Hemodynamic Mechanisms

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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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M. Dorobantu et al. (eds.), *Hypertension and Heart Failure*,
Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-93320-7_4

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

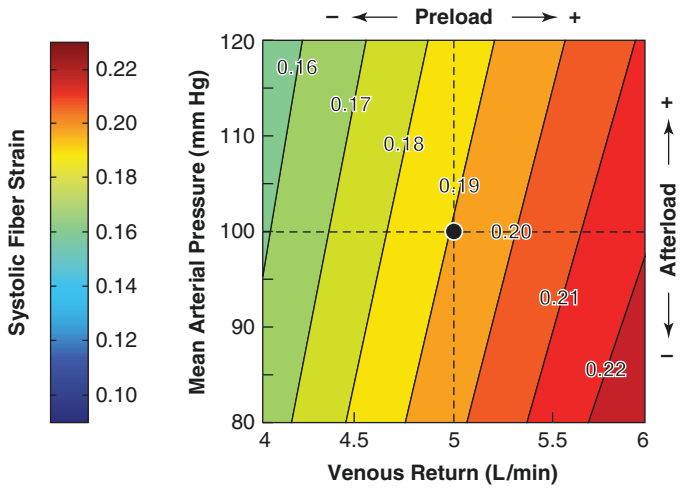

Fig. 4.1 Dependence of LV global LS (color gradient) to preload (venous return) and afterload (mean arterial pressure) in a normal heart. Reproduced from Lumens et al. [7] with permission

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

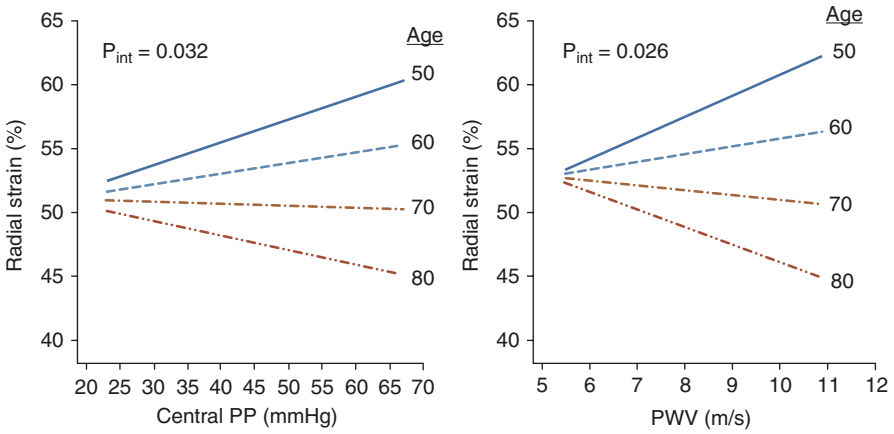

Fig. 4.2 Extrapolation from the multivariable-adjusted model of radial strain in relation to the continuous components of arterial stiffness at fixed levels of age. The number at the extrapolation line indicates the fixed level of age. P_{int} indicates the P values for interaction between arterial characteristics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

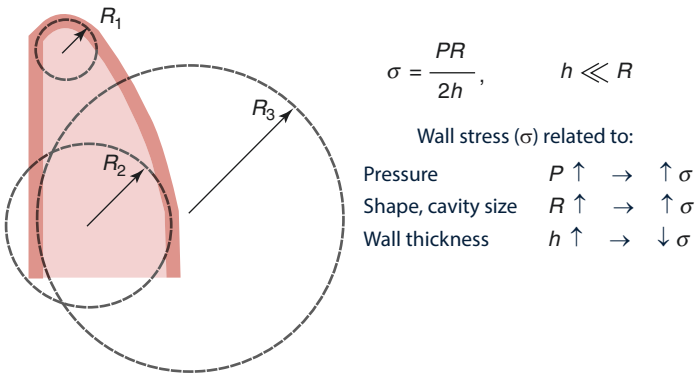

Fig. 4.3 Schematic representation of the law of Laplace, which states that wall tension is proportionate to the pressure (P) times radius (R). Therefore, wall stress (σ) is wall tension divided by wall thickness (h). At a given intraventricular pressure, wall stress increases with an increase in radius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

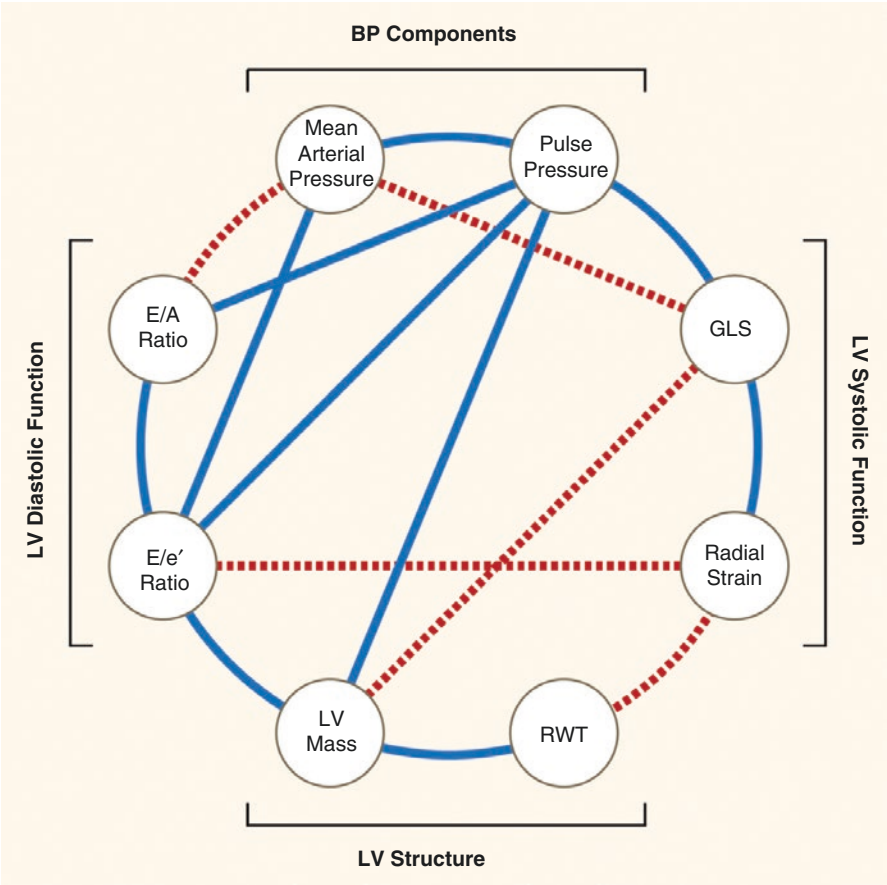

Fig. 4.4 Partial correlation diagram between blood pressure components and echocardiographic indexes of LV function and structure based on the data of 791 participants from the FLEMENGHO population study [30]. The full blue lines represent direct (positive) correlations, and dashed red lines represent 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

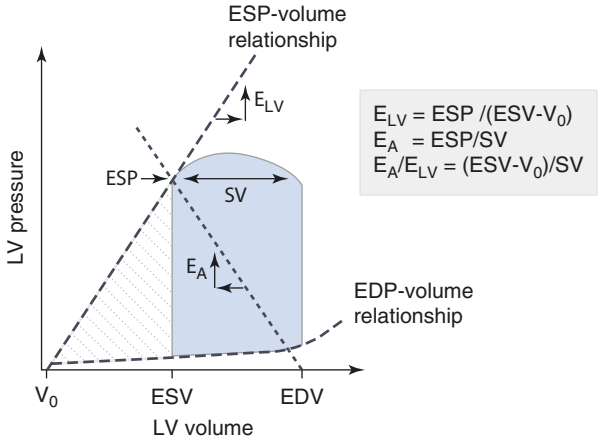

Fig. 4.5 Schematic representations of a pressure-volume loop and derived ventricular-arterial indexes. *EDV* end-diastolic volume; *ESV* end-systolic volume; *ESP* end-systolic pressure; E_A arterial elastance; E_{LV} left ventricular end-systolic elastance; *LV* left ventricular; *SV* stroke volume

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)

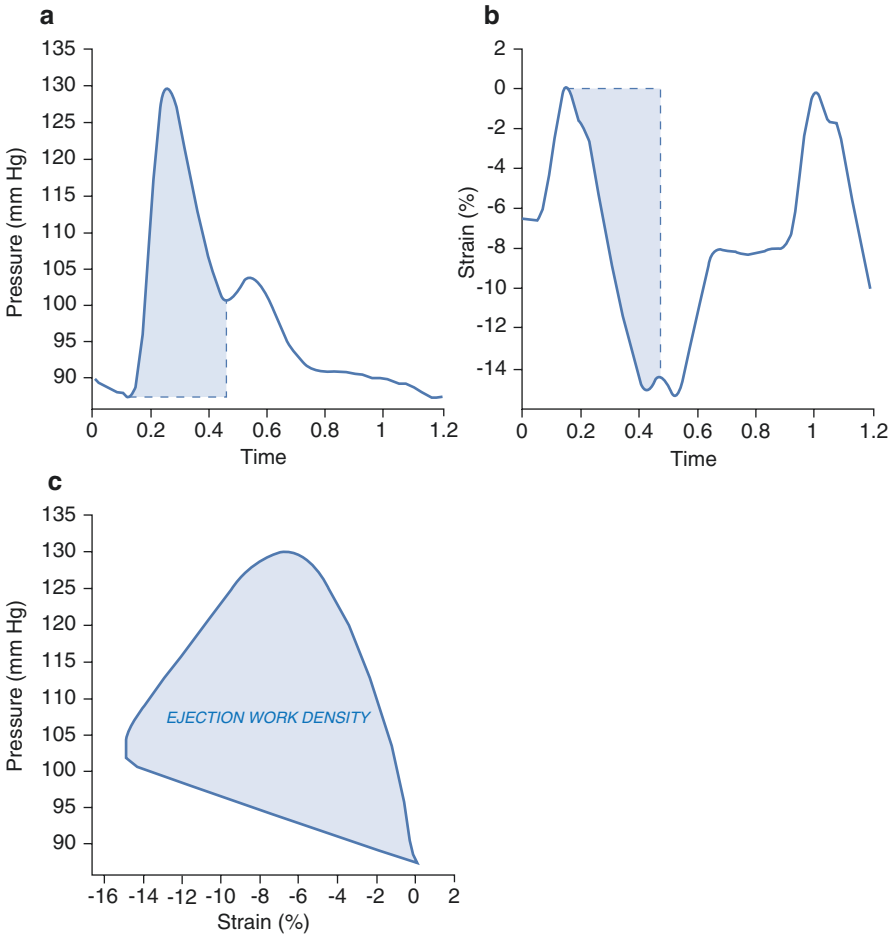

Fig. 4.6 Noninvasive assessment of LV ejection work density. From grayscale echocardiographic imaging and simultaneously recorded brachial pressure waveforms, we derived brachial artery pressure wave (**a**) and two-dimensional LV strain (**b**) curves to construct the pressure-strain loop (**c**). The 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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