Chapter 21
Heart Failure and Hypertension

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Epidemiology

A major burden of modern society is the progressive increase in age-associated disorders such as heart failure (HF) [59]. Symptomatic HF is affecting nearly 15 million Europeans and 10,000 people are newly diagnosed every day [59]. In the US, HF contributes to an economic burden close to $40 billion per year and affects 1–2 % of the US population [39]. With the high prevalence of systemic hypertension, obesity and diabetes mellitus in our society, it is expected that the incidence of HF will continue to increase [39]. Figure 21.1 highlights that the actual burden of HF exceeds the projected burden according to the American Heart Association [39, 53]. With the increasing prevalence of symptomatic HF there is a need for early and accurate diagnosis and a better treatment regimen in helping people deal with this progressive chronic condition.

While traditionally associated with the concept of pump failure or reduced left ventricular (LV) ejection fraction (EF), it has become widely recognized that HF can occur even when EF is preserved, constituting the syndrome of HF with preserved EF (HFpEF) or so called diastolic HF [53] which is characterized by impaired LV relaxation, increased LV stiffness, and modified extracellular matrix proteins. The majority of the patients with HFpEF have a history of hypertension [53]. HFpEF now accounts for more than 50 % of the HF hospitalizations. Symptomatic HF with or without reduced EF has a poor prognosis [10, 46, 52]. In the recent meta-analysis which included 10,347 patients with HFpEF and 31,625 patients with HF and reduced EF (HFrEF), the authors compared survival in these groups using individual patient data [46]. Overall, there were 121 [95 % confi-

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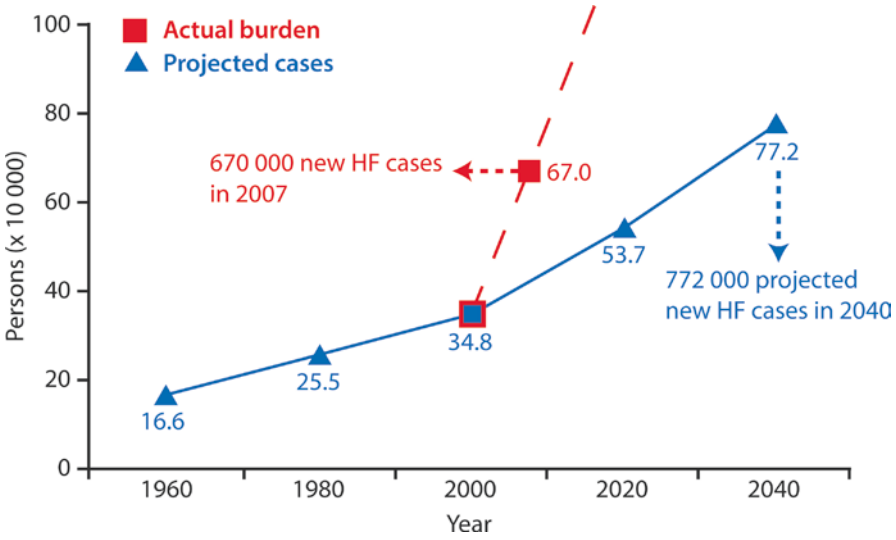

Fig. 21.1 Burden of HF. The actual burden of HF exceeds the projected burden based on a stable incidence of 10 per 1000 person-years in subjects aged > 65 year old (reproduced from Lam et al. [2] and Owan et al. [53] with permission)

dence interval (CI): 117, 126] and 141 (95 % CI: 138, 144) deaths per 1000 patient-years in patients with HFpEF and HFrEF, respectively [46]. Although the majority of resources are currently allocated to managing patients with symptomatic disease, in order to change the epidemic of HF, more resources need to be allocated to earlier recognition of HF as well as management of risk factors. Identifying patients at the early stages of HF would allow the institution of more aggressive risk management strategies and will likely decrease the progression to symptomatic disease.

HF is a progressive disorder that culminates with time and retards the standard of life of a person. HF begins with risk factors for LV dysfunction (e.g., hypertension and diabetes), proceeds to asymptomatic maladaptive LV remodeling (e.g., LV hypertrophy) and dysfunction (e.g., impaired ventricular relaxation or/and elevated LV filling pressure), and then evolves into clinically overt HF, disability and death [25]. Thus, the process of myocardial remodeling starts before the onset of symptoms (Fig. 21.2). Current guidelines distinguish four stages of HF, with stage A representing subjects who are at high risk for HF, because of hypertension, obesity and/or diabetes, but with still normal LV structure and function and no symptoms of HF [25]. Stage B includes patients with structural and/or functional LV abnormalities without clinical symptoms of HF (asymptomatic HF). Stage C represents patients with structural and/or functional LV abnormalities and symptoms of HF (symptomatic HF). Finally, stage D refers to patients with refractory symptoms of HF, requiring specialized intervention. Community-based studies [4, 40] identified the most important risk factors and underscored the magnitude of the population at

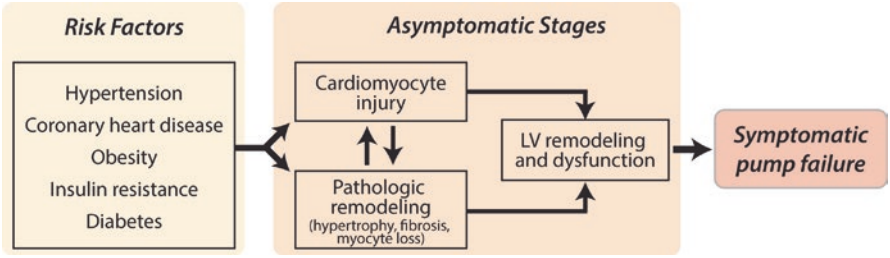

Fig. 21.2 Schema of progression from risk factors to clinically overt HF.

risk for progression to clinically overt HF. For instance, the Framingham study demonstrated that the hazard for developing HF in hypertensive patients, compared to normotensive subjects was approximately twofold in men and threefold in women after adjustment for age and other HF risk factors [40]. The 5-year survival rate for hypertensive symptomatic HF was 24 % for men and 31 % for women [40]. In Olmsted population 56 % of adults 45 years of age were classified as being in stage A (risk factors) or B (asymptomatic LV dysfunction) [4]. Transition from stage B to stages C is associated with a 5-fold increase in mortality risk [4], which underscored the importance of correct identifying persons at stage B for early diagnosis and intervention.

Role of Echocardiography in HF Staging in Patients with Hypertension

A routine physical examination does not allow diagnosing systolic or diastolic LV dysfunction in the preclinical phase (stage B). Similarly, a physical examination cannot accurately characterize the LV volumes and cardiac output. As a rapid and accurate modality, echocardiography can improve the non-invasive detection and definition of the hemodynamic and morphologic changes in HF [28].

The echocardiographic techniques to assess early subclinical changes in LV systolic and diastolic function evolved rapidly over the past 10 years. Nowadays, Tissue Doppler Imaging (TDI) and speckle tracking provide additional information about global and regional cardiac function over and beyond conventional echocardiography. TDI measures the velocity of mitral annular motion or myocardial wall, which reflects the shortening and lengthening of the myocardial fibers along the LV long-axis during the cardiac cycle [17, 45].

On the basis of color Doppler myocardial imaging, 1-dimensional regional systolic deformation (strain) and strain rate (SR) can be derived from tissue velocity measurements. Strain and SR quantifies the actual deformation of the myocardium (expressed as a percentage) in systole and diastole [17]. The major limitation of color Doppler myocardial imaging in the assessment of LV systolic strain is the

dependency on the angle of the ultrasound beam and the difficulties in assessing regional LV torsional movement. Newer techniques, such as "speckle tracking" algorithms, involve identification of multiple unique patterns of echocardiographic pixel intensity that are automatically tracked throughout the cardiac cycle. Each pixel's angular displacement is averaged to provide a measurement of both degree and direction of rotational motion for each segment of the myocardium. This method is not limited by angle dependency and compares favorably with magnetic resonance imaging [70].

LV Remodeling in Hypertensive Heart Disease

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. Conditions such as hypertension can cause LV remodeling or hypertrophy in order to accommodate an increased load. Indeed, hypertension induces a compensatory thickening of the ventricular wall in an attempt to normalize wall stress. Therefore, patients with hypertensive heart disease usually present with concentric remodeling or concentric LV hypertrophy, but have a normal-sized LV chamber and normal EF [16].

Worsening of LV geometry 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 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 [67]. The adjusted risk of all-cause mortality associated with baseline LV hypertrophy ranged from 1.5 to 8.0, with a weighted mean risk ratio of 2.5 for all studies combined (Fig. 21.3).

Another meta-analysis evaluating cardiovascular outcome in subjects with LV concentric remodeling (normal LV mass index and increased relative wall thickness) compared with those with normal geometry [54]. During the follow-up, 7465 subjects with concentric remodeling experienced 852 cardiovascular events. When compared with normal geometry, the overall adjusted hazard ratio was 1.36 (95 % CI 1.03–1.78; $P<0.03$) for concentric remodeling. Moreover, subgroup meta-analysis showed that increased cardiovascular risk in subjects with concentric remodeling was more relevant in studies evaluating hypertensive patients and reporting both fatal and non-fatal cardiovascular events [54]. Recently, Framingham investigators also reported in longitudinal echocardiographic study that exposure to multiple cardiovascular risk factors, such as elevated blood pressure and greater body mass index, were associated with the development of abnormal LV geometry [41].

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 congestive

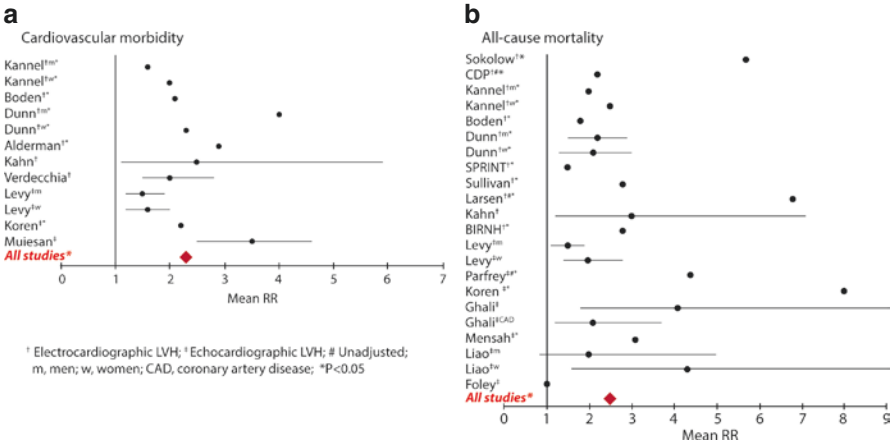

Fig. 21.3 Mean risk ratios (RR) (*solid circle*) and, when available, 95 % confidence interval (*horizontal lines*) of baseline LV hypertrophy for subsequent cardiovascular morbidity (panel **a**) and all-cause mortality (panel **b**) in available studies (reproduced from Vakili BA et al. [67] with permission)

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.

LV Diastolic Dysfunction

In parallel to changes in cardiac geometry, LV diastolic function tends to worsen over the adult life course in particular in patients with hypertension and hyperinsulinemia [37]. Diastolic dysfunction refers to a condition in which abnormalities in LV function are present during diastole. The gold standard for assessing diastolic function remains the LV pressure-volume relationship, but this requires an invasive approach. Conventional echocardiography together with Doppler measurements of transmitral and pulmonary veins flows, and the TDI mitral annular velocities created the possibility of detection of subclinical deterioration of LV diastolic function [49]. However, these techniques are complex and no single measurement on its own reflects diastolic function. Thus, a comprehensive assessment of a number of variables is required to evaluate diastolic function as correctly as possible [22].

Impaired myocardial relaxation, an early stage of LV diastolic dysfunction, is characterized by decreased transmitral early (E peak), and enhanced atrial (A peak) LV filling as well as less vigorous mitral annulus motion (e') during early diastole. On the other hand, one of the major unmet clinical needs is to improve non-invasive assessment of LV filling pressure, another feature of LV diastolic dysfunction. Some

experts suggested that the Doppler blood flow and the TDI mitral annulus velocities can reflect in some degree elevated LV filling pressure. For instance, combining early transmitral blood flow velocity with early mitral annular velocity (E/e' ratio) might be a tool for estimating LV filling pressure [27, 51]. The majority of patients with elevated LV end-diastolic filling pressure in the presence of normal EF (>50 %), as invasively determined in several previous studies from pressure-volume loops, had an E/e' ratio between 8 and 15 [51]. Ommen et al. [51] suggested that 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. Thus, non-invasive echocardiographic imaging criteria for evaluation of LV filling pressure still require further validation and refinement.

Prevalence and Determinants of Diastolic Dysfunction in the Community

Presently, few population studies [1, 29, 35, 58] described the prevalence of preclinical LV diastolic dysfunction, using the new TDI indexes along with classical pulsed wave Doppler velocities. These studies applied a comprehensive Doppler analysis to grade LV diastolic dysfunction in older adults (aged 60–86 years) [1], in subjects aged 45 years or older [58], or in the general population (aged 17–89) [29, 35]. The reported prevalence of diastolic dysfunction in these studies varied from 27.3 to 34.7 %, and was influenced by a number of factors, including the characteristics of the population studied, and the criteria applied to diagnose LV diastolic dysfunction.

Studies in the general population [35, 62] demonstrated that LV relaxation as reflected by the Doppler indexes substantially decreased with age not only in the whole study sample, but also in a selected healthy reference population. Current recommendations propose criteria to diagnose diastolic dysfunction, which are not standardized for age [49]. It is likely that by ignoring age and by applying the same threshold values for the Doppler indexes throughout the age range, one may underestimate the prevalence of subclinical diastolic dysfunction (impaired relaxation), especially in young subjects with risk factors, such as hypertension, obesity and diabetes.

Moreover, the risk of diastolic dysfunction increased significantly and independently with higher body mass index, heart rate, systolic blood pressure, serum fasting insulin and creatinine (Fig. 21.4) [35]. Women were more at risk than men (Fig. 21.4). In a cross-sectional study of participants of the Flemish Study on Environment Genes and Health Outcomes (FLEMENGHO), about 50 % of hypertensive subjects had impairment of LV diastolic function, whereas only

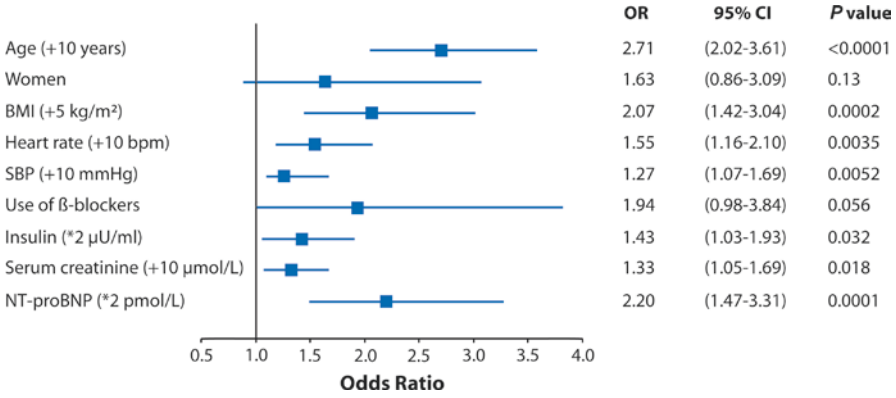

Fig. 21.4 Association between diastolic dysfunction and clinical and biochemical characteristics. *Black squares* and *horizontal lines* represent the odds ratio (OR) and 95 % confidence intervals for the mutually adjusted covariates, identified by stepwise regression (reproduced from Kuznetsova et al. [35] with permission)

12 % of normotensive subjects could be classified as having abnormalities of LV diastolic function [35].

Prognostic Significance of LV Diastolic Dysfunction

Recent clinical and community-based studies explored the prognostic role of classical Doppler and the new TDI-derived indexes. Transmitral E/A ratio and mitral annular early diastolic velocity (e') as well as E/e' ratio had an independent prognostic value in patients with overt HF [2, 19, 50], hypertension [64, 71] or myocardial infarction [24]. For instance, three studies [2, 19, 50] in patients with symptomatic HF demonstrated that high E/e' independently predicted cardiac mortality and HF re-hospitalization. These studies provided thresholds for the E/e' ratio in a range from 12.5 to 15. Moreover, in the ASCOT trial [64] E/e' was the strongest independent predictor of fatal and nonfatal cardiac events in a cohort of 980 high-risk hypertensive patients. The authors demonstrated that in an adjusted model, a 1-unit rise in the E/e' ratio was associated with a 17 % increment in risk of cardiac events ($P = 0.003$). Wang et al. [71] reported that low TDI e' velocity independently predicted cardiac mortality in 174 patients with hypertension.

On the other hand, community-based studies are essential to investigate the natural history of subclinical diastolic LV dysfunction and to determine its prognostic significance. So far, few studies explored the prognostic role of echocardiographic indexes reflecting LV diastolic function. In the Cardiovascular Health Study (mean age, 73 years) [5], the adjusted risk of symptomatic HF was highest at the extremes

of the distribution of the transmitral E/A ratio. The relative risk was 1.88 (95 % CI, 1.33–2.68) for an E/A ratio of less than 0.7 and 3.50 (CI, 1.80–6.80) for an E/A ratio higher than 1.5, compared with intermediate values. Similarly, among 3008 American Indians (mean age, 60 years) enrolled in the Strong Heart Study [9], all-cause and cardiac mortality also had a U-shaped relation with the E/A ratio. In the Copenhagen City Heart Study (n=2064; mean age, 60 years) [47], low systolic (s') and diastolic (e' and a') myocardial velocities derived from color Doppler imaging and averaged from 6 mitral annular sites were associated with increased risk of the combined end point (cardiovascular death or hospitalization due to either HF or myocardial infarction). In 793 FLEMENGHO participants we demonstrated that after adjustment for conventional cardiovascular risk factors, only TDI e' velocity analyzed as continuous variable was a significant predictor of fatal and nonfatal cardiovascular events [38]. We also found that TDI e' velocity improved the discrimination between subjects with and without events as compared to a model including only conventional cardiovascular risk factors [38].

In the FLEMENGHO cohort, we explored the predictive value of LV diastolic dysfunction grades based on conventional Doppler and new TDI velocities (categorical analysis) [38]. In this fully-adjusted analysis, hazard ratio of fatal and non-fatal cardiac events (4.50; $P = 0.002$) were significantly elevated in participants with increased LV filling pressure compared with subjects with normal diastolic function [38]. These findings are in line with report from the Olmsted study [58] which described the predictive significance of preclinical LV diastolic dysfunction, using also the comprehensive approach of assessing LV diastolic function. In multivariable-adjusted analyses while controlling for age, sex, and EF, mild diastolic dysfunction (HR, 8.31; $P < 0.001$) and moderate or severe diastolic dysfunction (HR, 10.17; $P < 0.001$) predicted of all-cause mortality. However, in this study, the authors did not adjust the models for other important cardiovascular risk factors, such as systolic blood pressure, body mass index, serum creatinine and total cholesterol.

LV Systolic Dysfunction

LV systolic function was initially quantified by contrast cineventriculography, using EF (the ratio of stroke volume divided by end-diastolic volume) before the introduction of echocardiography. Traditionally, EF measurement is used to diagnose of HF. The view that systolic function is entirely normal in patients with symptomatic HF and preserved EF has been challenged [13, 61]. The majority of the patients with HFpEF have a history of hypertension. As we already mentioned in the previous section, geometric remodeling of the LV is one of the key futures of hypertensive heart disease. Patients with maladaptive LV remodeling have increased wall thickness and myocardial fibrosis, particularly in the subendocardium [26]. The contraction of the myocardial layer, which is located in the subendocardium, is mainly responsible for systolic longitudinal shortening [23]. Thus, early subclinical changes of systolic function can be more readily detected by analyzing longitudinal

deformation (strain) and in the LV basal segments, because the gradient of average wall stress increases from the apex to the base [14].

LV longitudinal strain might be a sensitive tool in the detection of subclinical systolic dysfunction associated with adverse LV remodeling in hypertensive heart disease and might be important for risk stratification of patients with hypertensive heart disease [65]. Clinical studies in hypertensive patients [6] and in general population [36] showed that the LV longitudinal strain measured at baseline segments using the color Doppler imaging technique correlated inversely with mean arterial pressure and basal wall thickness. Another study in hypertensive patients with symptomatic heart failure [31] showed that the speckle tracking technique, by providing the combined assessment of LV longitudinal, radial and circumferential function, is a promising tool in the diagnosis of systolic LV dysfunction. As recommended in the recently published Task Force [70], LV global longitudinal strain appears to be the most robust and reproducible echocardiographic metric as compared to circumferential and radial strain, and, therefore, it might be easy implemented in clinical practice.

Recent clinical and community-based studies explored the *prognostic role* of the different LV systolic deformation indexes. In the TOPCAT trial [63], global longitudinal strain was a powerful predictor of HF hospitalization, cardiovascular death, or resuscitated cardiac arrest in a cohort of 447 HF patients with preserved EF. The authors demonstrated that in an adjusted model a 1-unit decrease in global longitudinal strain was associated with a 14 % increment in risk of primary outcomes ($P = 0.003$) [63]. In 1768 asymptomatic participants (mean age, 65 years) enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) [11], LV circumferential strain assessed by MRI provided incremental predictive value for incident HF. In the Framingham Heart Study (n = 2831; mean age, 66 years) [12], LV global longitudinal strain was borderline associated with incident coronary heart events (hazards ratio per standard deviation decrement 1.29; $P = 0.05$), whereas circumferential strain was a significant predictor of incident HF (1.79; $P<0.0001$). Decrements in longitudinal and circumferential strain were significantly related to all-cause mortality in the Framingham study [12]. In the FLEMENGHO study [32], participants belonging to the low sex-specific quartile of the distribution of the LV global longitudinal strain measured at the mid-wall level of myocardial wall (<18.8 % in women and <17.4 % in men) were older, more likely to have risk factor such as hypertension, previous history of cardiac disease, higher body mass index and total cholesterol. While adjusting for these risk factors in multivariable Cox models, only in the lower global longitudinal strain quartile group the risk for cardiovascular and cardiac events was significantly higher than the average population risk (Fig. 21.5). These findings suggest that the LV strain deformation might contribute to risk stratification of patients with hypertension.

Because LV hypertrophy [34] and diastolic function [38] are significant prognostic markers of cardiovascular events in addition to global longitudinal strain, we explored the risk for cardiovascular and cardiac events with increasing number of having any of three LV abnormalities [32]. Figure 21.6 illustrated that incidence rate of the composite cardiovascular events increased with increasing number of the LV

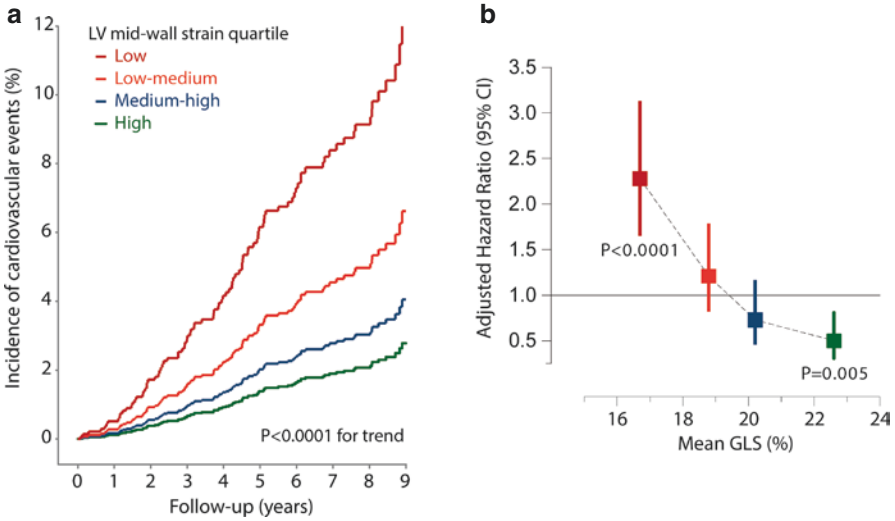

Fig. 21.5 (Panel **a**)*:* Multivariable-adjusted cumulative incidence estimates for fatal and nonfatal cardiovascular events. *P* values are for trend across the four quartiles of LV global longitudinal strain (GLS). Incidence was standardized to the mean values of the covariables (sex, age, body mass index, systolic blood pressure, serum cholesterol, current smoking, antihypertensive drug treatment, diabetes mellitus, and a history of cardiac disease) in the total study population. (Panel **b**): Multivariable-adjusted hazard ratios (95 % CI) for cardiovascular events by sex-specific quartiles of LV mid-wall strain in 791 subjects. The hazard ratios express the risks in quartiles compared with the average risk in the whole cohort and were adjusted as described above (reproduced from Kuznetsova et al. [32] with permission)

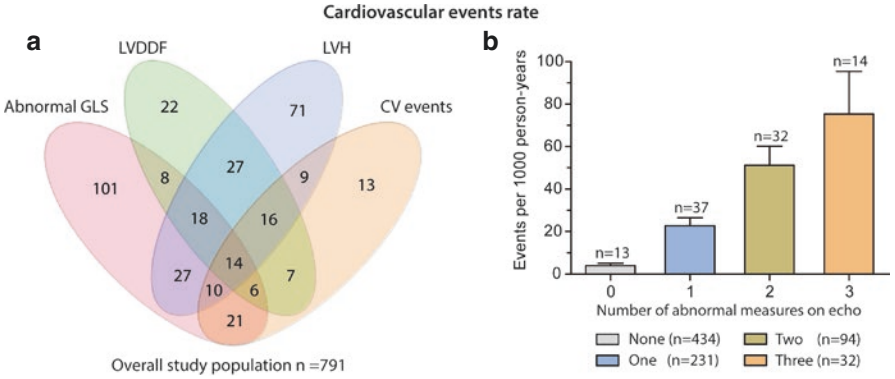

Fig. 21.6 (Panel **a**)*:* Venn diagrams demonstrating the overlap between abnormal global longitudinal strain (GLS), LV diastolic dysfunction (LVDDF), and left ventricular hypertrophy (LVH) in the whole cohort (n = 791). The Venn diagrams also show the incidence of cardiovascular events. (Panel **b**): Crude incidence rates of fatal and nonfatal cardiovascular events by the number of abnormal echocardiographic findings (reproduced from Kuznetsova et al. [32] with permission)

abnormalities, suggesting that all these features (abnormal global longitudinal strain, LV hypertrophy and diastolic function) are useful for risk stratification in the community. Therefore, the comprehensive assessment of cardiac function and structure in which global longitudinal strain plays a major role would be important for risk stratification.

Biomarkers

Contrary to popular belief, HF is difficult to diagnose. There is no system of diagnostic criteria that is considered a golden standard. Biomarkers might be used as a vital tool in differentiating high-risk patients among the rest of the population. According to the recent guidelines testing for BNP or NT-ProBNP is recommended for symptomatic HF diagnostics followed by an ultrasound of the heart if the test is positive [55]. Cardiac specific biomarkers such as BNP/NT-proBNP and high sensitive troponin are the gold standard for the diagnosis of cardiac diseases such including symptomatic HF [30, 60]. BNP is released from cardiomyocytes in response to an increase of atrial or ventricular diastolic stretch to stimulate natriures and vasodilatation and to facilitate LV relaxation and, therefore, might vary with the degree of LV diastolic dysfunction [48]. On the other hand, cardiac troponins release from cardiomyocytes due to normal cardiomyocyte turnover, or due to pathological myocyte necrosis, apoptosis, and increased cardiomyocyte wall permeability [72]. Along these lines, recent studies demonstrated that both high-sensitivity troponin T and NT-proBNP are very useful in identifying subjects with *early stages of cardiac maladaptation* in the community (left atrial enlargement, LV hypertrophy or diastolic dysfunction) [15, 20, 57].

In the future biomarker testing for detection of early stages of HF should go beyond the use of natriuretic peptide or troponin. There is going to be increased adoption of emerging biomarkers pathophysiological relevant to HF mechanisms such as those related to inflammation, metabolic dysregulation, and myocardial fibrosis. Indeed, inflammatory mediators may play a key role in the progression to HF in patients with hypertension [18]. Experimental and clinical studies demonstrated that the overexpression of cytokine cascades contributes to the process of LV remodeling by inducing myocytes hypertrophy, activation of the fetal gene expression program, degradation of the extracellular matrix, as well as progressive myocytes loss through apoptosis [44, 68]. Nowadays, a multiplex panel of 63 cytokines could be used to identify a set of inflammatory biomarkers that are associated with early LV remodeling and dysfunction as captured by echocardiography. Using this panel, we have recently demonstrated that cytokines related to inflammasome activation, mainly interleukin-18 (IL-18), CXCL9 (MIG) and hepatocyte growth factor, were significantly elevated in hypertensive patients with early asymptomatic stages of HF [33]. Previous studies also demonstrated that growth differentiating factor-15, a stress responsive cytokine, is associated with LV hypertrophy and HF [3]. Moreover, in the FLEMENGHO cohort, elevated baseline fasting insulin levels, a

marker of insulin resistance, were strongly associated with worsening of LV diastolic function during follow-up [37].

Cardiomyocyte micro-injury may be also associated with dysregulation of the collagen deposition process. A diffuse deposition of collagen fibers (mainly type I) in the interstitial and perivascular space characterizes the myocardial fibrosis that develops in HF whatever its cause. Indeed, the severity of myocardial collagen deposition is associated with serum levels of the C-terminal propeptide of procollagen type 1 (PICP) in HF patients [42, 56]. Collagen cross-linking determines the stiffness of the collagen type I fiber and its resistance to degradation by matrix metalloproteinase-1 (MMP-1), resulting in diminished cleavage of a small C-terminal telopeptide of the fiber (CITP) [43]. With regard to this, López et al. have recently shown that a low serum CITP/MMP-1 ratio is independently associated with a high myocardial collagen cross-linking and is an independent predictor of hospitalization in symptomatic HF patients of hypertensive etiology [43]. Building on these results, it is likely that patients with hypertension and with evidence of inflammasome activation and disturbances in the quality and quantity of the myocardial collagen matrix will be at increased risk of HF and, therefore, these biomarkers could be useful as an additional tool for earlier recognition and prognosis of HF.

Randomized trials are the gold standard for establishing the effectiveness of biomarker guided strategies. However, currently there are very few of such trials in HF patients. On the other hand, having such trials will increase the degree of evidence for biomarker-guided therapy in the management of hypertensive patients with cardiac maladaptation.

Prevention of HF in Patients with Hypertension

Recent HF recommendations place important emphases to preventive strategies in high-risk group patients (e.g. hypertension and diabetes). This would be important as currently there are no novel therapies in high-risk groups addressing specific mechanisms of adverse cardiac adaptation leading to symptomatic HF.

There is overwhelming evidence that primary prevention of symptomatic (congestive) HF is strongly dependent on blood pressure reduction. Verdecchia et al. undertook a meta-regression analysis to investigate the blood pressure-related and unrelated effects of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), or calcium-channel blockers (CCBs) in the prevention of CHF in patients with hypertension or high cardiovascular risks [69]. For this meta-analysis the authors selected 31 eligible trials, which included 225,764 patients and 6469 incident cases of congestive HF. This analysis provides clear evidence that blood pressure reduction is important for the prevention of congestive HF in patients with hypertension. Overall, the risk of congestive HF decreased by 24 % ($P < 0.001$) for each 5 mmHg reduction in systolic BP. On the other hand, the risk of congestive HF was 19 % less with ACEIs/ARBs than CCBs ($P < 0.001$). Another meta-analysis

which compared effect of beta-blockers with other antihypertensive agents in hypertensive patients, demonstrated that there was similar but no incremental benefit of beta-blockers for the prevention of congestive HF [7]. It has been also shown that the antihypertensive treatment of elderly patients who are 80 years of age or older was beneficial especially in regard to incident cases of congestive HF [8]. Indeed, in this clinical trial, active treatment with the diuretic indapamide, with or without ACEI perindopril, was associated with a 64 % reduction in the rate of congestive HF (95 % CI, 42–78; $P < 0.001$).

Adverse LV remodeling and LV diastolic dysfunction may precede development of HF in hypertensive patients. Blood pressure-lowering therapy also reduces LV mass and improves LV diastolic function which is important for prevention of symptomatic HF [21, 66]. Recent meta-analysis combined the 75 relevant publications involved and 6001 patients suggested that beta-blockers show less regression of LV mass as compared with other antihypertensive drug classes, including ARBs [21]. A clinical trial including 228 patients with uncontrolled hypertension, demonstrated that the degree of improvement in TDI early mitral annular velocity (e') was associated with the degree of systolic blood pressure reduction [66]. Patients who achieved the lowest systolic blood pressure demonstrated the highest TDI e' (better myocardial relaxation), independent of starting blood pressure. These data provide further support that achieving optimal blood pressures may be an effective means to reverse LV hypertrophy and improve LV diastolic function, which are features of cardiac target-organ damage in hypertension.

Conclusion

As shown by epidemiological studies, hypertension is one of the most important modifiable risk factors for the development of symptomatic HF. HF is one of the life-threatening conditions. Despite the high prevalence, HF is underdiagnosed as most patients incorrectly attribute the signs and symptoms to growing older. Currently there is an unmet need to identify easily applicable and cost-effective strategies for the early detection of asymptomatic HF stages in patients at risk. Identifying patients at the early 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, conventional echocardiography combined with TDI and speckle tracking techniques is a sensitive tool to assess early subclinical changes in systolic and diastolic LV function in patients at risk. Impairment of LV diastolic as well as systolic function appears very early in the course of hypertensive heart disease. Because systole and diastole are active and complementary components of the cardiac cycle, they are both contributing to overall myocardial performance. LV systolic and diastolic dysfunction coexists to varying degrees. Community-based studies revealed a higher than hitherto expected prevalence of LV systolic and diastolic dysfunction. The new echocardiographic indexes used to assess LV function

contain additive prognostic information over and beyond traditional cardiovascular risk factors and, therefore, might be used for assessing cardiovascular risk in a population-based cohort. These initial observations should be further validated in regard to the prognosis associated with early symptom-free LV dysfunction in hypertensive heart disease.

Stiffening of the large arteries is a common feature of ageing, leads to isolated systolic hypertension, and is exacerbated by many common disorders, such as hypertension and diabetes mellitus. The heart typically adapts to confront higher and later systolic loads by both hypertrophy and LV stiffening. Increased vascular loading on the heart likely contributes to LV dysfunction. Ventricular-arterial coupling disease has to be further explored in subjects with subclinical LV dysfunction.

A panel of biomarkers pathophysiologically relevant to maladaptive ventricular remodeling and dysfunction is needed for the diagnosis, risk stratification, and follow-up of patients at risk for HF. In the future, HF therapy is going to utilize a combination of multiple markers for risk assessment and diagnosis. Many of these biomarker tests are going to combine into a panel test rather than compete individually. Genetic risk markers and peripheral serum biomarkers need to be incorporated in algorithms for risk stratification of patients with hypertensive heart disease and to identify the optimal timing and type of therapy.

Future Direction Box

- Identifying patients at high risk of developing symptomatic HF and other cardiovascular outcome is an important step to an effective preventive strategy.
- Current "state of the art" management of subclinical LV remodeling and dysfunction relies only on the control of risk factors, such as hypertension, diabetes and kidney dysfunction.
- Existing imaging techniques should be further validated in terms of HF progression or the prediction of cardiovascular morbidity and mortality.
- A validated set of biomarkers pathophysiologically relevant to maladaptive ventricular remodeling and dysfunction is needed for the diagnosis, risk stratification, and follow-up of patients at risk for HF.
- Randomized controlled trials are needed for establishing the effectiveness of biomarker guided strategies.
- HF therapy is going to utilize a combination of imaging markers and biomarkers for risk assessment and diagnosis.

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