug. In the SAMPLE study [26], more than 50% of patients were treated with the combination of lisinopril plus a diuretic. The same remark applies to the LIFE study, where the beta-blocker or the angiotensin II blocker was associated with diuretics in 90% of patients.

In the RACE study [41], patients enrolled were also subdivided according to addition or no addition of a diuretic to the baseline therapy. The extent of the reduction in LV mass was similar in the two subgroups, and the advantage of ramipril over atenolol was evident also in patients who were in combination therapy.

A normalization of LV mass is more difficult and cannot be always reached in women [42], obese or diabetic patients [43], elderly subjects with isolated systolic hypertension [44], or patients with coronary artery disease, despite adequate treatment. A normalization of LV geometry is also possible during antihypertensive treatment [45], although treatment with diuretics is associated with smaller changes in relative wall thickness, i.e., with a tendency toward the persistence of a more concentric remodeling [46].

Correction of other additional CV risk factors may contribute to LVH regression, and for statins, allopurinol, or postmenopause hormonal therapy, a potential role in the regression of LVH was demonstrated, although further confirmations are clearly needed [47–49].

Prevalence of LVH is particularly high in patients with resistant hypertension [50] and renal denervation, a novel therapy for resistant hypertension, has been shown to have an effect on cardiac remodeling in several small studies, despite some conflicting results were reported [51]. A meta-analysis, including 139 patients examined with echocardiography and 84 undergoing cardiac MRI, showed a significant reduction of LV mass and concentric geometry, independent from changes in BP, after a renal denervation procedure [52].

It seems particularly interesting the evaluation of the effect of antihypertensive treatment on the myocardial tissue composition, possibly affecting the fibrous perivascular and interstitial tissue. This hypothesis has been recently addressed in a study in human beings by Brilla and coworkers [53]; in fact, they have demonstrated that treatment for 6 months with the ACE inhibitor lisinopril or with the diuretic hydrochlorothiazide induced a similar reduction of blood pressure; however lisinopril determined a decrease in collagen content of the myocardium, in association with an improvement of some diastolic function parameters, while the diuretic had no effect on these parameters and only reduced myocyte diameter. Recent experimental and human studies have shown that also angiotensin II antagonists and mineralocorticoid receptor antagonists may exert a favorable effect on regression of myocardial fibrosis [54]. In the future targeting mineralocorticoid receptors in T cells could represent a new approach for treating pathologic cardiac hypertrophy and preventing heart failure, as suggested by experimental data obtained by Li et al. [55].

The majority of clinical studies have shown improvement in diastolic function with angiotensin receptor blockers, although the Valsartan in Diastolic Dysfunction (VALIDD) trial found no benefit with valsartan over placebo on markers of diastolic function [56].

In conclusion, all classes of antihypertensive drugs can induce regression of LVH along with the decrease of BP. Differences on reduction of LV mass for the same decrease of BP are usually of lower magnitude than those achieved by effective BP control, but the effect on LV and RV structure and composition may not be the same with different antihypertensive drugs.

The improvement of systolic and/or diastolic function parameters in response to antihypertensive therapy is still controversial.

19.3.1 Regression of LVH and Prognosis

Large changes in ECG voltage, Cornell product, and strain result in improved prognosis [57, 58]. Changes in echocardiographic LV mass and in renal function may independently predict the occurrence of cardiovascular events [59].

The modifications of LV geometry, of left atrial size, and of systolic and diastolic dysfunction parameters have been also shown to be associated with the incidence of cardiovascular events and in particular of stroke, myocardial infarction heart failure, sudden death, and atrial fibrillation, independently of LVM change [45, 60, 61].

Regression of LVH may have a prognostic significance independently of BP values, even when measured by 24-h BP. The changes in ECG or echo LVH, induced by treatment, parallel the incidence of CV events during treatment; however a residual risk may be observed in patients with LVH regression, in whom LV mass remains higher, although in the normal range, than in patients with persistently normal LV mass [62]. This is particularly true for patients with chronic kidney disease, in whom no clear and consistent association between intervention-induced LV mass change and all-cause and cardiovascular mortality was demonstrated by a

meta-analysis of 25 intervention classes (erythropoiesis-stimulating agents, renin-angiotensin-aldosterone system inhibitors, and isosorbide mononitrate). It seems therefore that the clinical significance of treatment-induced reductions in LV mass in people with chronic kidney disease is uncertain and that LV mass cannot be considered a valid surrogate end point in these subset of very high-risk hypertensive patients [63].

Further studies will be required to evaluate whether specifically targeting patients with persistent LVH to further reduce BP and produce regression of LVH can improve prognosis in this high-risk subgroup of patients with hypertension.

19.3.2 Left Atrium (LA)

A large body of evidence indicates that LA size may be considered a marker of LV diastolic dysfunction [64, 65] and has prognostic relevance in patients with hypertensive heart disease [66].

Enlargement of the LA (LAE) is a strong risk factor for atrial fibrillation [67] and ischemic stroke independently from LVH [68–70].

LAE is a common finding in clinical practice, involving more than 30% of patients referred to echo labs for risk stratification; the prevalence is greater in women than in men. LV mass is the strongest correlate of absolute and indexed LA diameter, even when normalized for body size.

During the long follow-up period of the LIFE study, it was also observed that the favorable initial reduction in LA diameter induced by antihypertensive therapy diminished over time, in spite of persistent reduction in BP and LVH, possibly in relation to the continuous aging of patients and to the increasing prevalence of mitral regurgitation.

Several years ago, the effect of monotherapy with different antihypertensive drugs (atenolol, captopril, clonidine, diltiazem, hydrochlorothiazide, or prazosin) on left atrial size was assessed in a double-masked trial, lasting 2 years. Longitudinal analysis showed that hydrochlorothiazide was associated with greater overall reduction of left atrial size than other drugs; the reduction of left atrial size with therapy was in part independent of LV mass at baseline and LV mass changes during treatment [71].

In the LIFE study, a greater LA diameter reduction was observed in losartan-treated patients as compared to those randomized to atenolol, even when in-treatment changes in BP and body mass index were taken into account [72]. In addition a smaller LA size during treatment was associated with a lower incidence of new-onset atrial fibrillation [73].

In patients with resistant hypertension, LA volume, a better index of LA size than LA anteroposterior diameter, decreased 6 months after renal denervation; interestingly this decrease was independent of BP and heart rate measured at baseline or the reduction in BP and heart rate reached by renal denervation [74].

The role of aldosterone on cardiac structure, including LA enlargement, has been recently reviewed [6].

In hypertensive patients with elevated values of serum aldosterone, but not in those with low-normal levels of serum aldosterone, treatment with spironolactone was associated with a fast decrease of LA volume [75].

19.4 Conclusion

A robust evidence obtained from randomized clinical trials and meta-analyses supports the notion that treatment of hypertension can induce regression of LVH. The decrease in BP and in other adverse factors, such as obesity or increased aortic stiffness, is a main determinant of reduction of cardiac hypertrophy. Regression of hypertrophy is independently associated with improved cardiovascular outcome, although some residual risk may be observed, especially in some groups of patients and in the everyday clinical practice. Therefore, LVH should be recognized and aggressively treated with antihypertensive drugs as soon as possible, because once hypertensive cardiac damage is advanced, it may be difficult to slow or stop the progression to heart failure.

In the future more attention should be given to (1) the early recognition of cardiac damage (both structural and functional), possibly by the progressive improvement in noninvasive techniques; (2) the reduction of BP, including clinic, home, and 24-h peripheral and aortic pressure, in addition to metabolic risk factors; and (3) the precise targeting of molecular events involved in maladaptive cardiac hypertrophy and remodeling by pharmacological therapy [76].

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Part VI

Treatment of Heart Failure in Hypertensive Patients

New Drugs for the Hypertensive Failing Heart

20

Victor Voicu and Maria Dorobantu

20.1 Introduction

Multiple and complex studies consider hypertension either a disease or a risk factor. Regardless of these considerations, hypertension is one of the major cardiovascular-related death and disability causes worldwide [1].

Consequently, the antihypertensive drug therapy takes the forefront when discussing hypertension. Reducing systolic and diastolic blood pressure values leads to a significant decrease in the incidence of heart disease, including heart failure, ischemic heart disease, stroke, renal failure, etc.

This viewpoint is unanimously accepted across the scientific world; however, its main drawback is a lack in consensus regarding blood pressure target values with treatment [2]. Therapeutic targets can differ depending on the presence of other cardiovascular comorbidities or of a different nature, so antihypertensive drug therapy targets both prophylaxis of heart failure and treatment of hypertension associated with heart failure.

Comorbidities prior to or associated with heart failure are of major importance both in the diagnostic workup and in determining a treatment strategy [3]. A series of cardiac afflictions have been suggested to be involved in the pathogenesis of heart failure (acute coronary syndromes, severe hypertension, valvular and congenital heart disease);

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however, despite being successfully treated, *heart failure prevalence is on the rise* [3]. It is already known that certain afflictions (hypertension, type 2 diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, arrhythmias, etc.) can assume roles as both causes and comorbidities and contribute to the increasing prevalence of heart failure, with severe consequences on morbidity and mortality rates [4, 5].

The different approaches taken to identify and explain the mechanisms of heart failure have led to the development of the pathogenic models:

(a) *The hemodynamic model*—chronic dysfunction of the ventricular pump due to remodeling
(b) *The alteration in the shape, size, and width of the extracellular matrix*—with consequences on contraction, relaxation, and ventricular filling velocity
(c) *The cardiorenal model*—fluid and sodium retention
(d) *The neurohumoral model*—postulated following research on the compensatory mechanisms in heart failure that activate excessively, with severe consequences, such as sympathetic overdrive producing an immediate increase in contractility, with ulterior detrimental effects in the long term due to chronic activation of both the sympathetic nervous system and the renin-angiotensin-aldosterone system
(e) *The alteration of the mechanism of Ca^{2+} release from the sarcoplasmic reticulum*—reaching a critical calcium concentration for both contraction initiation and reuptake by the sarcoplasmic reticulum, followed by relaxation of the cardiomyocyte, which is an essential step and can also be altered

Progress has been made in the field of molecular biology by identifying gene regulatory and posttranscriptional control mechanisms and by characterizing a potential microRNA marker (μiR_s) involved in the control of certain complex processes related to heart failure (excitation-contraction coupling, myocyte hypertrophy, ventricular dilatation, apoptosis, myocardial fibrosis). Current theories and pathogenic models are mostly complementary and contribute to the complex perspective of heart failure pathogenesis.

The development of antihypertensive drugs that interfere with the pathogenic mechanisms of hypertension and/or with their effects leading to heart failure (see the classification) required a new approach based on discoveries in the field of molecular biology and molecular medicine [6].

A series of studies (the TOPCAT, PARADIGM-HF, and PARAMOUNT trials) [3, 7] highlight these progresses in the treatment of heart failure with preserved ejection fraction, namely, therapy with angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and aldosterone antagonists, as well as combination therapy with an angiotensin receptor blocker (ARB), a natriuretic peptide metabolism inhibitor, etc.

Given the complexity and the variable prognosis of heart failure as a syndrome, it is accepted that prevention of the various disorders that generate or worsen heart failure is essential. Therefore, the first targets in prevention of HF address coronary heart disease (the most common), hypertension, diabetes mellitus, and hypercholesterolemia. These risk factors should be identified and controlled before they generate clinically evident effects.

Drug therapy for hypertension (see Table 20.1) has different approaches that are complementary to one another. Table 20.1 (*The pharmacodynamic classification of*

Table 20.1 The pharmacodynamic classification of antihypertensive drugs[a]

Pharmacodynamical class	Site of action	Pharmacodynamical mechanism
I. Sympathetic nervous system modifiers		
Central		
Clonidine Guanfacine α-Methyldopa	Central α_2-adrenergic receptor agonists	Activation of the central depressor system Decrease in peripheral sympathetic nervous system activity
Moxonidine[b] Rilmenidine[b]	Imidazoline I_1-receptor agonists, acting at the rostral, ventrolateral pressor and ventromedial depressor areas of the medulla oblongata	Decrease in sympathetic nervous system activity
Peripheral		
Guanethidine[c]	Adrenergic nerve endings	Blocks adrenergic transmission
Ganglionic blockers[c]	Autonomic ganglia	Blocks ganglionic transmission
Selective α-adrenergic blockers (α1)		
Prazosin[b] Doxazosin[b]	Peripheral α1-adrenergic receptors	Selectively blocks peripheral α_1-adrenergic receptors resulting in vasodilation
Peripheral α1-adrenergic receptors	Selectively blocks peripheral α_1-adrenergic receptors resulting in vasodilation	Selectively blocks peripheral α_1-adrenergic receptors resulting in vasodilation
Nonselective α-adrenergic blockers		
Phentolamine[b]	Peripheral α-adrenergic receptors	Blocks peripheral α-adrenergic receptors
Peripheral α-adrenergic receptors	Blocks peripheral α-adrenergic receptors	Blocks peripheral α-adrenergic receptors
Nonselective β-adrenergic blockers		
Propranolol[c]	Peripheral $ß_1$- and $ß_2$-adrenergic receptors	Blocks $ß_1$- and $ß_2$-adrenergic receptors
Selective β-adrenergic blockers		
Atenolol Metoprolol Bisoprolol	$ß_1$-adrenergic receptors	Decrease cardiac output by blocking ß1-cardiac receptors Decrease renin secretion by blocking juxtaglomerular β1-receptors
α- and β-blockers		
Labetalol Carvedilol	Peripheral ß1- and α1-receptors	Added effects of α- and β-receptor blocking
Mixed		
Reserpine[c]	Central neurons, adrenergic nerve endings	Blocks NE reuptake and depletes NE deposits
II. Diuretics		
Thiazide diuretics		
	Distal tubule	Blocks Na^+, CI^-, and K^+ reabsorption

(continued)

Table 20.1 (continued)

Pharmacodynamical class	Site of action	Pharmacodynamical mechanism
Loop diuretics		
Furosemide Ethacrynic acid[b]	Ascending limb of loop of Henle	Blocks Cl^- and Na^+ reabsorption
Aldosterone antagonists		
Spironolactone	Distal tubule, aldosterone receptors	Blocks Na^+/K^+ exchange: Na^+ is excreted, K^+ is reabsorbed
Other K^+ non-sparing diuretics		
Triamterene Amiloride	Distal and collecting tubules	Blocks Na^+/K^+ exchange: Na^+ is excreted, K^+ is reabsorbed
III. Vasodilators		
Direct		
Hydralazine[b] Dihydralazine[b] Minoxidil[b] Diazoxide[b] Nitroprusside[b]	K^+ channels activation	Membrane hyperpolarization
Indirect		
Calcium channel antagonists (calcium channel blockers)		
	Calcium channels	Blocks calcium influx resulting in vasodilation
1. Dihydropyridines (arterial > cardiac)		
Amlodipine Lacidipine Nifedipine Nicardipine Benidipine Isradipine Lercanidipine		
2. Benzodiazepines (arterial = cardiac)		
Diltiazem Diltiazem ER		
3. Phenylalkylamines (arterial < cardiac)		
Verapamil Verapamil ER		
4. Phenylalkylamines benzimidazole (arterial > cardiac)		
Mibefradil		
IV. Renin-angiotensin-aldosterone inhibitors		
Renin inhibitors		
Aliskiren	Renin	Blocks renin through substrate analogy
Renin-angiotensin inhibitors		
Angiotensin I converting enzyme inhibitors Enalapril Ramipril Perindopril Trandolapril	Converting enzyme	Blocks angiotensin II synthesis and decreases bradykinin inactivation
Angiotensin II receptor blockers		
Losartan Valsartan Irbesartan Candesartan	Angiotensin II AT_1 receptors	Blocks angiotensin II AT_1 receptors

Table 20.1 (continued)

Pharmacodynamical class	Site of action	Pharmacodynamical mechanism
Aldosterone antagonists		
Mineralocorticoid receptor antagonists		
Spironolactone Eplerenone Finerenone	Mineralocorticoid receptor	Blocks the mineralocorticoid receptor
Aldosterone synthase inhibitors		
	Aldosterone synthase	Blocks the aldosterone synthase activity and decreases aldosterone levels
V. Vasopeptidase inhibitors		
Neprilysin inhibitors plus AT_1 receptor blocker		
Sacubitril and Valsartan (dual inhibitor combination)	Neprilysin and angiotensin II AT_1 receptors	Facilitates natriuretic peptide activity plus antagonizes compensatory reactions by blocking angiotensin II AT_1 receptors
Dual inhibitors of neprilysin and endothelin-converting enzyme		
Daglutril	Neprilysin (neutral endopeptidase) and endothelin-converting enzyme	Mixed (dual) blocking of neprilysin and endothelin-converting enzyme
VI. Endothelin receptor antagonists (sentans)		
Bosentan	Endothelin type A and B receptors (ETA and ETB)	Blocks endothelin receptors ETA and ETB

ER extended release
[a]Historical interest
[b]Specific indications
[c]Adapted from [40]

antihypertensive drugs) presents both the classic and latest pharmacological agents, as well as other means that target the fundamental molecular mechanisms involved in the onset and evolution of the hypertension-heart failure tandem. The chronic treatment of hypertension poses challenges both in reaching treatment targets and in monitoring treatment effects and patient adherence [8–10].

20.2 Novel Pathogenic Mechanisms of Hypertension Countered by Antihypertensive Drug Therapy

Novel pathogenic mechanisms involved in hypertension have been identified as treatment targets, in correlation to the progress made in the field of molecular biology and to other types of therapy that target the vascular endothelium, the myocardium, etc.

The pharmacodynamic classification of antihypertensive drugs (Table 20.1) includes direct renin inhibitors that sequentially block the conversion of angiotensinogen into angiotensin I and selective aldosterone antagonists such as spironolactone and eplerenone.

The exclusive utilization of neprilysin inhibitors has not proven its efficacy, in part due to the fact that these agents also inhibit neprilysin metabolism and increase the levels of other vasoactive peptides such as angiotensin II and endothelin-1 [11].

The association of a neprilysin inhibitor and an ACEI seemed efficient. Omapatrilat was the representative for this drug combination, and it was administered orally. However, the four-time increase in the incidence of angioedema, more than with enalapril due to accumulation of bradykinin, determined its withdrawal.

Another combination based on their synergic and sequential action on the processes that control vascular homeostasis was the neprilysin inhibitor and angiotensin II type 1 receptor-blocker dual combination therapy. Therefore, LCZ696 contains a neprilysin inhibitor (prodrug) and valsartan in a 1:1 ratio. Data retrieved from clinical studies are promising for heart failure treatment [12].

Resistant hypertension has been proven to be determined especially by hyperaldosteronism; therefore, spironolactone and eplerenone are an important component in the treatment of hypertension. Post-administration of ACEIs or ARBs, there is a rise in aldosterone serum levels. This is called the aldosterone escape phenomenon and is encountered in about 40% of patients [13]. The aldosterone escape phenomenon can be explained by an increase in the synthesis of angiotensin II, the stimulator of aldosterone secretion. Consequently, the need to produce selective aldosterone receptor blockers and selective inhibitors of aldosterone synthesis is evident.

The aldosterone synthase inhibitor, LCI699, causes a reduction in blood pressure readings at 24 h in the ambulatory setting, similar to the effect of 50 mg of eplerenone administered twice daily [11]. However, its interference with glucocorticoid synthesis and the compensatory increase in the secretion of ACTH have led to the cessation of clinical trials. Increasing the selectivity of the agent for aldosterone synthase may provide a solution. Production of aldosterone synthase inhibitors is currently of major clinical interest.

Among the components of the renin-angiotensin-aldosterone system (RAAS), of particular interest is the type 2 receptor for angiotensin II (AT2) agonists that represent a potential therapeutic target. AT2 is a G protein-coupled receptor and has seven transmembrane domains [11]. C21 is a compound acting as an AT2 receptor agonist in preclinical trials and possesses antihypertensive properties, as well as conferring tissue protection for target organs, and also presents anti-inflammatory properties. The effects of the AT2 agonist (C21) practically exclusively impact the peripheral tissues. Theoretically, such a compound can be of interest as an antihypertensive drug, and it can cross the blood-brain barrier; however, so far it lacks clinical applicability [11].

Another therapeutic approach to hypertension is the dual action of neprilysin inhibitors and the endothelin-converting enzyme inhibitor. Daglutril is a prodrug, metabolically activated in vitro, that has this particular dual action.

Essentially, the effects of the natriuretic peptides are facilitated by blocking their inactivation (through inhibition of neprilysin), associated with the inhibition of the endothelin-1-converting enzyme (E1CE). The latter is a metalloprotease that cleaves big endothelin-1 (ET-1) into its active form ET-1. There are two types of receptors

that interact with the endothelium-released active endothelin (ET-1): ETA and ETB. These are G protein-coupled receptors that produce IP3 (inositol triphosphate) that, in turn, determines an increase in calcium release from the sarcoplasmic reticulum, generating vascular smooth muscle contraction. ETA is predominantly found within the smooth muscle. On the contrary, ETB can be found in the endothelium, as well. Following activation, it stimulates production of NO (nitric oxide) with vasodilation as a consequence, sometimes with important effects when vascular smooth muscle contraction via ETA is absent. Due to these predominantly and intense vasoconstrictive effects, ET-1 is considered to have a role in the pathogenesis of hypertension and heart failure, having become a preferential therapeutic target in drug development.

Interestingly, E1CE is structurally similar to the neutral endopeptidase that hydrolyzes the atrial natriuretic peptide. Consequently, E1CE is considered to be involved in the degradation of atrial natriuretic peptide, thus making way for a new therapeutic perspective.

20.3 Progresses in the Pharmacological Control of the Renin-Angiotensin-Aldosterone System (RAAS)

The use of the ACEI has been recommended in HF, especially when associated with HT, as the first line of treatment, as they block the conversion of angiotensin I (AI) to angiotensin II (AII) and increase the concentration of bradykinin (Table 20.2). The RAAS is well known to have an essential role in the onset and evolution of HT and HF through multiple mechanisms (Fig. 20.1) which can be targeted. New components of the RAAS are approached in the last few years.

Table 20.2 Effects of angiotensin II via AT_1 and AT2

Activation of AT_1	Activation of AT2
• Sodium reabsorption • Aldosterone release • Arginine-vasopressin release • Inhibition of renin release • Pro-inflammatory effect • Promotes cardiomyocyte fibrosis (myocardial hypertrophy) • Cardiac contractility increase • Vasoconstriction and vascular hypertrophy (endothelin and smooth muscle) • Vagal control inhibition • Intensifies oxidative stress • Activation of sympathetic nervous system (increases release of noradrenaline/norepinephrine and inhibits its reuptake)	• Influences fetal organ development • Vasodilatation • Inhibits proliferation (antiproliferative) • Inhibits inflammation • Inhibits cardiac remodeling • Proapoptotic effects on the vascular smooth muscle

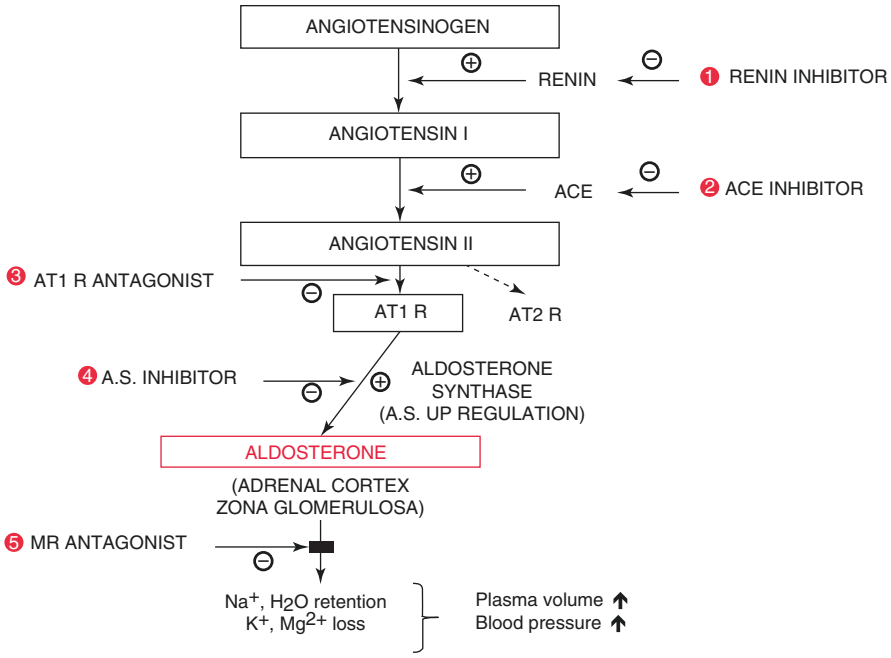

Fig. 20.1 Pharmacological control of renin-angiotensin-aldosterone system

20.3.1 Renin Inhibitors

Renin is a proteolytic enzyme, namely, an aspartyl protease that cleaves angiotensinogen into angiotensin I, an inactive decapeptide. Its precursor, prorenin, is synthesized at a rate of 10:1 with renin. Through proteolysis, a 43-amino acid fragment from the N-terminal portion is released. Prorenin is secreted by the juxtaglomerular apparatus, while renin is deposited in the secretory vesicles within the apparatus and released depending on the functional state through four different mechanisms: (1) a renal baroreceptor mechanism with sensors within the afferent arteriole, activated once absorption of NaCl decreases, (2) sensors to detect variations in the concentration of chloride ions within the macula densa of the juxtaglomerular apparatus, (3) sympathetic stimulation via ß1-receptors located within the juxtaglomerular cells, and (4) a negative feedback determined by angiotensin II on the juxtaglomerular cells.

The release and action of renin is the first rate-limiting step of the RAAS in connection with the sympathetic nervous system. Functionally, the link between these two systems represents an essential step within the integrated system of blood pressure control and regulation.

Renin is essential to the activity of RAAS by initiating the synthesis of two major components: angiotensin II and aldosterone that control fluid and electrolyte balance, plasma volume, vascular system compliance, and blood pressure (circulation homeostasis).

20.3.1.1 Aliskiren

Renin is a major proteolytic enzyme component of the renin-angiotensin-aldosterone system, synthesized, released, and stored in renal juxtaglomerular cells. The physiological stimuli of renin release are low blood pressure in the afferent arterioles, stimulation of the ß1-adrenoceptors from the juxtaglomerular cells, and low concentration of tubular sodium. It should be noted that the macula densa, a specialized cell structure in the distal tube, is in the vicinity of the juxtaglomerular cells of the afferent arterioles.

Macula densa possesses sodium sensors which stimulate the decrease in renin release, when sodium concentration increases and vice versa.

Renin controls an important link of the renin-angiotensin-aldosterone system, namely, the proteolytic cleavage of angiotensinogen to produce angiotensin I, a process followed by known sequences.

Aliskiren acts as a renin activity blocker. The compound is a substrate analogue, thus blocking the activation of angiotensinogen to angiotensin I. Consequently, the activity of plasma renin is reduced by approximately 75%, with a subsequent reduction in angiotensin I and II levels.

Oral absorption is limited, with a bioavailability of about 2.5–4% and can be additionally decreased by 70–80% if taken with fatty meals [14]. Approximately 47–52% of aliskiren transport is achieved through plasma protein binding. Halftime is about 24 h, and the drug is eliminated through hepatic (CYP3A4) and renal metabolism [15].

Aliskiren was approved in 2005. Antihypertensive effects are dose-dependent. It is contraindicated in pregnancy, renovascular hypertension, and preexistent renal disease. The usual dosage of aliskiren is 150 mg 2–4 times per day. Initiating dose is 150 mg per day. It can be associated with valsartan, amlodipine, and hydrochlorothiazide.

A stable antihypertensive effect is reached after about 2 weeks of treatment. Aliskiren interacts with other drugs [14]. It lowers peak plasma concentration (C_{max}) for irbesartan by approximately 50%. Atorvastatin lowers C_{max} for aliskiren by approximately 50%.

No clinically relevant interactions have been observed with lovastatin, atenolol, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, valsartan, metformin, or amlodipine.

Adverse events include headaches, dizziness, fatigue (2.5–8.5%), and diarrhea.

20.3.2 Mineralocorticoid Receptor Antagonists (MRAs)

Aldosterone is a component of the RAAS and an essential agent for extracellular fluid volume and electrolytes and blood pressure homeostasis. The RAAS is interconnected with the sympathetic nervous system, being integrated both to the control and regulation of the cardiovascular function, immediately and in the medium term (Fig. 20.1).

Aldosterone acts on the myocardium and is involved in the pathogenesis of myocardial hypertrophy and fibrosis, independent of systolic blood pressure, an effect considered to be mainly direct and less hemodynamic [16].

Angiotensin II, ACTH, and potassium are major activators of aldosterone secretion.

In heart failure, the RAAS reacts as a compensatory mechanism, an effect initiated and maintained by sympathetic activation, an increase in renin-angiotensin II secretion and an increase in aldosterone synthesis, as well as secondary stimulation of the sympathetic nervous system through a positive feedback mechanism that maintains and resets the function of the entire system. One of the immediate consequences is an increase in the effective circulating blood volume and circulation overload by fluid and sodium retention. In time, major structural disturbances appear in all target organs: the myocardium, blood vessels, and the kidneys with the already acknowledged consequences.

Angiotensin II acts to maintain homeostasis of the extracellular volume, by increasing aldosterone secretion from the zona glomerulosa of the adrenal gland and through activation of the AT-1 receptor (AT-1R), with subsequent vasoconstriction, norepinephrine and epinephrine secretion, central nervous system activation, and arginine-vasopressin (AVP) release.

The sympathetic nervous system, renin, angiotensin II, and aldosterone are chronically activated, initially as compensatory mechanisms in heart failure. Currently, these constitute a major pharmacological target in heart failure drug therapy.

The essential progress made in describing the effects of aldosterone on the cardiovascular system and other tissues, as well as the therapeutic effects of mineralocorticoid receptor antagonists (MRAs), regardless of normal or high aldosterone serum levels, reveals a new stage in the therapeutic approach to prevent and treat heart failure, particularly when associated with hypertension.

20.3.2.1 Spironolactone

Biosynthesis of aldosterone is increased in HTN that evolves with HF, owing to increased production of angiotensin II. Spironolactone is a steroidal compound introduced in therapy in 1959 [17]. Initially, spironolactone was added to non-potassium-sparing diuretics (thiazides or loop diuretics) to antagonize this effect. It belongs to the drug class of "potassium-sparing diuretics," revelatory for its therapeutic use.

Essentially, treatment with spironolactone targeted hypertension associated with edematous states. Currently, the therapeutic use of MRAs has a larger spectrum.

Spironolactone binds to the mineralocorticoid receptor through a mechanism of competitive antagonism, establishing hydrogen bonds with Arg 817 initially and then with Gln 776, thus preventing the conversion of the receptor to its active configuration and, therefore, blocking its interaction with coactivators [18].

A difference in the in vitro and in vivo efficacy between spironolactone and eplerenone has been observed. In vitro, spironolactone is about 40 times more active as an MRA versus eplerenone. The same could not be observed for in vivo

experiments, where eplerenone reaches 50–75% of the antihypertensive effect of spironolactone.

Up to 88% of spironolactone binds to plasma proteins (a considerably higher amount versus eplerenone). It also has an apparent distribution volume of 10 L/kg. These two aspects could explain the observations for in vivo versus in vitro activity for the two compounds.

Spironolactone binds not only the mineralocorticoid receptor (MR) but also the androgenic, progesteronic, and glucocorticoid receptors (however, less than MR).

Oral administration produces rapid absorption with a bioavailability ranging between 80 and 90%. Spironolactone is rapidly metabolized by the liver through deacetylation, dethiolation, and thiomethylation, catalyzed by CYP3A4. Its active metabolites contribute to the prolongation of the pharmacodynamical effect. Spironolactone has a halftime of 1.4 h, whereas its two active metabolites 7α-thiomethyl spironolactone and canrenone have a halftime of 13–15 h and 16.5 h, respectively.

Therefore, spironolactone reaches a plasma steady state after a few days. Halftimes are evidently prolonged if liver failure and heart failure are present [18].

The remarkable progress made in understanding the effects of aldosterone and their impact on the cardiovascular system, renal system, immune cells and the inflammatory process, on the retina, and on the skin has extended the therapeutic uses of MRAs.

Based on the results from clinical trials such as RALES, EPHESUS, and EMPHASIS-HF, spironolactone and other MRAs (second- and third-generation eplerenone and finerenone, respectively) are clearly beneficial in heart failure, reducing the morbidity and mortality related to this syndrome, with indications extended for the early stages of myocardial infarction [19, 20].

MRAs decrease the synthesis and plasma concentration of procollagenic propeptides, which represent a surrogate biomarker for myocardial fibrosis.

Spironolactone acts to prevent myocardial remodeling and dilatation, apoptosis, and atrial fibrillation in experimental models.

The effects of MRAs on electric remodeling of both atria and ventricles in heart failure have been revealed by the RALES and EPHESUS studies, with a decrease in sudden cardiac death (by 21%) and ventricular tachycardia (by 72%) [17]. Utilization of MRAs has beneficial effects on vascular tone and vascular wall remodeling.

The significant interaction with the androgenic and progesteronic receptor is considered a significant adverse effect, with secondary hyperprolactinemia and breast induration, increase in breast dimensions and pain, impotence in males, decreased libido, and menstrual disorders.

Another significant adverse effect is hyperkalemia, particularly when spironolactone is associated with ACEIs or sartans. Clinical manifestations include fatigue, weakness, and muscle cramps. Consequences can be severe, leading to atrioventricular blocks. Practically, all RAAS blockers can lead to hyperkalemia. This particular adverse effect is even more important to take into account when considering heart failure is associated with chronic kidney disease.

A rise in plasma potassium levels increases renin secretion from the juxtaglomerular cells, activating the RAAS, including aldosterone that, in turn, increases potassium excretion at the distal tubule.

It is generally considered that when administering spironolactone in those with kidney dysfunction, monitoring plasma potassium levels improves the risk/benefit ratio in favor of the MRA.

20.3.2.2 Eplerenone

Eplerenone is a steroidal compound; the second generation of MRAs has been introduced in therapy starting in 2002.

The affinity for the mineralocorticoid receptor is lower than spironolactone's, of about 20–40%; however, its selectivity is superior. Unlike spironolactone, eplerenone has a very low affinity for the androgenic and progesteronic receptors and consequently has a narrower adverse effect profile.

By blocking MR, eplerenone also inhibits the negative regulatory feedback exerted over renin and aldosterone secretion, resulting in an increase in the plasma concentration levels of both renin and aldosterone.

After oral administration, it is absorbed from the gastrointestinal tract, with a bioavailability of 69%. The peak plasma concentration is achieved at approximately 1.8 h. About 33–60% is transported bound to plasma proteins. The apparent volume of distribution is significantly less than spironolactone's, at 0.3–1.3 L/kg. Eplerenone undergoes hepatic metabolism (CYP3A4), with a halftime of 4–6 h. Its metabolites are inactive and undergo biliary and renal clearance.

Currently, indications for eplerenone are heterogeneous, some supporting its use in heart failure while others in hypertension or in heart failure post-myocardial infarction [21].

There are over 11 randomized clinical trials that document the efficacy of eplerenone in hypertension; however, the data presented so far is considered to be insufficient due to a lack in international multicenter studies on large populations.

So far, results from clinical studies reveal dose-dependent antihypertensive effects for eplerenone, either administered exclusively or in association with other antihypertensives. Compared to spironolactone, it is believed that 100 mg of eplerenone daily is equivalent to 50–70% of the antihypertensive effects of spironolactone.

In preclinical trials on experimental models, eplerenone diminishes the effects of aldosterone on the cardiovascular system, such as vascular inflammation, myocardial ischemia and fibrosis, atherosclerosis, endothelial dysfunction, vascular stiffness, and proteinuria.

Despite being more expensive than spironolactone, it is believed that eplerenone is more cost-efficient in chronic heart failure with reduced ejection fraction. In the EPHESUS study, patients who received eplerenone 25–50 mg daily had a significant reduction in the relative risk of death from any cause, while cardiovascular mortality was reduced by 13% compared to placebo [22, 23].

Eplerenone has a better adverse events profile than spironolactone. In the EPHESUS study, hyperkalemia due to eplerenone was of 5.5% vs. 3.9% in placebo subjects [24].

In the EMPHASIS-HF trial, 50 mg of eplerenone daily produced beneficial effects in all groups, with an improvement in the composite end point, defined as hospitalization for heart failure and mortality of cardiovascular cause, with no significant hyperkalemia or renal dysfunction.

20.3.2.3 Finerenone

Finerenone is a new MRA and has a dihydro-naphthyridine structure, a derivative of dihydropyridine. It is a nonsteroidal compound, a very active antagonist of the mineralocorticoid receptor and with a higher affinity for it compared to other MRAs. Specificity is due to an interaction at the Ala-773 and Ser810 positions on the specific structure of the mineralocorticoid receptor, through a hydrogen-bond donor interaction [25].

Consequently, it was observed that finerenone decreases the nuclear accumulation of MR as a result of the reduction in nuclear translocation and its stability, leading to suppression of MR recycling.

On experimental models of hypertension, heart failure, and chronic kidney disease, finerenone protects the cardiovascular and renal functions and increases survival rates in experimental animals in a superior number than spironolactone and eplerenone.

In a recent synthesis of phases II and III of clinical trials with finerenone, a relevant benefit has been observed in patients with heart failure and chronic kidney disease or diabetes, as well as diabetic nephropathy. However, there was also a marked risk of hyperkalemia [25].

In patients with heart failure (NYHA class II and III) with reduced ejection fraction and moderate chronic kidney disease, 5–10 mg of finerenone daily is at least as efficient as 25–50 mg of spironolactone daily. Effects have been evaluated by determining hemodynamic stress biomarkers, such as BNP and NT-pro-BNP and albuminuria. The compensatory increase in aldosterone is less pronounced than with spironolactone, and the same was noted with respect to hyperkalemia. Hyperkalemia is considered the main hindrance to prescribing MRAs.

The ARTS-HF was a multicenter phase 2b randomized double-blind placebo-controlled clinical trial conducted on 1060 patients with heart failure and chronic kidney disease and/or diabetes. Subjects received 2.5–20 mg of finerenone once daily or 25 mg eplerenone every other day or 50 mg eplerenone once daily. The study aimed to analyze the safety and efficacy of plasma NT-pro-BNP reduction compared to the other two MRAs [19]. At 90 days, the percentage of patients with a plasma NT-pro-BNP reduction over 30% was similar for finerenone and eplerenone.

Finerenone administered orally is rapidly absorbed, reaching a peak plasma concentration at 0.5–1 h (T_{max}), and has an elimination halftime of 1.7–2.83 h.

About 8–12% of finerenone is transported bound to plasma proteins and albumin. It undergoes hepatic metabolism (CYP3A4, 90%, and CYP2C8, 10%). It is estimated that the administration of fractionated doses twice daily does not offer an advantage compared to a single dose daily, a common feature for all MRAs.

The usual dose for finerenone is 5–10 mg daily.

20.3.3 Aldosterone Escape Phenomenon

The long-term treatment with ACEIs and/or with ARBs should reduce aldosterone production. However, it has been observed that current pharmacological agents designed to control the RAAS pose certain risks and, moreover, are inefficient in controlling aldosterone secretion. In addition, in certain clinical trials, after several months of treatment, an initial reduction in aldosterone levels was followed by an increase with a tendency to return to baseline values, an effect known as the aldosterone escape phenomenon.

The aldosterone escape phenomenon is found in over 40% of patients treated with ACEIs or ARBs [26–28]. This phenomenon further stresses the need to add an MRA to ACEI or ARB therapy.

The underlying mechanism of the aldosterone escape phenomenon is comprised of a few components, acting synergically:

1. *Production of angiotensin II, independent of the converting enzyme and uninhibited by ACEIs*. It is called the chymase pathway. In turn, the ACEIs do not fully inhibit the converting enzyme.
2. *Aldosterone production independent of angiotensin II*. There is convincing evidence that aldosterone has a distinct contribution in the pathogenesis of heart failure, constituting an important argument in favor of adding aldosterone antagonists to other antihypertensive agents (ACEIs, ARBs, beta-blockers, etc.).

This alternative does not entirely eliminate the risk of the escape phenomenon or an increase in aldosterone secretion through other pathways. Consequently, the need to elaborate new selective inhibitors of aldosterone synthase is becoming evident.

20.3.4 Aldosterone Synthase Inhibitors

Aldosterone is synthesized in the zona glomerulosa of the adrenal glands, under the stimulating control of ACTH, angiotensin II, and extracellular potassium. Under normal conditions, aldosterone secretion has a circadian rhythm similar to endogenous steroids secretion.

Aldosterone synthase is coded by the CYP11B2 gene that exclusively expresses in the zona glomerulosa.

In fact, aldosterone synthase describes three isoenzymes with three different catalytic functions exerted by the same molecule: 11ß-hidroxylation, 18-hydroxylation şi 18-methyloxidation (Fig. 20.2).

CYP11B2 and CYP11B1 are highly similar, with a sequence analogy of 93%. The 11ß-hydroxylase and 11-hydroxylase enzymes have identical activity. The 11-hydroxylase enzyme is coded by CYP11B1, which is expressed in the zona reticularis and zona fasciculata and controls cortisol secretion. In addition, it is exclusively controlled by ACTH [18].

The compensatory increase of aldosterone secretion following treatment with an ACEI and/or ARB can be countered by adding an MRA or an aldosterone synthase inhibitor.

Despite the availability of increasingly selective MRAs, the need for novel, selective aldosterone synthase inhibitors is becoming more evident. These agents could block the non-genomic effects of aldosterone, independent of those generated through the stimulation of the mineralocorticoid receptor.

Therefore, at least theoretically, these compounds prevent both genomic and non-genomic effects of aldosterone. Selective aldosterone synthase inhibitors could be alternatively used with MRAs in primary hyperaldosteronism or liver failure (primary or secondary to heart failure).

The pharmacodynamical/pharmacokinetic profile of the ideal aldosterone synthase inhibitor should act selectively and distinctively on CYP11B2 aldosterone synthase versus 11β-hydroxylase CYP11B1.

The increase in the 11-deoxycortisol substrate emphasizes the inhibition of 11β-hydroxylase, with a subsequent compensatory increase in steroid synthesis

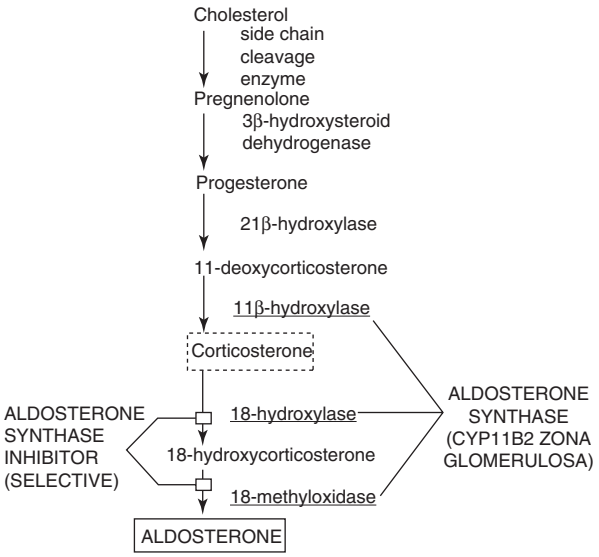

Fig. 20.2 Aldosterone biosynthesis and potential consequences of nonselective aldosterone synthase inhibitors

(glucocorticoids, mineralocorticoids, androgens) and hypertrophy of the adrenals glands, via the hypothalamic-pituitary-adrenal axis.

The aldosterone synthase inhibitor should have a halftime longer than LCI699, in order to be prescribed as a single dose daily. Of the recently studied compounds, LCI699 [28] inhibits 11β-hydroxylase; however, it does not present selective affinity, and as a consequence, it also inhibits 11β-hydroxylase (CYP11B1) that catalyzes glucocorticoid synthesis.

Following results from the phase 2 study, LCI699 production was halted as the requirements for a successful aldosterone synthase inhibitor were achieved [29]. However, a higher selectivity for CYP11B2 inhibition versus 11β-hydroxylase CYP11B1 and a longer plasma half-life would be beneficial. Selective inhibition of the 18-oxidase reaction in the aldosterone synthesis cascade would prevent conversion of less active mineralocorticoids such as 18-OH corticosterone and corticosterone to aldosterone.

As a conclusion, the ideal profile of an aldosterone synthase inhibitor consists of a higher selectivity to prevent inhibition of cortisol synthesis and the compensatory increase of 11β-hydroxylase.

It is also believed that a selective aldosterone synthase inhibitor could have sustained natriuretic and antihypertensive effects over a longer period of time with a safer profile compared to aldosterone antagonists that determine a compensatory increase in aldosterone secretion [30].

Another selective aldosterone synthase inhibitor with isoquinoline structure has been studied in preclinical trials and on selected human subjects to evaluate tolerance, safety, and PD and PK effects in humans [30].

Recent studies that focused on obtaining a selective inhibitor of aldosterone synthase have revealed a compound 100 times more active and more selective for aldosterone synthase versus 11β-hydroxylase (RO 6836191). The experiment demonstrated that this compound does not determine an increase in hydrocortisone (cortisol). Clinical trials on healthy volunteers show a decrease in plasma aldosterone levels, as well as urinary clearance without changes in cortisol levels.

20.4 Vasopeptidase Inhibitors

Combination therapy with sacubitril and valsartan is proof of the remarkable progress made in the field of molecular medicine. Currently, research is focused on novel targets in order to develop new drugs, starting from pharmacodynamical and pharmacokinetic profiles reliant on high-fidelity qualitative and quantitative biomarkers. In this case, of particular interest is identifying natriuretic peptides, characterizing its molecular functions in an integrative manner, as well as in correlation to the various cellular functions of other organs and systems. Also of major importance are the kinetics of natriuretic peptides within the body (from biosynthesis to inactivation) and the dynamic of these hormones in particular situations: normal versus pathological. Therefore, the natriuretic peptides and their metabolism become targets for

new drugs, as well as biomarkers for identifying and quantifying the specific effects for the drug in question.

The three types of natriuretic peptides that have been identified approximately 30 years ago are the atrial natriuretic peptide (ANP), the brain natriuretic peptide (BNP), and the type C natriuretic peptide (CNP) from swine brain samples (see Chap. 6).

The normal plasma levels for ANP in humans have a cutoff at 20 pg/mL. In heart failure, ANP levels increase 10–100 times the normal values. Both ANP and NT-pro-ANP are used as biomarkers to detect heart failure and assess its severity, as well as monitoring response to treatment. For diagnostic and prognostic purposes in heart failure, BNP is preferred due to superior stability [31].

The receptors for ANP are the NPR-A receptor for ANP, NPR-B for BNP, and NPR-C for CNP, respectively.

Through activation, receptors type A and B bind to guanylate cyclase, in turn activating it, with a subsequent increase in cGMP levels, triggering a reaction cascade with effects on the cardiovascular system, hemodynamics, the endocrine system, the renal system, and mitogen processes.

In heart failure, ANP plasma levels are constantly raised, in correlation to disease severity. An increase in the synthesis of ANP represents the subsequent response to acute volume overload or sodium retention in the early asymptomatic stages of heart failure.

The atrial stretch determined by volume overload is the main stimulus to increase ANP secretion. Another significant contributor to this effect is stimulation exerted by angiotensin II and endothelin. Consequently, it can be concluded that heart failure is, in this case, associated with a deficit of biologically active natriuretic peptides.

Considering the complex link between heart failure and the RAAS and ANP, the current preference is to reduce the activity of the RAAS and/or the rise of ANP [31].

Currently a widely accepted notion, ACEIs, ARBs, and beta-blockers reduce mortality rates in patients with heart failure with reduced ejection fraction. In those resistant to combination therapy with ACEIs, sartans, and beta-blockers, a neprilysin inhibitor and ARB can be added to the treatment [32].

A recent study analyzed the mechanisms of action of the sacubitril-valsartan combination, as well as the synergy of the two components, probably acting as potentiators for one another [33].

The authors of the study focused on identifying the action of each component on cardiac remodeling. For example, valsartan is associated with hypertrophy prevention, while sacubitril is associated with vasodilation by cleaving vasoactive peptides, including natriuretic peptides. At a molecular level, it has been observed that these two compounds as a combination therapy can reduce left ventricular extracellular matrix remodeling and cardiomyocyte death.

There are, however, other two new pharmacological targets for antihypertensive drugs—a neutral endopeptidase, neprilysin, and the endothelin-converting enzyme, both of which are metalloproteinases [34].

Numerous attempts have been made to create compounds or administer dual or triple drug combinations to interact with these targets; however, few have reached their goal [35–37].

Inhibition of two or three of these enzymes, apart from the antihypertensive effect, reduces target-organ damage through a series of antiproliferative, antifibrotic, and anti-inflammatory effects [34].

Moreover, it was believed that the creation of a drug to optimize the effects of the endogenous natriuretic peptides meant targeting the enzyme responsible for their metabolism and neprilysin's, respectively. The expected effects of natriuresis, diuresis, and vasodilation were, therefore, achieved [35]; however, it was concluded that the exclusive utilization of neprilysin inhibitors leads to a compensatory reaction implying an increase in the vasoconstrictive peptides, such as angiotensin II and endothelin-1, both of which are substrates for neprilysin as well.

Following this observation, the first suggestion was to associate a neprilysin inhibitor with an ACEI. However, omapatrilat, both a neprilysin inhibitor and ACEI, was found to produce angioedema more frequently than enalapril.

Ultimately, after attempts at other drug combinations failed, in order to avoid angioedema, a dual association between a neprilysin inhibitor as a prodrug and valsartan (an ARB) in a 1:1 ratio was tried. This approach came after concluding that in heart failure there is a deficit in the activity of natriuretic peptides, specifically a deficit in the processing of these peptides in their active form [31].

The interplay between the antinatriuretic and natriuretic systems should be implicitly resolved through pharmaceutical means, by favoring natriuresis and vasodilation. One step in this direction is the reduction of the RAAS activity and facilitation of the effects of the natriuretic peptides (particularly the ANP).

Exclusive inhibition of neprilysin has severe and conflicting consequences on water and sodium excretion and vascular muscle tone, considering the enzyme's multiple substrates. In addition, it increases angiotensin II levels, decreases angiotensin I levels (a vasodilator), and increases aldosterone and catecholamines [31]. Therefore, the association between a neprilysin inhibitor and an ARB was proposed, resulting in the sacubitril-valsartan combination. This aims to achieve a significant synergy and potentiation of the two compounds and reciprocal antagonism to their adverse reactions, including angioedema, vasoconstriction due to interaction with the angiotensin II receptor, and sodium retention, with the benefit of blood pressure lowering, a decrease in sympathetic nervous system activity, a decrease in aldosterone levels, and diminishing fibrosis and hypertrophy.

Antagonizing the functional deficit of the natriuretic peptides and facilitating their effects have the following consequences: vasodilation, natriuresis/diuresis, blood pressure lowering, a decrease in the sympathetic nervous system activity, a decrease in renin-aldosterone secretion, arginine-vasopressin, diminishing fibrosis, and hypertrophy. These effects can be facilitated by sacubitril-valsartan and annul the grave consequences of the RAAS on the heart.

A recent analysis [6], published 2 years after FDA approval, underlines several aspects that require clarification.

Therefore, it is mentioned that there are still unknown pharmacodynamic and pathophysiological mechanisms of action for the sacubitril-valsartan combination through which this association exerts its beneficial effects in patients with heart failure. For example, in the PARADIGM-HF trial, there aren't any data regarding cardiac remodeling, and the author acknowledges that the hemodynamic effects of the combination and other aspects concerning severity of heart failure could be, in fact, evidence of disease progress.

Moreover, the data collected so far are not sufficient to provide guidance in the administration of sacubitril-valsartan in patients treated with small doses of ACEIs or ARBs. In addition, there is no data concerning the safety and efficacy of the combination in heart failure stage D, in hospitalized patients or in those with heart failure complicated with myocardial infarction or in patients with heart failure and preserved ejection fraction.

A very recent analysis [38] regarding results from the PARADIGM-HF trial with respect to the superiority of sacubitril-valsartan versus enalapril in heart failure raises the question of the proportion of patients considered eligible for treatment with this drug combination. The same analysis mentions that the European Society of Cardiology recommends treatment with sacubitril-valsartan only for patients with a similar profile to those included in PARADIGM-HF. The authors, therefore, conclude that less than 25% of patients with heart failure with reduced ejection fraction fulfill the strict eligibility criteria set in the trial. However, preliminary reports underline significant differences regarding the proportion of patients deemed eligible for combination therapy with sacubitril-valsartan.

In conclusion, this proportion can rise when considering sacubitril-valsartan in patients with heart failure with reduced ejection fraction, when ACEIs or ARBs alone are not efficient or not well tolerated. Consequently, the eligibility of this subset of patients rises to 81%.

Initial dosage for sacubitril-valsartan is 49/51 mg twice daily. The dose can be doubled after 2–4 weeks of treatment, up to the maintenance dose of 97/103 mg, depending on response to therapy and tolerance.

In patients with no prior treatment with an ACEI or ARB or undergoing treatment with small doses of either drug class, starting dose should be 24/26 mg twice daily. Doses should be reduced in patients with severe kidney failure or moderate liver failure.

Contraindications include concomitant administration of sacubitril-valsartan with an ACEI, while replacing the latter can be pursued 36 h after ACEI treatment cessation.

Furthermore, aside from hypersensitivity reactions to both compounds, the combination is contraindicated in patients with history of angioedema, due to either ACEI or ARB administration.

In PARADIGM-HF [39], 12.2% of patients were withdrawn due to severe adverse reactions such as cough, hyperkalemia, renal dysfunction, or hypotension. In the sacubitril-valsartan group, hypotension was more frequently reported versus the enalapril group; however, it did not require treatment interruption. On the contrary, a potassium plasma level over 6.0 mmol/L was less frequently reported in

the sacubitril-valsartan group versus the enalapril group. It remains to be seen if the results of the PARAGON-HF study which will finalize in 2019 and which included patients with an EF >45% will bring new indications for this combination of sacubitril-valsartan.

From the perspective of short-term aims, additional clinical information concerning the efficacy and safety of the sacubitril-valsartan combination therapy in heart failure with preserved ejection fraction, its effects on cardiac remodeling, or on heart failure associated with myocardial infarction, acute heart failure, etc. is highly needed.

20.5 Conclusion

Current research focused on finding new pharmacological targets to control hypertension, prevent HF, and/or treat hypertension associated with HF has identified and characterized the natriuretic hormones and their effects on the myocardium, as well as the role of their variations in determining HF-specific modifications.

Essentially, the deficit of biologically active natriuretic peptides constitutes the main treatment target in HF. Benefits have been observed particularly in patients with HF with reduced ejection fraction.

Elaboration and the molecular design of novel compounds to neutralize newly discovered targets involved in the pathogenesis of heart failure can be anticipated, as is the case of the endothelin-converting enzyme. In fact, currently, the main focus is the pharmacological control of the mechanisms involved in the proliferation of myocytes, thrombogenesis, and inflammation within the myocardium.

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Heart Failure with Preserved Ejection Fraction: Current Management and Future Strategies

21

Enrico Agabiti Rosei and Damiano Rizzoni

Hypertension (HTN) represents the most important attributable risk factor for heart failure (HF). The measurement of left ventricular (LV) ejection fraction (EF) is the basis for the description of HF in different patients, from those with normal EF (above 50% HF with preserved EF (HFpEF)) to those with reduced EF (below 40%, HF with reduced EF (HFrEF)) [1]. Recent ESC guidelines have identified patients with an LVEF in the range 40–49%, defined as HFmrEF, which in different studies have been considered in the group with HFpEF [2]. HFpEF accounts for about 50% of HF cases, but its prevalence relative to HFrEF continues to rise. HFpEF carries similar risk of morbidity/mortality as HFrEF. Patients with HFpEF are frequently old women with HTN, usually also with diabetes and obesity, characterized by concentric LV hypertrophy (LVH), increased left atrial (LA) size, diastolic dysfunction, pulmonary hypertension, and elevated levels of natriuretic peptides.

21.1 Hypertension and HFpEF

The development of LVH in HTN is a strong predictor of HF, even when LV systolic function is normal and no evidence of ischemic heart disease is present, thus representing a leading risk factor for HFpEF [1, 3, 4]. It is believed that diastolic abnormalities may precede systolic chamber dysfunction, despite this aspect needs further clarification with longitudinal studies. HFpEF and HFrEF share similar symptoms, signs, and some pathophysiological features, such as endothelial dysfunction and neurohormonal imbalance. However, some evidences suggest that these two forms of HF may represent two distinct diseases, with different timings and different changes in myocardial structure and function. In fact, the development

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of HFpEF in patients with LVH is usually associated with a progressive change in the extracellular matrix and an increase in perivascular and interstitial fibrosis.

The presence of inappropriate LV mass, i.e., an increase in LV mass that exceeds the amount appropriate for individual cardiac workload, sex, and body size, is probably related to cardiovascular structural and functional abnormalities, which lead to cardiovascular events, in particular to the development of HF (Fig. 21.1). The incidence of HF is reduced with antihypertensive treatment able to correct LV mass inappropriateness.

Patients with HFpEF may have coronary microvascular rarefaction and also dysfunction, possibly as a consequence of a systemic inflammatory status and oxidative stress, accelerated by comorbidities which are frequent in this condition. Patients with HFpEF often present increased vascular stiffness and high pulse pressure as well as impaired flow-mediated dilatation.

21.2 Treatment of HFpEF (and HFmEF)

No specific treatment has yet been shown to reduce fatal and nonfatal cardiovascular events in patients with HFpEF or HFmEF. Thus, treatment should alleviate symptoms and target quality of life as well as the improvement of well-being.

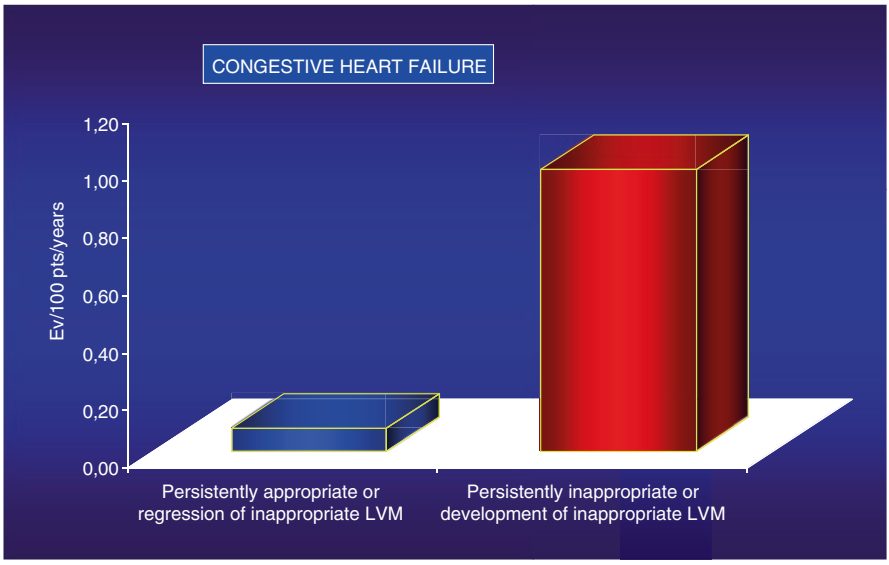

Fig. 21.1 Incidence of congestive heart failure in 436 hypertensive patients with a follow-up visit after a mean period of 72 + 38 months, followed for additional 50 + 25 months (range 36–216 months), 249 males and 187 females, age range 18–71 years, mean age 52 ± 9, according to the presence of persistently appropriate or regression of inappropriate or persistently inappropriate or development of inappropriate left ventricular mass. Re-drawn from: Muiesan ML, Salvetti M, Paini A, Monteduro C, Galbassini G, Bonzi B, Poisa P, Belotti E, Agabiti Rosei C, Rizzoni D, Castellano M, Agabiti Rosei E. Inappropriate left ventricular mass changes during treatment adversely affects cardiovascular prognosis in hypertensive patients. Hypertension. 2007; 49:1077–83

Cardiac decompensations can be substantially reduced by controlling fluid retention and treating risk factors and comorbidities. In fact, these patients with HFpEF are often affected by several concomitant cardiovascular and non-cardiovascular diseases (e.g., arterial hypertension, atrial fibrillation, coronary artery disease, pulmonary hypertension, diabetes, obesity, chronic obstructive pulmonary disease, sleep apnea, chronic kidney disease, anemia, and sarcopenia) that should be appropriately managed. In this context, particularly important is the correct management of arterial hypertension, with a target blood pressure at 130/80 mmHg or lower. The optimal treatment strategy for these patients is not clear.

21.3 Current Management of HFpEF

Comorbid conditions are associated with serious threats in HFpEF, particularly by triggering rehospitalization [2, 5]. This is particularly true for uncontrolled systolic and diastolic blood pressure, which explains the importance of angiotensin-converting enzyme inhibitors (ACEi), angiotensin-2 type 1 receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), diuretics, calcium channel blockers (CCB), and beta-blockers as preventive strategies [2, 5] (Fig. 21.2). ACEI, ARB, MRA, and beta-blockers possess a well-demonstrated efficacy in reducing morbidity and mortality in patients with HFrEF.

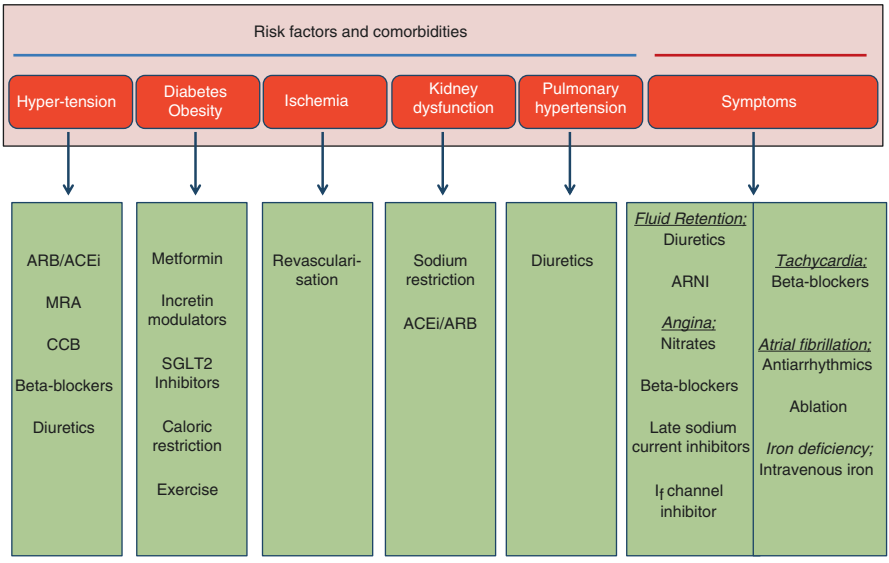

Fig. 21.2 Current management of risk factors, comorbidities, and symptoms in HFpEF. *ARB* angiotensin receptor blocker, *ACEi* angiotensin-converting enzyme inhibitor, *MRA* mineralocorticoid receptor antagonist, *HFpEF* heart failure with preserved ejection fraction, *CCB* calcium channel blocker, *RF* risk factors, *ARNI* angiotensin receptor and neprilysin inhibitor, *SGLT2* sodium–glucose cotransporter 2 (re-drawn from [2])

21.4 Diuretics

Loop diuretics, thiazide, and thiazide-like drugs are necessary to overcome total blood volume expansion and congestion also in HFpEF [5]. In the Hong Kong Diastolic Heart Failure Study [6], diuretic therapy significantly improved symptoms, and neither the ARB irbesartan nor the ACEi ramipril had a significant additional effect. Thus, diuretics appear indispensable for the improvement of symptoms and are recommended by current ESC guidelines, especially when postcapillary pulmonary hypertension is present [2]. However, an excessive preload reduction by diuretics can lead to an under-filling of the left ventricle and therefore to a reduction of stroke volume and cardiac output. This may be a problem particularly in HFpEF patients with pronounced concentric LVH and small ventricles, including patients with hypertrophic cardiomyopathies, storage diseases (amyloidosis), or cardiac inflammation (myocarditis) [5].

21.5 ACE Inhibitors and AT1 Receptor Antagonists

None of these agents improved hard clinical end points in HFpEF trials, and therefore current guidelines do not recommend the use of ACEi or ARB for the direct treatment of HFpEF, unless they are part of the regimen for their acknowledged effect on comorbidities such as hypertension [2, 5]. There is no evidence for an improvement in symptoms in those treated with ARBs, apart from an improvement in NYHA class observed with candesartan [2]. On the other hand, a trend toward a reduced hospitalization risk was observed with ACEi/ARB [7, 8], suggesting the need for future research with careful patient selection [9, 10], even according to specific phenotypes, as well as for well-designed and well-conducted clinical trials [7, 8].

21.6 Mineralocorticoid Receptor Antagonists (MRA)

Aldosterone antagonists are not generally recommended for patients with HFpEF. In order to further clarify the role of aldosterone antagonism in HFpEF, the SPIRIT-HF phase III trial has been initiated by the German Centre for Cardiovascular Research, to investigate the effects of spironolactone in well-characterized HFpEF patients [5]. In fact, in the TOPCAT trial, adding spironolactone to existing therapy in patients with HFpEF did not reduce the composite primary end point of death from CV causes, aborted cardiac arrest, or hospitalization for HF [5]. However, considering the individual components of the composite primary end point, the rate of hospitalization for HF was significantly reduced in the spironolactone group. Unfortunately, in this trial, a marked regional variation in event rates was observed, with patients enrolled in Russia or Georgia showing a much lower incidence of primary outcome events than those enrolled in America. In any case, patients treated

with spironolactone should be carefully controlled for possible elevations in serum creatinine and potassium levels. The safety and efficacy of new aldosterone antagonists including dihydropyridine-like CCB, nonsteroidal aldosterone antagonists (i.e., finerenone), and aldosterone synthase inhibitors are presently under investigation [5].

21.7 Beta-Blockers

Evidence for a general use of beta-blockers in patients with HFpEF is controversial. In the SENIORS study [11], a pre-specified post hoc analysis showed that nebivolol improved the outcome of HFpEF patients (in this case with an EF above 35%) to a similar degree as in HFrEF [11], although the echocardiographically measured diastolic function remained unaltered. However, other studies and registry data reported controversial or inconsistent results [5]. Current recommendations do not favor a general treatment recommendation for beta-blockers in HFpEF [2], unless they are not indicated to optimize the therapy of comorbidities and symptoms including the control of heart rate, angina pectoris, or hypertension [5]. When needed, beta-blockers with ancillary vasodilator properties should be preferred.

21.8 Others

21.8.1 If-Channel Inhibitor

Ivabradine cannot be recommended for the primarily treatment of HFpEF. However, according to guidelines, ivabradine is useful in patients with angina pectoris and persistent high heart rate despite ß-blocker therapy, independently of ejection fraction [5].

21.8.2 Calcium Channel Blockers (CCBs)

No large prospective trials investigated the effects of CCBs in HFpEF [5]. Thus, CCBs cannot be generally recommended for HFpEF, but they may be useful for the control of hypertension and angina [5].

21.8.3 Late Sodium Current Inhibitors

An inhibition of the late sodium current with drugs, such as ranolazine or eleclazine, might improve diastolic function. In the RALI-DHF study, intravenous administration of ranolazine in patients with HFpEF resulted in a reduction of the end-diastolic pressure [12]. Further studies are needed to investigate the role of ranolazine in

HFpEF. Ranolazine is available for the treatment of patients with angina pectoris and may thus be tested for symptom relief in patients with HFpEF and angina pectoris [5].

21.8.4 Cardiac Glycosides

Cardiac glycosides should not generally be used in HFpEF, since they have not been systematically investigated in this regard; however, they may have a place in the control of atrial fibrillation [5].

21.8.5 Statins

The results of a recent meta-analysis suggest a potential mortality benefit of statins in HFpEF [13]. Further prospective and randomized controlled trials should be planned to confirm these observations. Although the ACCF/AHA HF guidelines support the use of statin therapy for patients with known atherosclerotic disease [14], however, at present time they are not recommended for the treatment of HFpEF in the absence of specific additional indications [5].

21.9 Non-Pharmacological Therapeutic Approaches in HFpEF

21.9.1 Exercise in HFpEF

A dedicated training program was demonstrated to be associated with improved LV diastolic function and atrial dimension in patients with HFpEF compared with patients under standard recommendations [15]. The benefit of exercising was indicated in a recent meta-analysis by Pandey et al. [16], supporting the importance and safety of training programs for HFpEF patients [10].

21.9.2 Diet in HFpEF

Salt-restricted DASH diet improved diastolic function, arterial stiffness, and ventricular–arterial coupling in a small number of subjects with HFpEF [17]. In obese HFpEF caloric-restriction improved symptoms, peak oxygen consumption, and quality of life, even to a greater extent than exercise; the two non-pharmacological interventions had additive effects [18].

21.9.3 New Disease-Modifying Strategies

Novel strategies for the treatment of HFrEF are presently under investigation in order to evaluate whether they are able to control symptoms or disease progression and/or to improve outcome [5] (Fig. 21.2). Some of these new therapeutic approaches will be now briefly addressed (Table 21.1).

21.9.4 Targeting the NO–cGMP–PK Axis

In HFpEF, the intracellular nitrogen monoxide (NO)–cGMP–protein kinase (NO–cGMP–PK) signal cascade is impaired [5]. The reduced/altered activity of GMP in the myocytes appears to be a specific mechanism in HFpEF, a difference from what was observed in HFrEF [5]. This is of importance for the development of new therapeutic options, since it may be possible to intervene with inorganic nitrates, phosphodiesterase-5 (PDE5) inhibitors, orally available soluble guanylate cyclase stimulators, or with angiotensin receptor/neprilysin inhibitors (ARNI).

Table 21.1 New approaches to the treatment of HFpEF

Targeting the NO–cGMP–PK axis	*Organic nitrates and endothelial NO synthase activators*
	Inorganic nitrates (nitrites)
	Phosphodiesterase-5 inhibitors
	Angiotensin receptor neprilysin inhibitor
	Soluble guanylate cyclase stimulators and activators
Cytokine inhibitors	
Antidiabetic drugs	*Thiazolidines*
	Incretins
	Sodium–glucose cotransporter 2 inhibitors
Szeto–Schiller peptides	
Cross-link breakers	
Modulators of intracellular calcium homeostasis	
MicroRNAs	
Device therapy in HFpEF	*Online monitoring*
	Atrial shunt device
	Cardiac resynchronization therapy
	Cardiac contractility modulation
	Renal denervation
	Baroreflex activation therapy

21.9.4.1 Organic Nitrates and Endothelial NO Synthase (eNOS) Activators

Direct NO donors such as organic nitrates (isosorbide nitrate) are not considered to be particularly useful in the treatment of HFpEF, due to the risk of an excessive preload reduction and to the possible onset of tachyphylaxis. Short-acting nitrates are recommended in HFpEF, but only for the relief of angina symptoms. On the contrary, eNOS activators like the eNOS transcription amplifier AVE3085 have been promisingly investigated in animal experiments [5]; however, they still await specific clinical testing.

21.9.4.2 Inorganic Nitrates (Nitrites)

At difference with organic nitrates, the inorganic nitrate–nitrite pathway represents an important alternative route to restore NO signaling in HFpEF, through an increase in myocardial nitric oxide bioavailability. Acute intravenous infusion of sodium nitrite and inhaled sodium nitrate administration were both able to reduce diastolic LV pressures and pulmonary artery pressures [19, 20]. Inorganic nitrate (precursor of nitrite), administered daily as beetroot juice drink, was able to improve submaximal exercise endurance [21].

21.9.4.3 Angiotensin Receptor Neprilysin Inhibitor

LCZ696, a combination of the ARB valsartan and of the neprilysin inhibitor sacubitril, is able to stimulate the NO–cGMP–PK signal cascade. Inhibition of neprilysin prevents the degradation of several vasoactive peptides, including some biologically active natriuretic peptides such as ANP, BNP, and CNP. These peptides stimulate the formation of cGMP through specific receptors and may exert antifibrotic, vasodilatory, and natriuretic effects [5]. In addition, neprilysin inhibition prevents glucagon degradation, with consequent benefits for diabetic HFpEF patients [5]. A promising study (PARAGON-HF trial), whose results are awaited in May 2019, is presently evaluating the effects of LCZ696 on morbidity and mortality in 4300 patients with HFpEF.

21.9.4.4 Phosphodiesterase-5 Inhibitors

PDE5 inhibition represents an additional strategy able to stimulate the cGMP system, leading to an improvement of cardiac relaxation and diastolic performance in HFpEF. This has been specifically investigated in the RELAX trial [22]. Unfortunately, none of the investigated end points of the study reached statistical significance. Thus, sildenafil, and similar drugs, at present cannot be recommended in HFpEF patients, unless precapillary pulmonary hypertension is present [5].

21.9.4.5 Soluble Guanylate Cyclase (sGC) Stimulators and Activators

Stimulators and activators of sGC increase the enzymatic activity to generate cGMP independently of NO. Vericiguat and riociguat, direct sGC stimulators, appear promising as treatment strategies in heart failure, since they may increase stroke volume and cardiac index and may improve quality of life in HFpEF [5].

21.10 Cytokine Inhibitors

HFpEF is associated with chronic myocardial inflammation [5], with activation of the local cytokine cascade and increased cardiac expression of transforming growth factor (TGFß) [5]. In the D-HARD study, the effects of the interleukin-1 inhibitor anakinra were evaluated in 12 HFpEF patients. Load capacity and C-reactive protein levels were significantly improved compared with placebo [23]. New adhesion molecule antagonists targeting integrins, such as ICAM or VCAM, and/or colchicine are presently under investigation to prevent migration of inflammatory cells to the heart.

21.11 Antidiabetic Drugs

A large proportion of patients with HFpEF have diabetes mellitus as comorbidity. Thiazolidines, incretins, and inhibitors of the sodium–glucose cotransporter 2 (SGLT2) may possibly represent an additional therapeutic option for diabetic and even for nondiabetic HFpEF patients.

21.11.1 Thiazolidines

Pioglitazone, an agonist for the PPAR-y receptor, is able to improve myocardial energy production and glycolysis. The PIRAMID study showed that in patients with uncomplicated type 2 diabetes, myocardial glucose assimilation and diastolic function were improved after 24 weeks of therapy with pioglitazone [24]. It is not known whether thiazolidines may be a therapeutic option also for nondiabetic HFpEF patients. However, at present pioglitazone is contraindicated in patients with HFrEF and NYHA functional classes II–IV.

21.11.2 Incretins

Exenatide improved cardiac diastolic function in diabetic patients [25]. Similarly, linagliptin and sitagliptin improved diastolic function in diabetic HFpEF patients with chronic kidney disease [26]. Further studies are however needed in order to assess whether this class of drugs may be clinically useful in diabetic patients with HFpEF.

21.11.3 Sodium–Glucose Cotransporter 2 (SGLT2) Inhibitors

The EMPA-REG OUTCOME trial investigated the effects of empagliflozin in patients with type 2 diabetes and found an unexpected, marked relative risk reduction in cardiovascular mortality (38%), hospitalization for heart failure (35%), and death

from any cause (32%). Empagliflozin is now recommended by the ESC in diabetic heart failure patients, in combination with metformin [2]. Studies in nondiabetic HFrEF and HFpEF patients are presently ongoing.

21.12 MicroRNAs

The role of miRNAs as biomarkers in HFpEF is still unclear; miRNAs and/or certain inhibitors (antagomirs) are investigated as inducers of neoangiogenesis or modifiers of fibrosis. Anti-apoptotic and anti-fibrotic effects of miRNA21 were demonstrated in animal models of diastolic heart failure [27]. Thus, miRNAs are presently being taken into account as possible therapeutic targets for the treatment of HFpEF [5].

21.13 Device Therapy in HFpEF

Several studies evaluating the role of devices are presently ongoing in HFpEF patients (Fig. 21.2).

21.13.1 Online Monitoring

The CardioMEMS device is a small pressure sensor and monitor, which is implanted into the pulmonary artery. After discharge, the patients record their pulmonary artery pressure via a wireless radio-frequency transmitter. These values are continuously monitored by dedicated staff and may be used to adjust medication, especially the diuretic-based therapy. The use of CardioMEMS-transmitted information lowered hospitalization rates of NYHA III patients with either HFrEF or HFpEF [28].

21.13.2 Cardiac Resynchronization Therapy (CRT)

Approximately 20% of HFpEF patients have LV asynchrony, which is associated with myocardial energy and contractility loss [5]. Unpublished results of an Asian study, investigating about 130 HFpEF patients with mechanical asynchrony, suggest that temporary stimulation with a CRT system may improve some diastolic parameters [5]. However, at present, patients with narrowed QRS complexes are not eligible for CRT.

21.13.3 Atrial Shunt Device

The reduction of increased left atrial pressure may be considered the main hemodynamic objective of the treatment of HFpEF. The hypothesis that a small, artificially induced left–right shunt might function as an overflow valve is based on historical observations, showing that patients with an untreated mitral

stenosis and concomitant atrial defect (Lutembacher syndrome) had a better survival [5]. In 11 HFpEF patients, an interatrial septal device (IASD) was implanted in the septum, using a catheter-based technique, in order to induce a small shunt [29]. After 30 days, a reduction in the filling pressure and an improvement of the NYHA classification were observed [29]. More recently, the REDUCE LAP-HF study investigated 68 HFpEF patients who underwent IASD implantation, showing that more than 50% of patients had a reduction in wedge pressure [30].

21.13.4 Baroreflex Activation Therapy (BAT)

BAT electrically stimulates the carotid sinus via an implanted electrode. Potential benefits of such an approach include regression of left ventricular hypertrophy, normalization of the sympathovagal balance, inhibition of the RAAS, reduction of vascular tone, and preservation of renal function. BAT had been successfully investigated in HFrEF showing an improvement of functional status, quality of life, exercise capacity, and BNP reduction [31]. The clinical utility of BAT in treatment of HFpEF however needs further investigation.

21.13.5 Renal Denervation

HFpEF is associated with an increased sympathetic nervous system activity. Reduction of blood pressure by renal denervation therapy (RDT) improved left ventricular hypertrophy and diastolic left ventricular function in a small series of patients with refractory hypertension. This effect was prospectively investigated in single-center open trial [32], in which 25 patients with HFpEF were randomized to RDT or to medical therapy. At 12 months, there were no differences between groups in quality of life and markers of diastolic function. Some patients showed an improvement of peak VO_2. However, at present time, the clinical value of RDT in HFpEF remains unclear.

21.14 Conclusions

At present, the clinical management of patients with HFpEF remains a challenge, mainly due to the fact that HFpEF is a heterogeneous syndrome [5]. Trials of ACEIs, ARBs, beta-blockers, and MRAs have all failed to reduce mortality in patients with HFpEF or HFmrEF [2]. In fact, no treatment has yet been shown, convincingly, to reduce morbidity and mortality on patients with HFpEF. However, in older patients with HFrEF, HFpEF, or HFmrEF, nebivolol reduced the combined end point of death or cardiovascular hospitalization, with no significant interaction between treatment effect and baseline LVEF [2]. The future will show whether new treatment strategies, including disease-modifying approaches and/or device therapy, will be able to clearly improve outcome in HFpEF.

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Treatment of Acute Heart Failure in Hypertensive Crisis

22

Oana Gheorghe-Fronea

22.1 Introduction

Hypertensive emergencies and hypertensive urgencies are what we call hypertensive crisis (HC). From a clinical perspective it is very useful to distinguish between urgencies and emergencies because the treatment approaches are different.

The definition of a *hypertensive emergency* is a situation (usually systolic blood pressure [SBP] >180 mmHg or diastolic BP [DBP] >120 mmHg) that requires immediate reduction in BP because of acute or progressive target organ damage, while the same increase in BP values in an otherwise stable and asymptomatic patient, without any signs of target organ damage, is considered a *hypertensive urgency* [1–9].

Hypertensive emergencies constitute a collection of heterogeneous conditions. A useful classification of hypertensive emergencies is based on organ damage, although two or more target organs can be affected simultaneously (Table 22.1).

The emergency is not determined by the BP level but rather by the clinical status of the patient. The degree of target organ damage determines the speed of the required BP lowering [1–9].

Acute heart failure (AHF) is defined by the new onset or acute worsening of signs and symptoms of heart failure, which requires urgent treatment [10, 11].

Since the persistence of uncontrolled BP values will affect mainly the functionality of the left ventricle (LV), the acute heart failure episodes triggered by HC will

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Table 22.1 Hypertensive emergencies: classification based on organ damage

Target organ	Complications
Brain	Hypertensive encephalopathy Cerebral infarction Intracerebral hemorrhage Subarachnoid hemorrhage
Eyes	Advanced retinopathy
Heart	Acute coronary syndromes Acute congestive heart failure
Aorta	Dissection
Kidney	Acute renal failure
Placenta/maternal circulation	Severe (pre) eclampsia

present as acute onset of dyspnea with or without chest pain, with acute pulmonary edema being the most severe clinical manifestation [10, 11].

22.2 From Hypertensive Crisis (HC) to Acute Heart Failure (AHF)

Acute heart failure in HC occurs in the setting of hypertensive cardiopathy with diastolic dysfunction with or without systolic dysfunction [11–15].

Myocardial factors rather than the pressure factor play the main role in AHF, but decrease of BP is a major treatment objective.

Hypertensive patients with a history of uncontrolled BP values and LV hypertrophy are more frequent subjects of AHF episodes such as pulmonary edema because of the presence of the following factors [11–15]:

- small coronary occlusive disease owing to the specific structural lesions of hypertensive vascular disease (predominantly muscular hypertrophy),
- inadequate development of the microcirculation,
- increased coronary resistance, especially extravascular,
- reduction of coronary reserve,
- spasm in the microcirculation,
- increased oxygen demand.

Because other types of acute pulmonary edema can be associated with a significant temporary BP increase in the course of the sympathetic reflex, sometimes it is difficult to know whether or not the increase in BP value triggered the pulmonary edema. The persistence of high BP values—even with the reduction of LV failure signs and the presence of other clinical signs associated with target organ damage—is specific for an AHF episode driven by the increase in BP values, while if the AHF episode was triggered by another factor (such as myocardial ischemia), the BP tends to normalize rapidly, together with remission of the pulmonary edema, even without specific BP-lowering drugs.

There are several ways in which an HC can trigger the onset of an AHF episode [11–15]:

- through the steep increase in afterload that occurs as a result of extreme vasoconstriction (such as in flash pulmonary edema—see Chap. 15) or volume overload (such as occurs in the sudden interruption of a low-salt diet or of diuretic treatment) superimposed on a non-compliant hypertrophic LV with reduced functional reserve; this will result in the reduction of cardiac output and increased LV end-diastolic pressure that will be reflected backward through the left atrium and pulmonary veins to the pulmonary capillaries, resulting in increased pulmonary capillary wedge pressure (PCWP >25 mmHg) and alveolar fluid accumulation and the clinical debut of pulmonary edema.
- through acute dissection of the ascending aorta that can involve the aortic valve, leading to acute aortic regurgitation, which can precipitate AHF and pulmonary edema.
- through an acute coronary syndrome, which will trigger the onset of an AHF episode by impaired myocardial contractility with or without acute mitral regurgitation.

22.3 Treatment of Acute Heart Failure in Hypertensive Crisis

Besides obtaining a progressive reduction and control of BP values (NOT NORMALIZATION OF BP!), treatment in this clinical setting (as listed below) also targets the vicious circle leading to the progression of heart failure:

- *Reducing the afterload with arterial and venous vasodilators*
  In hypertensive AHF, intravenous vasodilators should be considered as initial therapy to improve symptoms and reduce congestion [7, 8–10, 13].
  The main drawback of these agents is the rapid development of tolerance, limiting their use to a maximum of 24 h only [11].
  Bearing in mind that pulmonary edema, as a form of AHF in the setting of HT crisis, represents fluid redistribution rather than fluid accumulation, data available in the literature support the recommendation that vasodilators are preferable to loop diuretics in this setting, while suggesting the employment of both veno-dilatation (reducing preload and PCWP) and arterio-dilatation (reducing afterload, increasing cardiac index CI and decreasing LV end-diastolic pressure and PCWP) [9–12, 16].
  Cotter et al. concluded that the most important predictor of immediate treatment success was the ability to reduce mean arterial pressure (MAP) at 15–30 min by 15–30%. This decrease in MAP reflects a parallel reduction in vascular resistance, emphasizing the importance of rapid arteriolar dilatation as the main goal of the immediate treatment of pulmonary edema [11].
- *Reducing the preload with diuretics*
  Intravenous loop diuretics (furosemide, bumetanide, torasemide) are recommended for all patients with AHF and signs and symptoms of congestion, to improve symptoms and decrease BP values (especially in those with a positive history of sudden interruption of a low-salt diet or of diuretic treatment) [9, 10–12].

The starting dose differs depending on whether or not the patient had been receiving chronic diuretic therapy prior to the AHF event: in diuretic-naive patients the recommended starting dose is 20–40 mg i.v. furosemide (or equivalent) and for patients undergoing chronic diuretic therapy, the initial i.v. dose should be equal to the chronic oral daily dose [10].

Loop diuretics can be administered either as intermittent boluses or as continuous infusions until the remission of congestion. Urine output, renal function, electrolytes, and BP should be regularly monitored [10].

In cases of refractory congestion a thiazide or an antimineralocorticoid drug (spironolactone, eplerenone) may be added in combination with the loop diuretic [10].

- *Improving systemic oxygenation*

  It is recommended that pulse oximetry, as well the evaluation of arterial blood gases and pH, be performed in all patients [10].

  In this setting, once peripheral capillary oxygen saturation (SpO_2) is <90% or partial pressure of oxygen (PaO_2) is <60 mmHg, oxygen therapy is usually performed by placing the patient in a sitting position, with O_2 delivery through a high-flow facemask [10, 11, 17].

  Non-invasive positive airway pressure ventilation (continuous positive airway pressure [CPAP]; bilevel positive airway pressure [BiPAP]) is not recommended as a routine procedure, although it is superior to O_2 facial mask delivery in improving oxygenation , because it can further impair cardiac function by increasing intrathoracic pressure, resulting in the potential exacerbation of pulmonary congestion. Therefore non-invasive ventilation is reserved for those patients not responding to conventional oxygen supply (SpO_2 <90% and respiratory rate >25 breaths/min) [10, 11, 18].

  If respiratory failure cannot be managed non-invasively (PaO_2 <60 mmHg, $PaCO_2$ >50 mmHg and/or pH <7.35) orotracheal intubation and invasive ventilation is recommended [10, 11].

22.3.1 Principles of Blood Pressure Lowering Treatment

- *Target BP and speed at which target BP should be reached depend on the underlying condition*

  Except for patients with acute aortic dissection (when BP should be lowered within 5–10 min to <120 mmHg), BP values in hypertensive emergencies with AHF should be lowered within the first hour by a maximum 25% of the value on admission and then gradually lowered to 160/110 mmHg in the next 2–6 h, reaching the normal BP values over the next 24–48 h [1, 3, 9, 11, 12, 19].

  This gradual BP reduction is crucial for the maintenance of cerebral, cardiac, and renal perfusion when BP is lowered, allowing for the restoration of normal autoregulation between BP and blood flow, which is shifted upward (to higher values) in patients with uncontrolled hypertension, who usually experience HC. A rapid decrease of BP values can therefore lead to under-perfusion and

ischemia, with the onset of acute renal failure, cardiac ischemic events, cerebral ischemic events, and retinal artery occlusion (blindness) [1, 8, 20].

- *Rapidly acting parenteral agents*
  Rapidly acting parenteral agents are the drugs of choice because they can be precisely managed and effectively stopped if the drop in BP is larger than the set target [1, 3, 9, 11, 12, 19, 20].
- *Prevention of overtreatment*
  When we start treatment we must define the upper and lower BP limits we want to reach in a certain time. Overtreatment happens rather frequently when we treat patients with hypertensive emergencies.
  In a retrospective study addressing BP control in malignant hypertension treated by i.v. infusion with antihypertensive agents, where appropriate BP reduction was defined by 25% reduction in BP within the first 2 h and the BP goal was 160/100 mmHg at 6 h, the proportion of patients with appropriate BP reduction at 2 h was only 32% while the proportion of patients with excessive BP reduction at 2 h was 57%. There were also treatment failures of about 11% at 2 h, and at 6 h the proportion of patients with appropriate BP reduction was 13%. The overall proportion of patients meeting the 2-h and 6-h BP goals in this study was only 28%. These results show that there is room for improvement in the management of hypertensive emergencies [21].
- *No diuretics, unless there is volume overload*
  Usually, patients who experience hypertensive emergencies with AHF have increased vasoconstriction and are volume-depleted, requiring vasodilators; therefore, diuretic treatment is not necessary, at least not in the initial phase, unless there are signs/symptoms of congestion [1, 3, 9, 11, 12, 19].
  Because continuous i.v. vasodilator therapy for more than 12 h induces sodium retention and volume overload, the use of low-dose diuretics may be necessary to prevent so-called tachyphylaxis (resistance to further BP reduction) [1].
- β-*Blockers and calcium channel blockers are contraindicated in the setting of AHF!*[10]

22.3.2 Intravenous Agents

22.3.2.1 Sodium Nitroprusside (Classic Vasodilator for i.v. Use)

Sodium nitroprusside (SN) is an arteriolar and venous dilator that lowers afterload and preload and is associated with an increase in HR and stroke volume [22–24]. The main advantages of this drug are its very rapid onset of action and short duration that make it extremely potent [22, 23].

Nevertheless, this drug has side-effects that can limit its use in certain hypertensive emergencies, such as coronary steal syndrome in coronary artery disease; the drug increases the intracranial pressure and reduces the cerebral blood flow and can also induce cyanide toxicity, because 44% of the weight of this drug is represented by cyanide, which is metabolized in the liver by thiosulfate in nitroprusside-thiol

sites; these factors therefore limit the duration of the drug exposure (particularly in regard to patients with renal and liver insufficiency) [24–26].

The starting dose of SN is 0.25 μg/kg i.v. and the drug can be titrated in increments of 0.5 μg/kg/min to obtain the optimal decrease in BP, up to the maximum dose of 10 μg/kg i.v. for a maximum of 10 min. The administration of this drug should be performed only under continuous BP monitoring. Severe renal dysfunction and recent use of phosphodiesterase inhibitors are contraindications for the use of SN [1, 9].

A very important aspect that should be taken into consideration before starting the administration of i.v. SN is the effect that this drug has on systemic and cerebral vascular resistance. Compared with the administration of i.v. labetalol, with SN infusion there is a greater decrease in systemic vascular resistance than in cerebral vascular resistance, whereas with labetalol the decreases in systemic and cerebral vascular resistance are the same. Also, the reduction in MAP and the decrease in middle cerebral artery blood flow velocity as a function of BP reduction, mean that, for the same decrease in systemic BP there is a greater decrease in cerebral blood flow with SN than with labetalol [26].

In conclusion, SN should only be used only when other i.v. antihypertensive agents are not available [27]. Having several disadvantages compared with other vasodilators, SN is therefore a second-choice agent [27].

22.3.2.2 Nitroglycerine

Nitroglycerine (NTG) is a potent venodilator and arteriodilator only at higher doses. Continuous i.v. infusion starts with a 5 μg/min infusion rate that is up-titrated by 5 μg/min every 3–5 min, up to 20 μg/min. If optimal BP and symptom control is not reached, up-titration by 10 μg/min every 3–5 min can be performed, up to a maximal dose of 200 μg/min [1, 9].

The onset of action begins at 2 min for the i.v. infusion, and the effect lasts for 1 h after discontinuation. NTG decreases BP by reducing preload and cardiac output and it decreases coronary spasm and cardiac workload [1, 9].

NTG is the drug of choice in hypertensive emergencies associated with pulmonary edema and/or acute coronary syndromes (except for right ventricle myocardial infarction) [1, 3, 10, 19, 20].

Similar to SN, NTG can decrease cerebral blood flow; NTG may cause hypotension with reflex tachycardia, which is exacerbated by volume depletion and by the use of phosphodiesterase type 5 (PDE-5) inhibitors [1, 9, 28].

NTG should be avoided in cases of compromised cerebral and renal perfusion, raised intracranial pressure, and concurrent use of PDE-5 inhibitors [1, 9, 28].

22.3.2.3 Enalaprilat

Enalaprilat is the only angiotensin-converting-enzyme inhibitor (ACEI) available for intravenous use. It is used in hypertensive emergencies associated with pulmonary edema and/or acute coronary syndromes. It is also used for therapeutic testing of the contribution of high renin to a patient's elevated BP level, since a patient who responds to enalaprilat with an optimal decrease in BP level is likely to have elevated plasma renin levels [1, 8, 29].

The starting dose of enalaprilat is 1.25 mg over 5 min; this is repeated at 4- to 6-h intervals, and up-titrated at 12- to 24-h intervals to a maximum of 5 mg at 6 h. Onset of action is 5–10 min after administration and action is shown for 6–12 h after discontinuation [1].

Caution should be exercised in patients with high renin states, in whom the first dose usually induces hypotension. In these patients a test dose of 0.625 mg is recommended [1, 29, 30].

Enalaprilat should be avoided in pregnancy because it is associated with fetal defects [1, 29, 30].

22.3.2.4 Phentolamine

Phentolamine is an α1-/α2 adrenergic receptor blocker (ARB). It is the drug of choice in patients with pheochromocytoma and hypercatecholaminergic-induced HC such as that caused by cocaine abuse [1, 30, 31].

Intravenous administration starts with a bolus load of 5–20 mg every 5 min, followed by continuous infusion at an infusion rate of 0.2–0.5 mg/min [1, 30].

Phentolamine should be avoided in patients with myocardial infarction and cerebrovascular ischemia [1, 30, 31].

22.3.2.5 Fenoldopam

Fenoldopam is a dopamine 1-receptor agonist that induces vasodilatation predominantly in the renal, cardiac, and splanchnic beds. The decrease in BP is often accompanied by an increase in renal perfusion; several studies have documented that fenoldopam improves creatinine clearance, urine output, and sodium excretion compared with other antihypertensive drugs administered in HC—it is therefore a useful drug if acute renal failure is associated with AHF [1, 30, 32, 33].

Intravenous administration starts at 0.1 μg/kg/min and it is up-titrated by up to 1.6 mcg/kg/min every 15 min. Onset on action starts in 5 min with a peak dose effect at 15 min, and it has a total action duration of 30–60 min after i.v. cessation [1, 30].

Fenoldopam is metabolized by the liver independent of the cytochrome p450 system. The administration of acetaminophen may increase fenoldopam levels, and this can trigger reflex tachycardia. Fenoldopam may also cause flushing, dizziness, vomiting, sulfite allergy, and hypokalemia [1, 30].

22.3.3 Particularities of Treatment in Different Clinical Settings

22.3.3.1 Treatment of Acute Heart Failure Triggered by Hypertensive Crisis with Excessive Vasoconstriction

One prototype of this clinical setting is represented by "*flash pulmonary edema*". Usually these patients have significant underlying renal stenosis with subsequent overstimulation of the renin-angiotensin-aldosterone system (RAAS) resulting in excessive vasoconstriction; the patients are relatively euvolemic. Therefore vasodilators such as NTG or SN are the drugs of choice in this setting [15]. Having

high plasma renin levels, these patients could also benefit from the use of the ACEI enalaprilat i.v., but the patients, especially those in high renin states, should be monitored for first dose hypotension, when a test dose of 0.625 mg is recommended [1, 29, 30]. The use of i.v. loop diuretics in these patients could result in further renal injury as a consequence of volume depletion with the consequent over activation of RAAS [29, 30]. Specific treatment addressing the revascularization of renal artery stenosis should be considered after these patients have been stabilized (see Chap. 15).

Another clinical prototype is represented by catecholamine excess secondary to pheochromocytoma or the use of cocaine, amphetamines, phencyclidine, or monoamine-oxidase inhibitors, or secondary to the abrupt cessation of clonidine or other sympatholytic drugs. The drug of choice in this setting is phentolamine, in 5-mg i.v. boluses given every 10 min until the BP target is reached [30–32]. Another useful drug in this setting is fenoldopam [30–33].

Apart from the AHF setting in which β-blockers and calcium channel blockers are contraindicated [10], the use of β-blockers in HC with catecholamine excess can lead to the abrupt elevation of BP caused by the unopposed stimulation of α-adrenergic receptors [12]. Moreover, in HC induced by cocaine abuse, the use of β-blockers results in coronary vasoconstriction and increases in HR and BP! [12].

22.3.3.2 Treatment of Acute Heart Failure Triggered by Hypertensive Crisis with Acute Aortic Dissection

Aortic dissection is clinically associated with an acute, severe, sharp or tearing posterior chest or back pain. Also, symptoms triggered by the involvement of other organs (owing to vascular occlusion) can be present.

The main risk factors for aortic dissection are hypertension, atherosclerosis, advanced age, and collagen disorders.

The medical management of a patient with acute aortic dissection, as recommended by current guidelines, includes [1, 12, 19, 34]:

- Pain relief with morphine sulfate.
- Immediate BP reduction at a target SBP of 100–120 mmHg and HR reduction to <60 bpm.
- The drugs of first choice are to β-blockers (labetalol, metoprolol, esmolol), which decrease the force of LV contraction, relieving the shear stress force on the dissection fold. The drug of choice is i.v. esmolol administered at a loading dose of 500–100 μg/kg/min over 1 min, followed by continuous i.v. infusion at 50 μg/kg/min, up to a maximum dose of 200 μg. If the patient is intolerant to β-blockers, other options are verapamil or diltiazem.
- If the BP target is not reached after appropriate β-blocker administration, the addition of a vasodilator is recommended (SN, nicardipine, NTG, fenoldopam). The use of a vasodilator prior to a β-blocker is to be avoided, as this administration can trigger reflex tachycardia and increase the HR, therefore increasing the shear-stress force and promoting the progression of dissection.

After initial stabilization, patients with acute ascending aortic dissection should be immediately referred for urgent surgical intervention [34].

22.3.3.3 Treatment of Acute Heart Failure Triggered by Hypertensive Crisis with Acute Coronary Syndrome

An acute increase of BP leads to increased demand over supply, with severe ischemia (unstable angina) and even necrosis (extending to non-Q myocardial infarction—more often, or even to transmural acute myocardial infarction). In this setting, AHF is triggered not by the elevated BP per se, but secondary to LV failure, valve/free wall rupture, or arrhythmias that are often driven by the ischemia.

Acute coronary syndrome may trigger an HC owing to a hyper-catecholamine state and increased sympathetic tonus induced by pain.

In this clinical setting, treatment consists of reducing the BP with caution, to avoid compromising coronary perfusion.

In cases of acute STEMI (ST elevation myocardial infarction) requiring reperfusion therapy, either by thrombolysis or by primary percutaneous coronary intervention (PCI), BP levels should be decreased below 180/110 mmHg in order to permit the initiation of thrombolytic therapy or premedication with anticoagulant before primary PCI [35].

Nitroglycerine i.v. is the drug of choice, as it reduces afterload and improves coronary flow by the dilatation of intracoronary collaterals rather than the small resistance vessels; it also decreases the preload [1, 3, 10, 19, 20, 30, 35, 36].

Nitroprusside should be avoided, as it could worsen myocardial ischemia through the "coronary theft" phenomenon; it should be reserved only for cases that are refractory to treatment with nitrates [1, 24–26].

Afterload reduction should be carefully monitored, as myocardial perfusion is dependent on the coronary perfusion pressure. Special attention should be paid to avoid decreasing the DBP to <60 mmHg, a value below which coronary perfusion decreases significantly, leading to the worsening of myocardial ischemia [8, 20].

An alternative option in patients with AHF triggered by HC with acute coronary syndrome is the use of enalaprilat, with particular caution being exercised regarding potential first-dose-induced hypotension, since hypotensive episodes may worsen myocardial ischemia and promote infarct expansion [1, 29, 30].

Vasodilators such as diazoxide, hydralazine, and short-acting dihydropyridines are contraindicated because they cause reflex sympathetic activation and increase myocardial oxygen demand [1, 30, 35, 36].

Treatment of the underlying coronary lesions should be performed as recommended by current European Society of Cardiology (ESC) guidelines for STEMI, non-ST-elevation myocardial infarction (N-STEMI), and unstable angina [35, 36].

22.3.4 Conclusions and Future Perspectives

Since BP control in hypertensive patients is still suboptimal worldwide, and given the high prevalence of hypertension, which is forecast to increase in the next 20 years, HC—with or without AHF—will be frequently encountered in clinical

practice. Therefore prompt recognition and optimal treatment initiation in these patients are of paramount importance in reducing cardiovascular mortality by preventing permanent cardiac damage.

Hypertensive patients who present with AHF triggered by HC transition from an area with evidence-based therapies to one where the medical management has changed little in the past few decades. Traditional therapies, such as oxygen supply, intravenous dilators, and loop diuretics, remain the cornerstone of management today.

Moreover, currently available drugs with well-established evidence-based life-saving effects for chronic heart failure and hypertension, such as ACEIs, ARBs, β-blockers, and digoxin have not yet been tested in AHF settings; therefore, the search for such an ideal drug remains.

Despite the same medical management of patients with AHF triggered by HC being implemented at different medical facilities, there are different results, with some facilities having better results. This implies that socioeconomic and psychosocial factors should also be taken into consideration when we try to optimize the therapeutic strategy for these patients.

The future of treatment of AHF triggered by HC holds promise for an evidence-based treatment strategy, with the quest for an ideal drug that will improve the hemodynamic and neurohumoral profile without adversely affecting the HR and BP, and without causing myocardial and/or kidney damage, while being affordable and demonstrating efficacy in reducing both in-hospital and post-discharge mortality.

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Part VII

Invasive Approaches

Carotid Baroreceptor Stimulation

23

Jens Jordan, Jens Tank, and Hannes Reuter

23.1 Physiological Rational for Baroreflex Modulation

Baroreceptors located in carotid artery and aortic walls sense changed vascular stretch elicited by blood pressure fluctuations. An increase in blood pressure raises baroreceptor output, while blood pressure reductions elicit the opposite response. The signal generated in baroreceptors is conveyed through afferent baroreflex fibers to cardiovascular control centers in the brain stem where it is integrated with information from other afferent inputs and brain regions. An example for the complex integration of afferent signals is the mutual inhibitory interaction between arterial baroreflex and peripheral chemoreflex responses [1]. Then, counter-regulatory adjustments in sympathetic and parasympathetic activity and, less recognized, vasopressin release help in stabilizing blood pressure. Indeed, vasopressin release appears to be an important backup mechanism when sympathetic nervous system and renin–angiotensin system fail to maintain blood pressure [2, 3].

Afferent baroreflex stimulation be it through electrical stimulation or mechanical means could attenuate sympathetic activity and vasopressin release while augmenting cardiac parasympathetic drive in patients with hypertension or with heart failure. Indeed, direct electrical stimulation of baroreflex afferents in patients acutely attenuated efferent sympathetic activity and blood pressure [4]. However, such treatment

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would require that baroreflexes contribute to long-term cardiovascular control. No doubt, baroreflex mechanisms have a central role in short-term blood pressure maintenance. Loss of sympathetic efferents in autonomic failure patients is associated with profound orthostatic and postprandial hypotension [5]. Conversely, afferent baroreflex failure is associated with volatile hypertension [6, 7]. Yet, following experiments in dogs in whom baroreflex afferents were severed, leading physiologists argued that the baroreflex does not contribute to long-term blood pressure control [8]. These experiments were conducted in animals with minimal sensory input, which strongly affects autonomic tone and blood pressure in the absence of baroreflex restraint [6]. Others showed that interrupting afferent baroreflex input can induce sustained neurogenic arterial hypertension in rats [9]. More recently, unilateral carotid sinus unloading with contralateral carotid sinus and aortic denervation produced sustained increases in blood pressure in dogs [10]. Together with preclinical and clinical data obtained with electrical carotid sinus stimulators, the literature suggests that baroreflex mechanisms, indeed, contribute to long-term autonomic cardiovascular control.

The efferent pathways regulated through baroreflex mechanisms as well as baroreflexes themselves are perturbed in many patients with arterial hypertension and in almost all patients with heart failure. In patients with arterial hypertension, sympathetic efferent nerve activity tends to be increased, particularly in obese individuals [11] and in patients with treatment-resistant arterial hypertension [12]. Sympathetic baroreflex curves are shifted toward higher blood pressure levels in these patients [11, 12]. Furthermore, baroreflex heart rate control, which is strongly affected by efferent parasympathetic activity, is often attenuated in patients with arterial hypertension [13]. Baroreflex-mediated vasopressin release appears to be normal in hypertensive patients but resets to higher blood pressure levels [14]. In patients with heart failure, sympathetic efferent activity is increased together with an impairment of sympathetic baroreflex restraint [15, 16]. Baroreflex heart rate control is also perturbed in heart failure patients. Baroreflex-mediated vasopressin release is thought to contribute to the hyponatremia in such patients. Sympathetic activation, impaired baroreflex heart rate regulation, and hyponatremia herald a poor prognosis.

Overall, baroreflex mechanisms appear to be sensible treatment targets for management of arterial hypertension and heart failure. Yet, some caveats should be considered. The contribution of sympathetic activity to blood pressure in hypertensive patients is highly variable [17]. Thus, not all patients will respond to a measure lowering sympathetic activity. The response to stimulation of baroreceptor afferents may be diminished in patients with impaired baroreflex function. At least in an acute experiment, baroreflex loading did not reduce baroreflex-mediated vasopressin release in heart failure patients [18]. Finally, excess reduction in sympathetic activity may increase mortality in heart failure patients as evidenced by the MOXCON trial [19].

23.2 Electrical Carotid Baroreceptor Stimulation Technology

Electrical stimulators with electrodes placed around baroreflex afferents have been developed several decades ago for the management of angina pectoris and subsequently for the treatment of arterial hypertension [20, 21]. Technological issues and

Fig. 23.1 First (Rheos)- and second-generation (Neo) carotid sinus stimulation electrodes. First-generation bipolar electrodes in tripolar configuration had to be placed around the carotid sinuses on both sides of the neck. The smaller second-generation unipolar electrode is sutured directly to the carotid sinus wall, preferentially on the right side of the neck (Heusser et al. Hypertension. 2016;67:585–91 [25], Permissions obtained from Wolters Kluwer Health, Inc.)

side effects, such as involuntary muscle contractions, and advances in cardiovascular pharmacotherapy led to the termination of the program.

Baroreflex activation through electrical carotid sinus stimulation has been developed more recently. Early on, electric field stimulation was shown to acutely reduce blood pressure during carotid surgery [22]. The system comprises a pacemaker device subcutaneously implanted in the chest, tunneled wires, and carotid sinus stimulator electrodes. The surgical implantation is not trivial because careful mapping of putative baroreflex areas is required. In an acute mapping study conducted during carotid endarterectomy, electrode position strongly affected the depressor response to electrical stimulation [23]. The first-generation carotid sinus stimulators applied electrical impulses bilaterally using electrodes placed around the carotid sinus (Fig. 23.1) [24]. Electrodes featured a tripolar design with one centrally located cathode and two lateral anodes. The first-generation device is no longer available. The second-generation device (Fig. 23.1), which is approved and clinically applied in Europe, utilizes a small unilateral unipolar disk electrode to decrease invasiveness and to improve battery life. Preclinical data regarding the safety of the electrode was recently published [25]. However, much of the published data in animal models and a significant proportion of clinical studies have been conducted with the first-generation carotid sinus stimulator design [26].

23.3 Preclinical Experience in Animal Models

Carefully conducted experiments in dogs provided important insight in mechanisms mediating the depressor response to electrical carotid sinus stimulation in various hypertension models and encouraging results in experimental heart failure. In normotensive dogs, bilateral electrical carotid sinus stimulation elicited sustained

reductions in plasma norepinephrine concentrations and blood pressure [27]. Surgical renal sympathetic denervation [28] or complete pharmacological alpha-1 and beta-1,2 adrenoreceptor blockade did not abolish the depressor response [29]. The treatment was particularly efficacious in high-fat feeding-induced obesity-associated arterial hypertension [30], which is characterized by increased sympathetic activity. Spontaneous baroreflex heart rate control and heart rate variability, which are primarily affected by parasympathetic efferent traffic, were also ameliorated in this model [31]. Electrical carotid sinus stimulation was less effective in hypertension produced through angiotensin II [32] or aldosterone infusions [33]. The treatment was also effective in lowering blood pressure in hypertension induced via high-salt feeding in dogs who had been submitted to surgical approximately 70% reduction of renal mass [34].

One study in dogs with obesity-associated hypertension tested how electrical carotid sinus stimulation affects the interaction between carotid baroreflexes and peripheral chemoreceptors [35]. Electrical carotid sinus stimulation attenuated tachypnea, which may have resulted from tonic peripheral chemoreceptor activation.

In dogs with pacing-induced heart failure, electrical carotid sinus stimulation substantially improved survival [36]. Treated dogs survived 68 days compared with 37 days in control dogs. Moreover, electrical carotid sinus stimulation reduced plasma norepinephrine concentrations by approximately 65% [36]. In dogs with microembolization-induced heart failure followed for 3 months, the treatment improved circulating norepinephrine, left ventricular ejection fraction, and left ventricular end-diastolic volume [37].

These preclinical studies while providing proof of concept cannot be simply extrapolated to patients implanted with the second-generation device with unipolar electrode placement. Most preclinical hypertension studies have been conducted with the first-generation electrode design and all with bilateral stimulation. All preclinical heart failure studies applied the first-generation device, and animals did not receive standard heart failure therapy.

23.4 Mechanism-Oriented Investigations in Patients

Careful human investigations tested influences of acute or chronic electrical carotid sinus stimulation on neurohumoral activity in patients with resistant arterial hypertension and heart failure. In patients with severe treatment-resistant arterial hypertension implanted with the first-generation device, electrical stimulation acutely lowered centrally generated sympathetic activity and blood pressure [38]. However, the response varied and some patients did not respond at all. Plasma renin concentration, which is at least in part related to renal sympathetic activity, also decreased. There was a tendency for baroreflex heart rate control to improve with electrical carotid sinus stimulation. In a subsequent study in patients implanted with the second-generation device and unilateral unipolar electrodes, reductions in sympathetic activity and blood pressure were less pronounced (Figs. 23.2 and 23.3) [26]. Several patients reported stimulation-related side effects. Heart rate variability

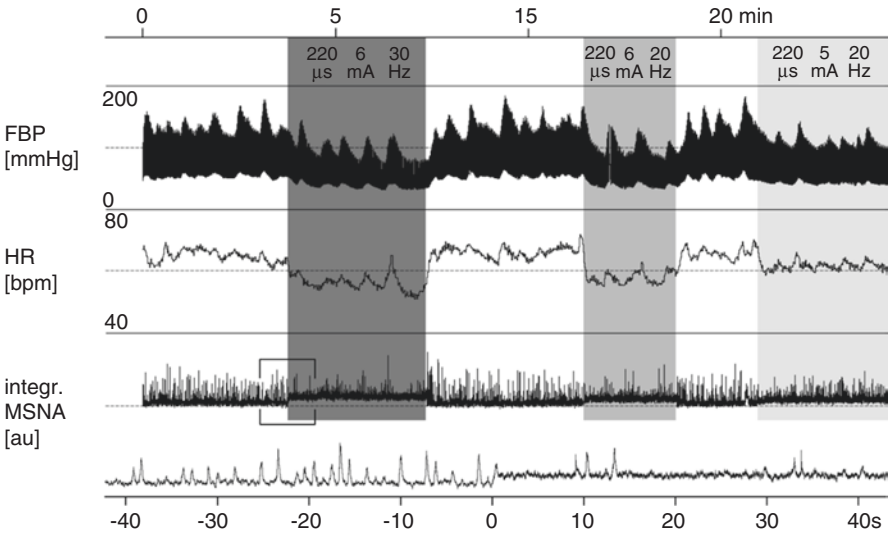

Fig. 23.2 Finger blood pressure (FBP), heart rate (HR), and muscle sympathetic nerve activity (MSNA) in a patient responding to unipolar (Neo) electric carotid sinus stimulation. Shaded areas indicate stimulation intervals. The darkness level indicates stimulation intensity. Top, stimulator settings. Each time the stimulator was on, BP, HR, and MSNA decreased in a stimulation intensity-related fashion. Please note that the baseline of the MSNA recording increased with stimulation intensity likely indicating stray currents. Bottom, trace represents the enlarged view of the framed portion of the MSNA recording. Electric baroreflex stimulation was switched on at 0 s. Note the marked reduction in MSNA burst frequency and the effect of stray currents (Heusser et al. Hypertension. 2016;67:585–91 [26], Permissions obtained from Wolters Kluwer Health, Inc.)

in 24-h Holter electrocardiograms increased after 3 months on treatment compared with baseline measurements in patients with resistant hypertension [39].

In patients with heart failure and reduced left ventricular ejection fraction who had been implanted with the second-generation electrical carotid sinus stimulator, sympathetic activity was assessed at baseline and 1, 3, and 6 months into the treatment [40]. The investigators observed a substantial reduction in sympathetic activity that was sustained throughout the follow-up period. In the surviving patients, reductions in sympathetic activity were maintained for 43 months [41, 42]. Control groups were not included in these investigations.

23.5 Treatment of Resistant Arterial Hypertension

The first feasibility study with the first-generation device was conducted in 45 patients with severe treatment-resistant arterial hypertension in a prospective, multicenter, open-label nonrandomized fashion [43]. Blood pressure had to be ≥160/90 mmHg on medications. In addition, patients had to have a suitable anatomical location of the carotid bifurcation on ultrasound scanning. Baseline office

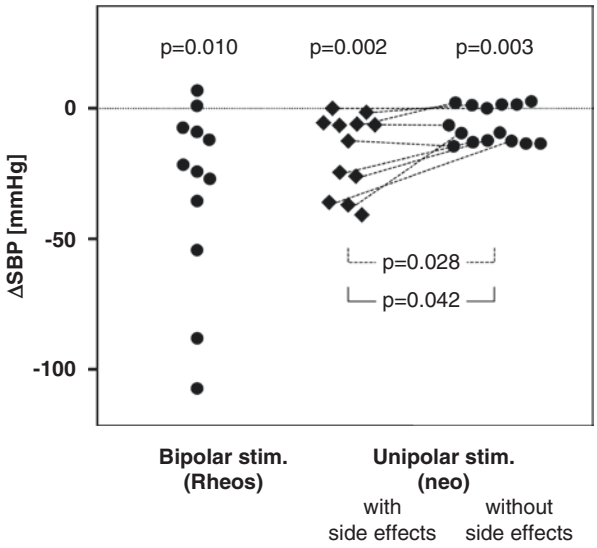

Fig. 23.3 Individual changes in systolic blood pressure (SBP) with electric carotid sinus stimulation. Left, data points represent data from a study in patients implanted with a Rheos device. Middle and right represent data from a study in patients implanted with a Neo device. Top, *P* values refer to group responses against null (one-sample tests). Bottom, *P* values refer to group differences, that is, the comparison of stimulation effects with vs. without side effects. In nine patients, measurements were obtained under both conditions (dashed lines). In the remaining nine patients, data were obtained with side effects (three patients) or without side effects only (six patients). Baroreflex stimulation was less effective without side effects irrespective of whether whole groups or only paired data were compared statistically (Heusser et al. Hypertension. 2016;67:585–91 [26], Permissions obtained from Wolters Kluwer Health, Inc.)

blood pressure was 179/105 mmHg with a median of five antihypertensive drugs. After 3 months on electrical carotid sinus stimulation, blood pressure had decreased 21/12 mmHg. In 17 patients with 2 years of follow-up, blood pressure was decreased 33/22 mmHg below baseline. Procedure- and device-related serious adverse events were reported, and one patient died in the postoperative phase. A subsequent double-blind, randomized pivotal trial included 265 patients with resistant arterial hypertension. They were randomized 2:1 to early device activation 1 month or late device activation 6 months after device implantation [44]. Study endpoints were assessed during the controlled phase of the trial and thereafter when the device was switched on in all patients. The prospectively defined acute efficacy endpoint during the controlled phase was ≥10 mmHg reduction in systolic blood pressure. While blood pressure was significantly lower in the actively treated group, the endpoint was not significantly different between groups. Indeed, acute efficacy was 54% in the early treatment group and 46% in the delayed treatment group. In the uncontrolled phase, blood pressure was reduced compared with the baseline measurement. A main disadvantage of the first-generation device was the short battery life and the invasiveness of the implantation procedure.

Meanwhile a pooled analysis of 383 patients implanted with the first generation in clinical trials has been conducted. Of those, 143 patients had completed 5 years of follow-up, and 48 patients had completed 6 years of follow-up. Overall, blood pressure was 179/103 before and 144/85 mmHg at the end of follow-up. Average heart rate decreased from 74 to 71 beats per minute [45].

The second-generation device was first tested in an uncontrolled trial with 30 patients with resistant arterial hypertension [46]. Data from properly designed controlled clinical trials testing the currently available second-generation device does not exist. A multicenter, randomized controlled trial has been registered (NCT01679132) in 2012, yet the last update in 2017 stated that it does not recruit patients. Nevertheless, the device received a CE sign and is approved for clinical use in Europe. Ambulatory blood pressure responses likely provide more realistic estimates of the true blood pressure response. Such measurements have been obtained in series of patients implanted with the second generation with and without previous catheter-based renal nerve ablation [47, 48]. Ambulatory blood pressure measurements revealed moderate and variable blood pressure reductions. In a randomized withdrawal study, ambulatory blood pressure increased 10/8 mmHg, while home blood pressure remained unchanged following switching off of the device over 4 weeks [49]. A propensity-matched cohort analysis was applied to gauge blood pressure responses following implantation of the first- and of the second-generation device [50]. While the authors suggested that the first- and second-generation device produced similar therapeutic benefits and that the second-generation system may be superior to sham control, such an analysis is no substitute for a properly controlled clinical trial.

Pooled analyses from feasibility studies suggested improvements in left atrial dimension, left ventricular mass, central hemodynamics, and pulse wave velocity [51, 52]. Reductions in proteinuria were reported in patients with chronic kidney disease [53]. Acutely, electrical carotid sinus stimulation did not improve glucose metabolism assessed by frequently sampled intravenous glucose tolerance testing [54]. Similarly, 6 months of treatment was not associated with major changes in glucose metabolism in a case series [55]. The Table 23.1 gives an overview on the available evidence of electrical baroreflex stimulation on end-organ damage and glucose metabolism.

23.6 Carotid Sinus Stimulation in Human Heart Failure

Studies in patients with heart failure have been conducted with the second-generation electrical carotid sinus stimulator. One trial included 146 patients with moderately severe (NYHA functional class III) chronic heart failure secondary to ischemic or nonischemic cardiomyopathy with left ventricular ejection fraction of 35% or less [57]. Patients had to be on stable pharmacotherapy including diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and beta-adrenoreceptor blockers if tolerated. Among other inclusion and exclusion criteria,

Table 23.1 Overview on the available evidence of electrical carotid sinus stimulation on end-organ damage and glucose metabolism with the first-generation Rheos™ and the second-generation Barostim Neo™ device

Original article	Device generation	*n*	Prospective	Randomized	Blinded	Controlled	Follow-up (months)	Findings
Bisognano et al. (2011) [44, 51]	First	21	x				12	Reductions in: • Left atrial dimensions • Left ventricular wall thickness • Left ventricular mass • Left ventricular stroke work
Alnima et al. (2013) [56]	First	236	x			x	12	Acute response: • Mild decrease in eGFR Chronic response: • No further decrease in renal function • No change in albumin/creatinine ratio
May et al. (2014) [54]	First	16	x	x	x	x	Acute	No significant changes in: • Muscular glucose delivery • Whole-body insulin sensitivity
Wallbach et al. (2014) [53]	Second	23	x				6	CKD patients with trHTN: • Reduction of blood pressure • Reduction of proteinuria by 29% • No change in eGFR
Wallbach et al. (2015) [52, 55]	Second	25	x				6	Significant reductions of: • Central blood pressure • Pulse wave velocity • Augmentation index at 75 bpm
Wallbach et al. (2015) [52, 55]	Second	30	x				6	• Reduction of fasting glucose levels No effect on: • Glucose tolerance • Fasting insulin levels • C-peptide levels • Hemoglobin A1c • HOMA-IR or HOMA-β

CKD chronic kidney disease; *eGFR* estimated glomerular filtration rate; *trHTN* therapy-resistant arterial hypertension; *HOMA-IR* homeostasis model assessment–insulin resistance; *HOMA-β* homeostasis model assessment–beta-cell function

functional capacity had to be impaired as evidenced by a 6-min walking distance between 150 and 450 m. Patients were randomized to continued pharmacological therapy or pharmacological therapy and carotid sinus stimulator implantation. The investigators determined safety and efficacy endpoints such as changes in NYHA functional class, quality of live score, and 6-min walking distance. The authors stated that the sample size was based on a desire to obtain initial experience with the device in heart failure rather than statistical requirements for formal hypothesis testing. Six months following implantation, patients in the electrical carotid sinus stimulator group showed significant improvements in NYHA functional class, quality of life score, and 6-min walking distance compared with the control group. N-terminal proBNP measurements were reduced in the actively treated group; however, none of the echocardiography measurements differed significantly between groups. The procedure was well tolerated. A separate analysis conducted in subgroups of patients with and without cardiac resynchronization therapy revealed that the clinical response might be more pronounced in those without cardiac resynchronization therapy [58]. The conclusion that ejection fraction improves in this subgroup is questionable given the overall nonsignificant result.

Meanwhile, case reports have been published reflecting the experience with the technology in real life. For example, in a patient with dilated cardiomyopathy and severely impaired left ventricular ejection fraction, symptoms and left ventricular function substantially improved on treatment with electrical carotid sinus stimulation [59]. Others suggested that the presence of an implantable cardioverter defibrillator does not preclude implantation of an electric carotid sinus stimulator and vice versa [60, 61].

Overall, the literature suggests that electrical carotid sinus stimulation may have utility in treating patients with heart failure. Yet, the hypothesis that the treatment improves symptoms has not been confirmed in rigorously designed and properly controlled clinical trials. Outcome data will be crucial given the negative experience with pharmacological sympathetic inhibition in the MOXCON trial [19].

23.7 Mechanically Modulating Carotid Baroreceptor Transduction

Changing the geometry of the carotid sinus such that baroreceptor stretch at a given blood pressure is amplified could have a favorable effect on neurohumoral activity and blood pressure. A recently developed intravascular device, which is deployed in the carotid artery through a catheter, modifies the axial geometry of the carotid artery with the goal to augment wall strain. In a first-in-human study, the procedure was applied in a patient with type 2 diabetes mellitus and arterial hypertension uncontrolled with five antihypertensive medications [62]. Blood pressure remained unchanged during device application but was substantially reduced during several months of follow-up. Thereafter, the device was tested in 30 patients with resistant hypertension with average office blood pressure of 184/109 mmHg on 4.4 antihypertensive medications. Six months following implantation, office

blood pressure was 24/12 mmHg lower with similar reductions in mean ambulatory blood pressure. Five serious adverse events were reported [63]. The device received approval in Europe. A sham-controlled clinical trial is on its way (clinicaltrials.gov identifier: NCT02804087). Data on the use of this approach in heart failure patients has not been published.

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Renal Nerve Ablation

24

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Abbreviations

AT1R	Angiotensin II type 1 receptor
AT2R	Angiotensin II type 2 receptor
BP	Blood pressure
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MSNA	Muscle sympathetic nerve activity
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OMT	Optimal medical therapy
RNA	Renal nerve ablation

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24.1 Renal Nerve Ablation: From Pathophysiology to the Patient

Autonomic imbalance stands out as a principal pathophysiological pathway that promotes the natural history of the failing heart, and sympathetic activation assessed by circulating norepinephrine levels is associated with worse cardiovascular outcomes [1]. It is clear that sympathetic activity is strongly modulated by the kidney. Specifically, renal afferent arterioles branch from the renal artery and supply the nephrons, playing an important role in the regulation of blood pressure (BP) as a part of the tubuloglomerular feedback mechanism. Renal nerves provide efferent fibers from the brain that decrease renal blood flow and increase sodium retention. When stimulated, renal afferents promote sympathetic efferent activation to the kidney [2]. In heart failure (HF), renal dysfunction associated with a sympathetic overdrive, an increase in the release of renin and vasoconstrictive substances, renal sodium and water retention, and a decrease in renal blood flow is associated with poor prognosis [3].

Well before medical therapy that confronts sympathetic overactivity, such as b-blockers, was even introduced to our pharmacological arsenal, *nonselective* surgical nerve sympathectomy was performed in the 1950s to treat severe hypertension [4]. Debilitating side effects and the advent of effective drugs led to the practical abandonment of this rather radical procedure. But as there was clear evidence of persistently high rates of cardiovascular disease attributed to uncontrolled and resistant hypertension, as well as limitations of pharmacological therapy such as the lack of patient adherence, side effects, and multidrug interactions, an interventional approach to hypertension based on a solid pathophysiological background was an intriguing idea [5]. Technology played an important role, as well as the knowledge and experience from coronary angiographies that would help develop endovascular catheters that could *selectively* denervate the human kidney; it was clear that radiofrequency energy delivered in the renal artery lumen could access the renal nerves located in the adventitia of the renal arteries. The first case of renal nerve ablation (RNA) was reported in 2007, involving a 59-year-old male with resistant hypertension; bilateral nerve ablation led to a decrease in antihypertensive drug need, noradrenaline spillover, sympathetic activity measured by muscle sympathetic nerve activity (MSNA), normalization of sympathetic nerve firing rates, and improvement in echocardiographic measurements (reduction in left ventricular mass) [6].

24.2 The Procedure of Renal Nerve Ablation

Like any interventional, intravascular procedure, all patients should sign a written consent form after being informed thoroughly of the procedure. Practice guidelines have been published and should be followed in order to perform a standardized procedure and minimize any adverse event risk [7]. An initial, noninvasive visualization of renal anatomy with duplex ultrasound, computed tomography angiography, or

magnetic resonance angiography helps the interventionalist evaluate anatomic eligibility criteria and perform further preprocedural planning including appropriate guide and ablation catheter selection. All medications that may affect renal function (such as nonsteroidal anti-inflammatory drugs, metformin, high-dose diuretics, or chemotherapy such as cyclophosphamide) should have been stopped for at least 48 h prior to the procedure. Due to the high-dose usage of intravenous contrast agents during the procedure, appropriate hydration with intravenous saline fluid is also recommended. Anticoagulative treatment with a heparin intravenous bolus of 3000–5000 units is suggested, with a target activated clotting time of >250 s [7]. After introducing a 6-9 Fr sheath into the femoral artery, an aortography is performed in order to intraoperatively visualize renal arteries anatomy and select the appropriate guiding catheter. Most RNA systems utilize radiofrequency energy delivered from catheters of various designs (e.g., spiral, basket, balloon), even though devices performing ultrasound or chemical ablation have also been released in the market. Accordingly, each catheter follows its own protocol throughout the procedure. Procedure-related pain caused by the radiofrequency delivery is essential to be managed effectively using analgesic treatment with opioids, such as midazolam, fentanyl, and morphine. At the end of the procedure, special care should be taken to avoid complications at the wound site, and the use of a wound-closure device is advised.

24.3 Renal Nerve Ablation and Hypertension Studies

The first proof-of-concept, safety, and feasibility study of RNA was the Symplicity HTN-1 that enrolled 45 patients with severe resistant hypertension. After 1 year of follow-up, it was shown that radiofrequency RNA was *safe* and *efficient*, as office BP was reduced by 27/17 mmHg [8]. In spite of the unblinded and uncontrolled status of the study, these ground-breaking findings led to the design of larger randomized controlled trials to evaluate the efficacy of RNA in resistant hypertension. The Symplicity HTN-2 study that followed was an open-label, multicenter prospective trial that randomized 106 patients to RNA ($n = 52$) or optimal medical therapy (OMT) ($n = 54$) who were followed up for 6 months. In the RNA arm, office blood BP decreased by 32/12 mmHg, whereas no significant changes appeared in the control arm. There were no safety-related serious adverse events [9]. Extension of the follow-up period up to 36 months confirmed a durable BP reduction by 33/14 mmHg [10].

In 2014, the neutral Symplicity HTN-3 trial was published and considered a deal-breaker at the time from the scientific community and press. This was the first single-blind, randomized sham-controlled trial that enrolled 535 patients with true resistant hypertension, randomized (2:1) to renal denervation or sham procedure. The study failed to present a statistically significant change in office BP measurements in the RNA arm compared to the control group, demonstrating a between-group difference of −2.39 mmHg with a 95% confidence interval of −6.89 to 2.12 and $p = 0.26$ for superiority. Again, no serious safety differences have been shown between the two arms [11]. These controversial results triggered an overall

reassessment of the procedure and related clinical trial design; establishing optimal clinical and anatomical eligibility criteria, finding ad hoc or early markers of RNA success and examining the optimal positioning of the RNA catheters within the renal arteries are important issues to be scrutinized. In this context, final results of the SPYRAL HTN trials (NCT02439775), using the next-generation Symplicity Spyral™ multielectrode renal denervation system, are eagerly awaited.

24.4 Renal Nerve Ablation Beyond Lowering Pressure

Evidence of diverse beneficial effects of RNA beyond BP reduction have been published including glucose metabolism, atrial fibrillation, cardiac structure and function, sleep apnea syndrome, and HF [12]. For instance, in a small pilot randomized trial, 17 patients with hypertension and metabolic syndrome were enrolled and randomized 3:1 to RNA or conservative treatment and were followed up for 3 months. Muscle sympathetic nerve activity at rest and during standard 75 g oral glucose tolerance test was assessed. The investigators demonstrated a reduction in metabolic parameters such as waist circumference and improvements in sympathetic nerve activity. Resting MSNA decreased from 55 ± 9 bursts per minute to 46 ± 8 bursts per minute ($p = 0.0008$) at month 3 post-RNA. Improved MSNA responses during oral glucose tolerance test were also recorded. There were no equivalent beneficial effects reported in the control arm [13].

Regarding echocardiographic parameters of cardiac function, in a sub-study of the EnligHTN I trial, positive effects of RNA in 17 patients with true resistant hypertension and left ventricular hypertrophy were demonstrated. At the 6, 12, and 24 months of follow-up visit, there was a significant reduction in the LV mass/body surface area (LV mass/height$^{2.7}$) by 9.1% (8.8%), 11.3% (10.5%), and 15.5% (14.1%), respectively, and in the mitral lateral E/E' by 14.0, 15.3, and 29.7%, respectively [14]. In another study, the efficacy of RNA in left atrial remodeling was also evaluated [15]. This was a single-arm study that enrolled 66 patients with resistant hypertension, who underwent RNA and were followed up for 6 months. Blood pressure, heart rate, LV mass, left atrial volume index, diastolic function, and premature atrial contractions (PAC) (Holter electrocardiogram) were assessed at baseline and at the end of the follow-up period. Six months after RNA, a significant improvement in left atrial structure was demonstrated, as left atrial volume index was reduced by 4.0 ± 0.7 mL/kg/m^2 ($p < 0.001$) independently of the BP decrease. Similarly, Mahfoud et al. conducted a prospective, multicenter randomized (3:1) study to evaluate the impact of RNA on left ventricular mass and function [16]. Seventy-two patients with resistant hypertension were enrolled and randomized (3:1) to RNA or control and evaluated by cardiac magnetic resonance. They demonstrated that RNA leads to a statistically significant reduction in left ventricular mass index by 7.1%, compared to the control arm. Additionally, there was an improvement in systolic function, especially in those with an impaired left ventricular ejection fraction

(LVEF) at baseline (<50%). Finally, there was an improvement in diastolic function in the denervation arm, evaluated by a significant increase of left ventricular circumferential strain, by 21% (−14.8 vs. −17.9; $p = 0.001$) compared to the control group (−15.5 vs. −16.4; $p = 0.508$). It is noteworthy that these effects were independent of BP changes, a fact that, as noted by the authors, points to a probably direct way of altering the sympathetic nervous system activity in an HF population. All these studies led investigators to further explore any possible impact of RNA in the natural history and treatment of HF.

24.5 Animal Studies of Renal Nerve Ablation in Heart Failure

One of the first animal studies of RNA was carried by Villarreal et al. in dogs carrying an arteriovenous fistula and having high-output HF syndrome. Dogs that underwent RNA, compared to controls, showed an improvement in postprandial urinary sodium excretion and fractional sodium excretion after a high-salt meal containing 125 mEq of sodium. This finding suggested that renal nerves interfere with the expression of postprandial natriuretic mechanisms via a direct action on the renal tubules [17]. In another study of a rat model of myocardial infarction-induced HF, it was shown that the use of surgical RNA prior to myocardial infarction via coronary artery ligation improved LV remodeling and ventricular function as assessed by a lower LV end-diastolic pressure and volume. Reduced sodium excretion after RNA was also confirmed, suggesting that the restoration of natriuresis plays an important role in the physical history of HF, as well as that the increased renal sympathetic activity after myocardial infarction contributes to the progression of HF [18].

Excessive renal sympathetic activity leads to decreased renal flow and may be associated with changes in angiotensin II type 1 receptor (AT1R) and angiotensin II type 2 receptor (AT2R) expression. This was shown in a study carried out in rabbits with pacing-induced HF (denervated vs. control), which demonstrated that renal AT1R expression was increased by ∼67% and AT2R expression was decreased by ∼87% in rabbits with HF; however, the kidneys from denervated rabbits with HF showed a near normalization in the expression of these receptors [19]. A recent animal trial using a sham arm showed that RNA also improves ventricular function after myocardial infarction. Pinkham et al. randomized rats after infarction to receive either bilateral RNA or sham RNA. At the end of the follow-up period, cardiac function was assessed by echocardiography, and ventricular sympathetic nerve fiber density was determined via histology. It was demonstrated that the RNA arm showed increased ventricular sympathetic innervation ($0.76 \pm 0.14\%$, $P < 0.05$) and tissue norepinephrine content as well as an improvement in LV ejection fraction and LV end-systolic and end-diastolic volume, compared to the sham arm. The research group concluded that RNA not only improves LV remodeling but also attenuates fibrosis of the non-infarcted ventricular tissue after myocardial infarction. This is the first study to suggest an interference between renal nerve activity and cardiac sympathetic nerve innervation in the failing heart [20].

The novel Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial which showed that the use of sacubitril-valsartan in comparison with enalapril reduced cardiovascular mortality and hospitalization for HF in patients with HF with reduced ejection fraction (HFrEF) and decreased symptoms and physical limitations of HF [21]. PARADIGM-HF made a significant impact in cardiovascular medicine influencing HF guidelines and suggested treatment algorithms [22, 23]. In this context, new data were provided by Polhemus et al. who carried out a study to investigate the effects of renal denervation on the pathophysiology of HF and the correlations between the renal sympathetic activity and the metabolism of the natriuretic peptides. Normotensive and hypertensive rats were subjected to coronary artery ligation and reperfusion and followed up for 12 weeks. At week 4, the rats were randomized (1:1) to bilateral RNA and sham RNA. At the end of the observation period, it was demonstrated that RNA in both normotensive and hypertensive rats, compared to sham RNA arms, led to the preservation of LV function, reduction in myocardial fibrosis, an increase in plasma natriuretic peptide levels, and inhibition of neprilysin activity, the natriuretic peptide degrading enzyme [24]. They clearly showed that RNA had a "sacubitril-like effect" [22]. These quite revolutionary results prove that we are in the deep learning process of how RNA attenuates the natural history of hypertension and HF, through the multiple pathophysiological targets of the method, signifying the need for more novel studies to be carried out, in order to clearly understand the true potential of RNA.

24.6 Human Studies of Renal Nerve Ablation in Heart Failure

The renal denervation in chronic heart failure (REACH)-Pilot was the first-in-man, open-label, non-randomized trial to evaluate the safety and efficacy of RNA in patients with chronic stable HF (Table 24.1) [25]. Seven patients with systolic HF and New York Heart Association (NYHA) class III or IV (baseline LVEF of 43 ± 15%, BP of 112/65), on maximal tolerated medical therapy, including β-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and spironolactone, were subjected to bilateral RNA and followed up for 6 months. Patients with chronic kidney disease and unfavorable renal anatomy were excluded. No significant hemodynamic disturbances were noted during the acute phase post-RNA. At the end of the follow-up period, the researchers demonstrated that there was a significant increase in the 6-min walk distance by 27.1 ± 9.7 m ($p = 0.03$) and a self-reported improvement in symptoms. There was no significant improvement in systolic heart function, as evaluated by the difference in LVEF. Regarding safety and BP changes, they documented a slight reduction in systolic BP by 7.1 ± 6.9 mmHg (from 120 ± 21 to 113 ± 19 mmHg; $p = 0.35$) and diastolic BP by 0.6 ± 4.0 mmHg (from 68 ± 9 to 67 ± 8 mmHg; $p = 0.88$), while there was no deterioration of renal function. The study had several limitations and may have been underpowered but highlighted the need for more data and evidence from randomized studies.

Table 24.1 Studies of RNA in HF

Study	Study status	Sample size	Study population	Design of study	Follow-up (months)	Safety endpoints	Efficacy endpoints
REACH-Pilot [25]	Completed	7	Chronic HF, NYHA III or IV, OMT	Open-label, non-randomized, feasibility, and safety study of bilateral RNA	6	Nonsignificant BP reduction No renal function deterioration	Significant increase in 6MWD Self-reported improvement in symptoms
Olomouc I-Pilot [26]	Ongoing	51	NYHA III, LVEF≤35%, OMT	Single-center, randomized (1:1) controlled trial, RNA + OMT vs. OMT	12	No significant BP decrease No change in renal function	Significant increase in LVEF Left ventricular end-systolic and end-diastolic volume decreased N-terminal-pro BNP significantly decreased
Chen et al. [27]	Completed	60	NYHA III, LVEF ≤40%, OMT	Single-center, randomized, open-controlled study, RNA vs. OMT = 1:1	6	No change in renal function No device-related SAEs	Statistically significant improvement in LVEF, 6MWD, NYHA class, N-terminal-pro BNP and office heart rate
Gao et al. [28]	Completed	14	NYHA III-IV, LVEF<45% OMT	Single-center, single-arm bilateral RNA	6	No change in renal function No device-related SAEs	Statistically significant improvement in LVEF and 6MWD
Dai et al. [29]	Completed	20	Symptomatic HFrEF, NYHA III-IV, OMT	Single-center, randomized (1:1), open-controlled study, RNA vs. OMT	6	No change in renal function No device-related SAEs	Increase in 24-h urine volume Decreased levels of plasma renin activity, aldosterone, angiotensin II, BNP, and noradrenaline in RNA arm
Geng et al. [30]	Completed	17	Consecutive HF patients, NYHA II–III, OMT	Single-center, open-label, single-arm, early HF (<3 years) vs. late HF (>3 years)	12	No change in renal function No device-related SAEs	Statistically significant improvement in LVEF, LVEDD, and markers of systemic inflammation in early-stage HF arm compared to late-stage HF arm

(continued)

Table 24.1 (continued)

Study	Study status	Sample size	Study population	Design of study	Follow-up (months)	Safety endpoints	Efficacy endpoints
Symplicity HF [31]	Completed	39	NYHA II–II LVEF <40%, OMT	Multicenter, prospective, single-arm feasibility RDN study	12	No deterioration in renal and cardiac function No device-related SAEs	Statistically significant reductions in N-terminal-pro-BNP and 120-min oral glucose tolerance test No significant change in LVEF and 6MWD
RDT-PEF [34]	Early terminated	25	NYHA ≥II, HFpEF, OMT	Single-center, randomized (2:1), open-controlled study, RNA vs. OMT	12	Two patients with renal artery wall edema treated with balloon angioplasty	No statistically significant difference in VO_2, BNP, *E*/*e*′, LAVI and LVMI Comparable change in eGFR

RNA renal nerve ablation; *HF* heart failure; *NYHA* New York Heart Association; *OMT* optimal medical therapy; *6MWD* 6-min walk distance; *LVEF* left ventricular ejection fraction; *BNP* brain natriuretic peptide; *HFpEF* heart failure with preserved ejection fraction; *LAVI* left atrial volume index; *LVMI* left ventricular volume index; *eGFR* estimated glomerular filtration rate; *SAE* serious adverse events

Similar results were demonstrated in another open-label study, the Olomouc 1-Pilot study, which recruited 51 patients with a symptomatic HF, an NYHA class III/IV, and an LVEF of 25 ± 12% on optimal OMT, who were 1:1 randomized to RNA and OMT versus OMT [26]. Preliminary data at a follow-up period of 12 months showed that the denervated arm exhibited a significantly higher LVEF compared to those patients who were on OMT only (31 ± 14 vs. 28 ± 12%, $p < 0.01$). Furthermore, a biochemical analysis of natriuretic peptide levels in both arms showed that RNA led to a significant reduction in NT-pro-brain natriuretic peptide compared to OMT. The RNA arm also showed less hospitalizations for HF and a slight subjective improvement of symptoms, evaluated by a self-assessment questionnaire.

Chen et al. also designed a randomized, prospective study to evaluate the efficacy of renal denervation in HF. They enrolled 60 patients with symptomatic HFrEF, NYHA II-IV, who were 1:1 randomized to RNA with a saline-irrigated catheter versus optimal OMT [27]. Over a 6-month follow-up period, they demonstrated that LVEF significantly improved in the RNA group; it increased by 10%, from 31.1 ± 5.7% at baseline to 41.9 ± 7.9% at 6 months ($p < 0.001$). Renal denervation improved secondary endpoints, 6-min walk distance ($p = 0.043$), NYHA class ($p < 0.001$), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) ($p < 0.001$), and office heart rate ($P = 0.008$), compared to OMT alone. Regarding safety, there were no severe adverse events and no significant difference in BP and renal function, between the two groups. In another open, prospective single-arm study conducted by Gao et al., 14 patients with a symptomatic HFrEF (LVEF<45%) and a NYHA class III or IV on OMT were subjected to bilateral RNA and were followed up for 6 months [28]. A significant improvement in the 6-min walk test (from 152.9 ± 38.0 to 334.3 ± 94.4 m, $p < 0.001$) was demonstrated, while LVEF increased from 36.0 ± 4.1% to 43.8 ± 7.9% ($p = 0.003$). There were no serious adverse events, neither RNA-related complications nor deterioration of renal function. Furthermore, the researchers recorded a noteworthy reduction in BP, both systolic (from 138.6 ± 22.1 to 123.2 ± 10.5 mmHg, $p = 0.026$) and diastolic (from 81.1 ± 11.3 to 72.9 ± 7.5 mmHg, $p = 0.032$). Although this study was also small-sized and underpowered to prove efficacy, it did show that RNA affected and improved LVEF, in contrast to REACH-Pilot and Olomouc that did not result in LVEF recovery, implying a beneficial effect of RNA in HF.

An interesting small randomized study was also conducted to determine the efficacy of RNA in symptomatic HFrEF [29]. Twenty hospitalized patients with symptomatic HF and NYHA class III–IV, on optimal medical treatment (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers taken by all patients for at least 1 month), were enrolled and 1:1 randomized to either RNA and medical therapy or standard medical therapy (serving as the control arm). During the hospitalization period, the same drug treatment, including loop diuretics, digoxin, and nitrates, was given to both groups. The patients were followed up for 6 months, laboratory (blood and urine) analyses and echocardiographic examinations were performed, and major adverse cardiovascular events were reported at baseline (before the intervention) and after 6 months. The

procedure was free of procedure-related safety adverse events in all patients. Compared with the standard therapy group, the 24-h urine volume was significantly higher in the RNA group 24 h after the procedure ($P < 0.05$), implying a "diuretic" effect of RNA that improves impaired renal natriuresis in HF. Levels of plasma renin, aldosterone, angiotensin II, BNP, dopamine, noradrenalin, and adrenalin were significantly lower in the RNA group, compared to baseline and to the standard therapy group. These neurohormones were also significantly lower after radiofrequency ablation when compared to baseline values. Heart failure symptoms improved in both groups. After treatment LVEF was significantly increased in the RNA group, compared to the medical treatment arm. In conclusion, RNA not only seems to improve symptoms and echocardiographic elements but also may restore renal diuretic resistance in HF, implying that RNA may have multiple pleiotropic ways to alter HF pathophysiology and natural history.

In a recent small safety and efficacy study of RNA in HF, the investigators demonstrated that the effect of RNA on HF-related parameters is affected by the duration of the disease [30]. A total of 17 patients with HF and NYHA II–III in OMT were enrolled in the study and divided into two groups: the early-stage HF group (duration of HF less than 3 years) and the late-stage HF group (duration of HF more than 3 years). Patients from both groups were subjected to bilateral RNA and were followed up for 12 months. In the early-stage HF group, there was a statistically significant improvement in echocardiographic elements such as LVEF and left ventricular end-diastolic diameter and functional tests compared to the late-stage HF group, where an improvement was not demonstrated. No changes in natriuretic peptides were observed in either group after 1 year. Moreover, RNA showed a beneficial impact in markers of systemic inflammation, namely, a decrease in tumor necrosis factor-α and C-reactive protein, in the early-stage HF group. The results of this study suggest that the earlier RNA is performed in HF patients, the better the outcome, although further randomized, blinded sham-controlled clinical trials are required to assess the true impact of RNA on the early and late stages of HF.

Lately, the 1-year follow-up results of the Symplicity HF Feasibility Study were published [31]. Symplicity HF was an open-label, single-arm, prospective, multicenter feasibility study that enrolled 39 patients with chronic systolic HF, NYHA II–III, and LVEF ≤40% on OMT. All patients underwent RNA and were followed up for 1 year, and no serious intervention-related safety adverse events were reported. Statistically significant reductions in NT-pro-BNP (1530 ± 1228 vs. 1428 ± 1844 ng/mL; $p = 00.006$) and 120-min glucose tolerance test (11.2 ± 5.1 vs. 9.9 ± 3.6; $P = 0.026$) were demonstrated at 12 months, but no significant changes in LVEF (28 ± 9% vs. 29 ± 11%; $p = 0.536$), 6-min walk test (384 ± 96 vs. 391 ± 97 m; $p = 0.584$), or renal function were recorded.

HF with preserved ejection fraction (HFpEF) is a prevalent phenotype of HF for which no treatment has, as yet, been shown to improve prognosis [32]. It is a rather frequent condition, accounting for about 50% of HF. Hypertension is the most common comorbidity in HFpEF patients; therefore controlling hypertension is of great importance in modifying the natural history of HFpEF. Evidence showing that RNA may reduce LV hypertrophy and improve diastolic dysfunction in patients with resistant hypertension has triggered an interest to explore its role in HFpEF

[33]. Brandt et al. recruited and randomized 64 patients with resistant hypertension to bilateral RNA or medical therapy at a 3:1 ratio. A significant improvement of both diastolic and systolic function and regression of LV hypertrophy was demonstrated in the RNA arm compared to controls. Specifically, they documented a decrease in LV mass index, estimated by echocardiography, from 53.9 ± 15.6 to 44.7 ± 14.9 g/m$^{2.7}$ ($p < 0.001$), which was also associated with a reduction in the mitral valve lateral E/E' ratio (from 9.9 ± 4.0 to 7.4 ± 2.7, $p < 0.001$) indicating a reduction in LV filling pressures. Diastolic dysfunction is a complex result of multiple pathophysiological processes; however, we may expect that the reduction of LV filling pressures and the regression of LV wall thickness, following attenuation of sympathetic overactivity via RNA, may prevent the progression to HFpEF. Still we know little of the impact of RNA on myocardial fibrosis. Nevertheless, since hypertension is the most important cause of HFpEF and there is no evidence-based therapy to improve mortality in HFpEF patients, further evaluation of the role of RNA on the conundrum of the pathogenic mechanisms of HFpEF is needed.

The RDT-PEF trial was the first, and only until now, randomized trial of RNA in patients with HFpEF [34]. The primary outcome of the study was a composite efficacy endpoint including macrovascular and microvascular function measures. Macrovascular measures included 24-h ambulatory pulse pressure, aortic distensibility, aortic pulse wave velocity, augmentation index (peripheral tonometry), and renal artery blood flow indices, whereas microvascular elements consisted of endothelial function and urine microalbuminuria. The investigators enrolled 25 patients with HFpEF and NYHA class II–III on medical therapy consisting mostly of loop diuretics, angiotensin blockers, and β-blockers, who were 2:1 randomized to RNA or control and followed up for 12 months. There was no significant improvement in the composite efficacy endpoint in the intervention arm compared to controls. RDT-PEF joined the list of randomized trials that did not accomplish significant proof of reducing aortic stiffness in patients with HFpEF. Many reasons for the inefficacy of the intervention have been proposed by the authors including the heterogeneity of this HFpEF population, the fact that stiffness might not be an ideal endpoint for HF trials but rather for hypertension studies, and the multiple mechanisms beyond sympathetic nervous system activity affecting the autoregulation of the kidneys.

24.7 Conclusion

Interfering with the interaction between the kidney and the autonomic nervous system in order to halt the neurohormonal activation in HF stands as an intriguing treatment option. From a pathophysiological perspective, RNA seems to attenuate salt and water retention, the increase of angiotensin release, the reduction in renal blood flow, the peripheral vasoconstriction, and the harmful sympathetic overflow to the heart, thus potentially improving the course of the disease. In any case, as ongoing research provides data that will help perform complete renal denervation and ideally reveal markers of a better clinical effect, the promising results of studies in humans with HF need to be replicated in larger clinical trials.

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Part VIII

Hypertension, Heart Failure and Guidelines

Prevention and Treatment of Heart Failure in Hypertension Guidelines

25

Giuseppe Mancia

25.1 Introduction

The notion that hypertension is a major risk factor for heart failure [1, 2] goes back to several decades. Yet, guidelines on the management of high blood pressure (BP) have for a long time devoted only a limited space and attention to the hypertension–heart failure relationship. This has been the case because early trials on the relationship between antihypertensive treatment and outcome mainly focused on myocardial infarction and stroke, i.e. events that can be precisely diagnosed. In contrast, heart failure did not offer a similar diagnostic precision because in its incipient phase symptoms and signs can be shared by other conditions, e.g. respiratory diseases, insufficiency of lower limbs veins, obesity and poor exercise performance, which made heart failure closer to "soft" than to "hard" end points as myocardial infarction and stroke were defined. Furthermore, diagnosis of incipient heart failure was also subjected to the confounding effect of antihypertensive agents, e.g. (1) an overdiagnosis in patients under calcium channel blockers due to the association of these drugs with ankle oedema and (2) an underdetection in patients treated with diuretics because of the masking effect of these drugs on heart failure symptoms and signs.

Some of the above inconveniences persist today. Nevertheless, in the last 20 years, heart failure, as diagnosed in the hospital setting, has become a regular component of the assessment of the protective effect of antihypertensive treatment, almost invariably as a major secondary end point and not unfrequently also as a composite of the primary end point. This has considerably increased knowledge of the effect of blood pressure (BP)-lowering treatment on this important outcome.

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This chapter will summarize current evidence on the ability of BP-lowering interventions to reduce new-onset heart failure. It will also review the position of the European guidelines on how to treat patients with heart failure, an aspect of antihypertensive treatment that has lately been addressed also by other guidelines.

25.2 Antihypertensive Treatment and Prevention of Heart Failure

25.2.1 Prevention of Heart Failure

A large number of randomized clinical trials have shown that reducing an elevated BP by antihypertensive drugs is associated with a reduction in the risk of developing heart failure and that the magnitude of this beneficial effect is comparable to or greater than the one which is universally regarded as the paradigma of the beneficial effects of BP-lowering treatment, i.e. reduction of stroke. In a recent very large meta-analysis, for example, Ettehad et al. [3] have shown that for a 10 mmHg reduction of systolic BP, the risk of heart failure was reduced by 28%, a figure similar to the 27% reduction of stroke (Fig. 25.1). Similarly in another large meta-analysis, heart failure and stroke were reduced by antihypertensive treatment by 46% and 39%, respectively, the results being similar when calculation was limited to trials in which BP reduction was intentional and in those in which it was not (e.g. those using antihypertensive drugs in coronary patients) [4]. This has been found also by other meta-analyses, although in some instances the reduction of heart failure associated with the treatment-induced BP reduction has been reported to be less pronounced, i.e. around 15% [5–7]. It can thus be concluded that antihypertensive treatment has a major preventive effect on the development of heart failure. Based on the evidence collected either by meta-analyses or by individual trials, it can also be added that protection against new-onset heart failure by

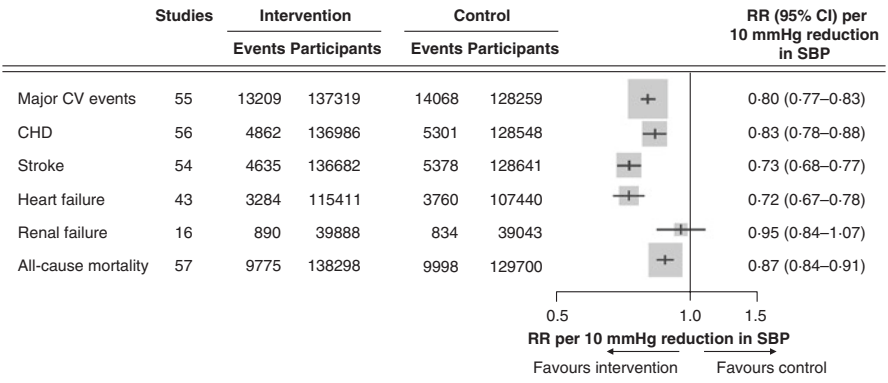

Fig. 25.1 Standardized effects of a 10 mmHg reduction of systolic blood pressure (SBP) on cardiovascular events, renal events and mortality. Data taken from 123 randomized trials for a total of 613,815 patients. *RR* relative risk, *CHD* coronary events, *CV* cardiovascular (from [3], by permission)

BP-lowering interventions (1) includes both patients without and patients with a previous cardiovascular event, the protective effect of antihypertensive treatment on this outcome thus involving either primary or secondary cardiovascular prevention, (2) extends to type 2 diabetes mellitus and (3) becomes progressively greater as the BP reduction induced by treatment becomes greater, the slope of the linear relationship between the two variables being steeper than that of any other relationship between BP reductions and cardiovascular events (Fig. 25.2) [4].

25.2.2 BP Threshold and Target

There appears to be no question that in patients with an initial systolic BP > 140 mmHg, a BP reduction leads to a reduction of new-onset heart failure. A debated question, on the other hand, remains whether this benefit extends to patients with an initial systolic BP in the high normal range, i.e. between 130 and 139 mmHg or a diastolic BP between 85 and 89 mmHg. In the meta-analysis of Ettehad et al. [3], these patients showed a significant reduction of heart failure when systolic BP was reduced from initial values >160 mmHg , 150–159, 140–149, 130–139, but also <130 mmHg. This was less clear in the meta-analysis of Thomopoulos et al. [4] in which heart failure was significantly reduced when treatment was implemented in patients with an initial systolic BP > 150 or

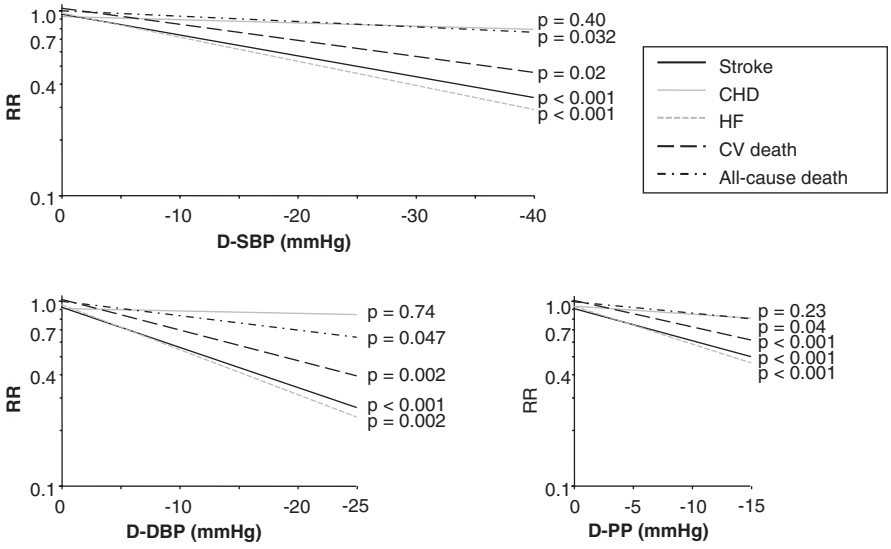

Fig. 25.2 Relationship between outcomes and reduction of systolic blood pressure (SBP), diastolic BP (DBP) and pulse pressure (PP) by antihypertensive drug treatment. Data from randomized trials in which different treatments were used. The relationship was linear for almost each outcome, and the one between BP and HF was the steepest. *HF* heart failure. Other symbols as in Fig. 25.1 (from [4], by permission)

140 mmHg, but not when systolic BP was between 130 and 139 mmHg. Thus the BP threshold for a drug treatment that aims at protecting against the development of heart failure needs further evidence. This applies also to the target BP to be pursued by treatment because while most meta-analyses agree that reducing systolic BP < 140 mmHg protects against heart failure, data on the effects of systolic BP reductions <130 mmHg are not univocal [3–8].

25.2.3 Selective Effects of Antihypertensive Drugs

There is also no question that BP-lowering interventions reduce the risk of heart failure, regardless of the drug class employed. This has been shown by the above-mentioned meta-analysis of Thomopoulos et al. [8] in which the reduction of heart failure was progressively greater as BP reduction was greater, despite the use of different treatments. It is further documented by the findings obtained in other meta-analyses [9] as well as by the evidence that treatment with all major drug classes are capable of reducing the risk of HF when used to lower BP vs. placebo (Fig. 25.3) [10, 11]. On the other hand, meta-analyses have also shown that for a given reduction of BP, protection against incipient heart failure can be different with different drugs, i.e. more pronounced with diuretics and less with calcium channel blockers (Fig. 25.4) [3]. Whether different drugs have a different preventive effect on new-onset heart failure remains an open question, however, because these different effects might be favoured by factors other than the different ability of these drugs to affect the development of heart failure. As mentioned in the Introduction, diuretics may mask signs and symptoms of heart failure rather than preventing it, whereas ankle oedema may erroneously favour a diagnosis of heart failure in individuals who may exhibit shortness of breath because their exercise performance is poor or their respiratory reserve impaired, a rather common event in the elderly as well as in obese individuals. The use of specific diagnostic markers of heart failure, such as

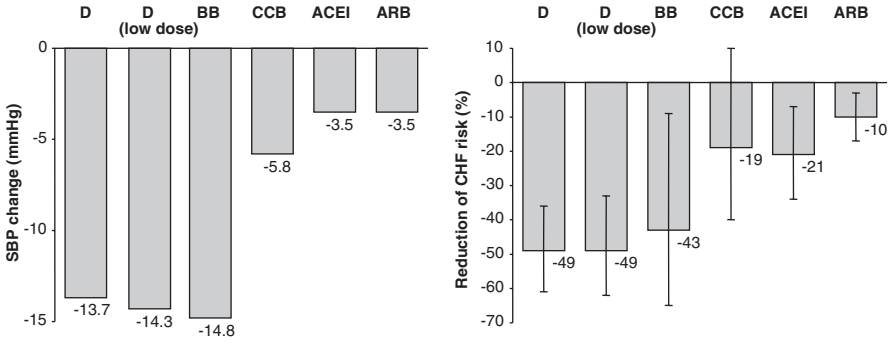

Fig. 25.3 Reduction in SBP and risk of congestive heart failure (CHF) by treatment with different antihypertensive drugs. Data from trials in which drug treatment was compared with a placebo or controlled group. *D* diuretics, *BB* beta-blockers, *CCB* calcium channel blockers, *ACEI* ACE inhibitors, *ARB* angiotensin receptor antagonists (redrawn from [11])

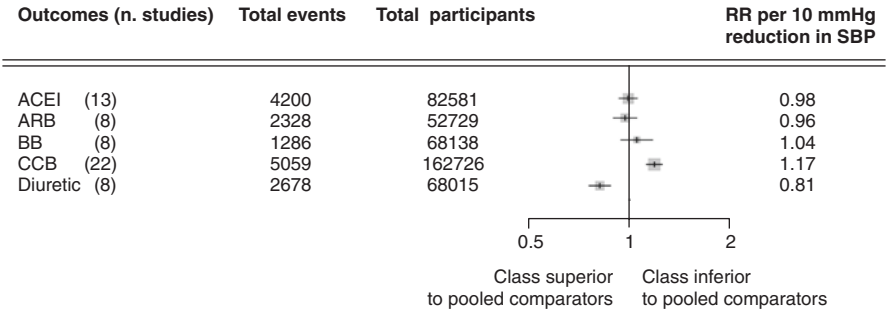

Fig. 25.4 Standardized effects of 10 mmHg reduction of SBP by antihypertensive treatment based on different drugs on heart failure. Symbols as in preceding figures (from [3], by permission)

BNP values, might reduce this inconvenience and increase the diagnostic accuracy of heart failure in future trials.

Alfa-blockers are widely regarded as drugs that do not protect hypertensive patients against the risk of heart failure. This is based on the results of one large scale trial (ALLHAT) on high-risk hypertensive patients, in which administration of doxazosin was associated with an incidence and risk of heart failure that was more than twice that of the administration of the diuretic chlorthalidone [12]. A puzzling finding of this trial, however, was that incidence curves started to diverge already few days after treatment initiation, which is compatible with an alternative possibility, i.e. that, because diuretics were the most common pre-trial drugs, a pre-existing heart failure was maintained asymptomatic by diuretic treatment before the trial and became clinically manifest when diuretic was withdrawn and patients were randomized to doxazosin. Doxazosin has later not been shown to be accompanied by an increased risk of heart failure in the resistant hypertensive patients of the ASCOT trial [13], but no other favourable evidence has since been collected. Considering the adverse prognostic role of sympathetic hyperactivity in heart failure, further trials on the effect of sympatho-inhibitory drugs on the risk of incident heart failure would be desirable.

25.3 Hypertension Guidelines and Patients with Established Heart Failure

Hypertension is not common in patients with an established heart failure because an impairment of the cardiac pump leads to a reduction of cardiac output, which in turn lowers a previously elevated BP to normal or even low BP values in many hypertensive patients, a phenomenon known as hypertension decapitation. Regardless whether patients have a BP elevation or only a history of hypertension, an established heart failure condition calls for some specific treatment aspects that have been addressed in progressively greater details by the European Society of

Hypertension (ESH) and the European Society of Cardiology (ESC) in the guidelines issued in 2003, 2007 and 2013 [14–16].

25.3.1 2003 ESH/ESC Guidelines [14]

No mention was made of the BP threshold at which to start antihypertensive drugs or of the target BP values to aim at during treatment in patients with established heart failure The recommendation was issued, however, to primarily consider beta-blockers, ACE inhibitors and antialdosterone compounds because of the evidence that these drugs have the ability to reduce events and hospitalization as well as to prolong life in heart failure. The use of an angiotensin receptor antagonist was only recommended in case of intolerance to the ACE inhibitor-based treatment, and combination of the two renin-angiotensin blockers was not discouraged. Addition of long-acting calcium channel blockers of the dihydropyridine class was advised whenever an elevated BP could not be reduced to the normal range by the previously prescribed drugs.

25.3.2 2007 ESH/ESC Guidelines [15]

Although mention of the BP threshold and target for drug treatment was still absent, more details were given on the drugs to employ, and mention was made of heart failure with preserved ejection fraction which was referred to, however, by the then current terminology of diastolic heart failure. Beta-blockers, antialdosterone drugs, ACE inhibitors and angiotensin receptor antagonists were indicated as suitable drugs in all cases, with the additional mention of loop diuretics not only for their specific use in heart failure but also for their BP-lowering ability in that specific clinical setting. Dihydropyridine calcium channel blockers were not recommended except for the need to control a BP that was unresponsive to previous drugs as well as to treat concomitant anginal symptoms.

Mention was also made that a significant proportion of patients with chronic heart failure do not show a systolic but a diastolic dysfunction of the left ventricle, and that this is particularly the case in old hypertensive patients. Data from the CHARM trial were reported as supporting a possible, albeit modest, benefit of angiotensin receptor antagonists in this condition [17], but the conclusion was cautious, i.e. for “diastolic heart failure there is no evidence on the superiority of specific antihypertensive drugs”.

25.3.3 2013 ESH/ESC Guidelines [16]

In the 2013 ESH/ESC guidelines, treatment of heart failure in patients with a BP elevation or a history of hypertension received considerable attention. Emphasis was given to the epidemiological aspects, i.e. (1) hypertension is the leading

attributable risk factor for the development of heart failure; (2) among the hypertension-related complications, heart failure is almost as common as stroke; and (3) prevention of heart failure may be the largest benefit of antihypertensive treatment at all ages, including very elderly patients. Treatment recommendations were not substantially different from those of the 2007 ESH/ESC guidelines, with emphasis on treatments guided by relief of symptoms (diuretics for relief of congestion, beta-blockers for heart rate control, etc.) as well as by reduction of hospitalization and death (beta-blockers, ACE inhibitors, angiotensin receptor antagonists and/or mineralocorticoid receptor antagonists). Dihydropyridines continued to be recommended only to control angina or a high BP unresponsive to multiple antihypertensive agents, while double blockade of the renin-angiotensin system was strongly discouraged [18] because of its serious adverse effects, particularly in patients with diabetes and an impaired renal function, the latter not uncommon in heart failure. BP-lowering treatment was recommended in the presence of a systolic BP > 140 mmHg with the aim of reducing its value to <140 mmHg. No low safety BP value was indicated, but mention was made of a meta-analysis in which lower BP values were associated with reduced survival, suggesting that an excessive BP reduction should be avoided. For the first time evidence grading was used, a high score (1A) being attributed to recommendations on usable drugs and a low score (2aC) to those on BP threshold and targets for drug treatment. The low score was justified by the absence of randomized trials in patients with heart failure "with the specific interest of testing the effects of reducing BP" as well as by the exclusion from trials on antihypertensive treatment of patients with a history of heart failure. Data on the adverse effects of excessive BP reduction by treatment were also interpreted with caution because of the possible confounding effect of reverse causality, i.e. the possibility that a low BP was not the cause but the expression of a more severe heart failure.

The 2013 ESH/ESC guidelines addressed more in detail also heart failure with preserved ejection fraction, a pertinent aspect of hypertension guidelines because a history of hypertension is particularly common in this condition. Based on the negative findings of the I-PRESERVE trial (no benefit by angiotensin receptor antagonist treatment in heart failure with preserved ejection fraction) [19], the conclusion was reached that evidence on which treatment strategies should be adopted remained extremely limited. Thus, no recommendation was issued on which drugs might be preferred and which threshold and target BP values should be adopted in these patients. Mention was made, however, that, because in PRESERVE initial BP was 136/76 mmHg, the possibility that lower BP values might have beneficial effects remained alive.

25.3.4 2018 ESC/ESH Guidelines

Most of the recommendations on how to deal with hypertension in heart failure issued by the 2013 ESH/ESC guidelines have been confirmed by the most recent guidelines published by the two Societies in 2018 [20]. Namely, that in heart failure

patients with reduced ejection fraction (1) antihypertensive treatment should start (if not already initiated) when BP is equal or higher than 140 mmHg systolic or 90 mmHg diastolic; (2) ACE inhibitors, angiotensin receptor antagonists, beta-blockers and antialdosterone agents (spironolactone or eplerenone) are all effective in reducing clinical outcomes, whereas for diuretics evidence is limited to improvement of clinical symptoms; and (3) if further BP lowering is required, a dihydropyridine calcium channel blocker may be considered while non-dihydropyridine calcium channel blockers as well as centrally acting agents such as moxonidine have to be avoided.

The 2018 guidelines, however, include novel recommendations and deal more extensively than previous guidelines with key issues for heart failure in hypertension. First, the important role of antihypertensive treatment for prevention of heart failure [3, 4, 21–23] as well as for regression of left ventricular hypertrophy, a structural cardiac abnormality which is associated with a marked increase in the risk of cardiovascular outcomes, including heart failure [24–26]. Second, the use for antihypertensive treatment of sacubitril/valsartan, a new agent that can lower BP and has been shown to reduce outcomes in heart failure, in alternative to ACE inhibitors or angiotensin receptor antagonists [27]. Third, the persistingly poor information on how much BP should be lowered in patients with heart failure and which absolute BP values should be achieved. In this context, the 2018 guidelines again emphasize that the observational studies which show that in patients with low BP levels prognosis is poor are difficult to be interpreted because of the problem of "reversed causality" generated by their non-randomized nature. Nevertheless, they argue that it may be wise to avoid actively lowering BP < 120/70 mmHg, although adding that in several patients low BP values have to be accepted, if tolerated, because of the desirability to remain treated with heart failure medicaments that have a life-saving value [28]. Finally, the 2018 guidelines emphasize that antihypertensive treatment is commonly needed in patients in whom heart failure is not due to a reduction of myocardial contractility and ejection fraction but to an impaired relaxation of the left ventricle in diastole. Although very little is known on the BP threshold and target for treatment in these patients, the 2018 guidelines suggest to adopt criteria and drugs similar to those adopted for heart failure with reduced ejection fraction. Future antihypertensive treatment trials are highly desirable for this specific condition for which hypertension represents the most important determinant.

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