Diastolic Dysfunction as a Link Between Hypertension and Heart Failure

Anil Verma, MD[a], Scott D. Solomon, MD[b],*

Left ventricular diastolic dysfunction (DD) is characterized by abnormalities in left ventricular (LV) filling, including decreased diastolic distensibility and impaired relaxation, and it may represent an important pathophysiologic link between hypertension and heart failure, in particular in patients who have heart failure with normal or preserved ejection fraction. LVDD has been found to be commonly prevalent in the community setting, with isolated DD as common as systolic dysfunction, and worsening diastolic function of the left ventricle has been associated with an increased frequency of heart failure development.[1] Hypertension significantly contributes to cardiovascular (CV) morbidity and mortality by causing substantial structural and functional adaptations, including DD, LV hypertrophy (LVH), ventricular and vascular stiffness, and progressive renal dysfunction. Heart failure with preserved ejection fraction (HFPEF) is now recognized as a major public health problem because nearly one half of the patients presenting with heart failure syndrome have preserved LV ejection fraction (LVEF).[2,3] The prevalence of HFPEF has increased over the past decade, with unchanged rates of death.[3] Although various therapies, including inhibition of renin angiotensin and aldosterone system (RAAS), have been shown to improve survival in patients who have heart failure with LV systolic dysfunction, no pharmacologic therapy has been shown to be effective in improving outcomes in patients who have heart failure with a preserved LVEF. These trends underscore the importance of this growing public health problem and a need to understand the potential mechanisms primarily responsible for this clinical syndrome and its relationship to hypertension and DD.

[a] Ochsner Clinic Foundation, 1514 Jefferson Highway, New Orleans, LA 70121, USA
[b] Non-Invasive Cardiology, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
* Corresponding author.
E-mail address: ssolomon@rics.bwh.harvard.edu (S.D. Solomon).

EPIDEMIOLOGIC ASPECTS OF DIASTOLIC DYSFUNCTION AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Hypertension and aging contribute significantly to adverse cardiac morphology and poor outcomes. Advancing age and female gender are associated with increases in vascular and ventricular systolic and diastolic stiffness, even in the absence of CV disease.[4] The Strong Heart Study, which was a population-based cohort study of cardiac risk factors and prevalent and incident cardiac disease, used mitral inflow patterns to characterize diastolic function. Its investigators reported that simple Doppler evidence of grade I DD was present in 16% of the cohort group and that evidence of Grade II to IV DD was present in 3% of the cohort group. DD is more common with advancing age and in people with hypertension, coronary artery disease, or risk factors for coronary artery disease.[5] Similarly, Redfield and colleagues,[1] using Doppler parameters, graded DD as mild in subjects with impaired relaxation but without evidence of increased filling pressures, as moderate in subjects with impaired relaxation and a moderate elevation of filling pressures or a pseudonormal pattern, and as severe in subjects with advanced reduction in compliance and reversible or fixed restrictive filling. They found that 20.8% of the subjects had mild DD, 6.6% had moderate DD, and 0.7% had severe DD, with 5.6% of the population having moderate or severe DD with normal ejection fraction. The presence of any DD imparted an eightfold to 10 fold increased mortality risk in their population.

The proportion of patients who have HFPEF increases with age, from 46% in patients younger than 45 years to 59% in patients older than 85 years.[6] In epidemiologic studies and clinical trial settings, patients presenting with HFPEF were more likely to be older, of female gender, have a higher mean body-mass index, and have higher rates of hypertension and atrial fibrillation but lower prevalence rates of coronary artery disease and any valvular disorders.[3] Owan and colleagues[3] reported a higher survival rate among patients who had preserved ejection fraction than among those who had reduced ejection fraction, although the difference was small (29% versus 32% at one year and 65% and 68% at five years, respectively). Bhatia and colleagues[7] reported similar mortality rates among patients who had HFPEF and heart failure with reduced ejection fraction, at 25.5% and 22.2%, respectively, after one year.[8] Clinical presentation of HFPEF is indistinguishable from that of heart failure with reduced ejection fraction, with echocardiography providing the only reliable discriminator.[8] Thus, among patients hospitalized for heart failure, approximately 50% will have LVEF greater than 50%, with mortality rates similar to those of patients who have reduced ejection fraction heart failure.

PHYSIOLOGIC ASPECTS OF THE DIASTOLE

The diastole of the cardiac cycle occurs during the period of time from the aortic valve closure to the mitral valve closure, with the rest of the cardiac cycle being defined as the systole. There are four distinct phases to the diastole: (1) isovolumetric relaxation, (2) early LV filling, (3) diastasis, and (4) filling at atrial contraction. Isovolumetric relaxation begins with aortic valve closure and ends with mitral valve opening. The LV pressure decreases without a change in volume during this phase. Isovolumetric relaxation ends when the LV pressure decreases to less than the left atrial pressure. LV relaxation is an energy-dependent process that starts with sodium/calcium exchanger–induced extrusion of calcium from the cytosol and sarcoplasmic reticulum calcium ATPase (SERCA2a)–induced calcium sequestration into the sarcoplasmic/endoplasmic reticulum, which in turn inactivates the troponin-tropomyosin complex, detaching the actin-myosin cross-bridge and bringing the sarcomere to its resting length.[9–11] The

concentration of the products of ATP hydrolysis (ADP and inorganic phosphate) must remain low and produce the appropriate relative ADP/ATP ratio to maintain this energy-dependent phase of LV relaxation and thus maintain normal diastolic function.[12]

The time constant of LV relaxation (τ), estimated from the rate of intracavitary pressure decay during isovolumetric relaxation, is the time that it takes the LV pressure to fall to approximately two-thirds of its peak value, and it provides a quantitative assessment of global LV relaxation.[11,13] Measurement of the end systolic pressure and fiber stretch, coronary flow, and stored energy (elastic recoil) helps determine the rate of myocardial relaxation. The near-simultaneous and rapid relaxation of the left ventricle decreases the LV intracavitary pressure during the early diastole and creates a pressure gradient across the mitral valve, drawing blood from the left atrium and rapidly filling the left ventricle. The ensuing rapid LV filling is followed by a fall in the transmitral pressure gradient and a phase of passive LV filling (diastasis) that is dependent on the LV chamber stiffness. Late in the diastole, atrial contraction increases, re-establishing the transmitral pressure gradient and LV filling. Diastolic function can be impaired at any point in this sequence as a result of changes in the passive stiffness of the myocardium or in the process of active myocardial relaxation, which is indicated as a shift upward and to the left in a graph of the end diastolic pressure volume relationship (**Fig. 1**), reflecting enhanced sensitivity of intraventricular filling pressures to even small changes in filling volume. The consequential limitations on myocardial reserve narrow the window for clinical compensation, enhancing vulnerability to the development of heart failure symptoms as a consequence of rapid changes in afterload (eg, during bouts of uncontrolled hypertension), dietary sodium indiscretion, onset of new arrhythmias, or development of myocardial ischemia.[14]

PATHOPHYSIOLOGIC ASPECTS OF DIASTOLIC DYSFUNCTION AND DEVELOPMENT OF HEART FAILURE WITH PRESERVED EJECTION FRACTION

In the Valsartan in Diastolic Dysfunction (VALIDD) trial, the authors demonstrated that the mean lateral mitral relaxation velocity (a measurement of LV diastolic function performed using tissue Doppler imaging) in patients who had hypertension and underwent screening was substantially reduced and was inversely related to age. Notably, LVH was only present in 15 (3%) of the screened patients, despite their
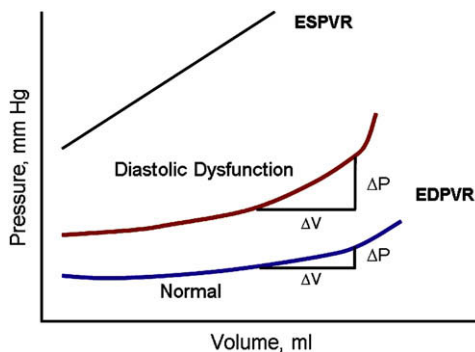
Fig. 1. Graph of the end-diastolic pressure volume relationship in patients who have normal filling and DD (end systolic pressure volume relationship [ESPVR] is also included as part of the pressure volume curve). In patients who have DD, increased ventricular stiffness in the diastole is expressed as an increase in the slope of the end diastolic pressure volume relationship (EDPVR), such that any given filling volume occurs only at the expense of higher filling pressures.

histories of hypertension.[15] Thus, abnormalities of ventricular relaxation and the consequences of DD may signify an early measure of myocardial end-organ damage in patients who have hypertension that might precede ventricular hypertrophy[15,16] Thus, DD could represent a potential mechanism by which treating hypertension might attenuate progression to heart failure.

Hypertension and Aging

The prevalence of hypertension increases with advancing age, to the point at which more than one half of the people between 60 and 69 years of age and approximately three fourths of those 70 years of age and older are affected.[17] Hypertension and aging are closely linked and interact with each other to cause various morphologic changes in the CV system, such as increased vascular stiffness, coronary insufficiency, and LVH. It is systolic blood pressure and not diastolic pressure in patients who have hypertension that represents the greatest blood pressure–related risk for adults older than 50 years of age who have cardiac and cerebrovascular diseases.[18] Aging is associated with increased blood pressure sensitivity to dietary sodium intake, and advancing age could exacerbate the adverse CV effects of high salt consumption because an increase in dietary salt intake raises arterial pressure and increases arterial stiffness in elderly patients who have systolic hypertension.[19] A study by Gates and colleagues[20] showed that large elastic artery compliance in humans improved with dietary sodium restriction and that rapid improvements in central arterial compliance with dietary sodium restriction were strongly related to corresponding reductions in systolic blood pressure. Structural changes involving ECM proteins in the arterial wall are believed to play a major role in the reductions in central arterial compliance and consequent increases in systolic blood pressure associated with human aging.[20,21] Increased salt load could result in activation of local tissue renin–angiotensin systems, increased production of tissue ouabain-like substances, endothelial dysfunction, and elevated secretion of marinobufagenin (a potent inhibitor of the sodium–potassium pump) that could accelerate ventricular fibrosis and dysfunction.[19] Increased collagen deposition and cross-linking, and increased interstitial fibrosis with disturbance of calcium homeostasis are associated with aging, as is decreased coronary reserve and increased oxidative stress,[22] which combined with hypertension could contribute to DD and a predisposition to heart failure development.

Extracellular Matrix and Cytoskeleton in Hypertension

Extracellular matrix

Under ideal physiologic conditions, collagen synthesis and degradation are maintained in equilibrium in the extracellular matrix (ECM). Among structural alterations, changes in the cardiac myocyte cytoskeleton and ECM have been implicated as potential underlying causes of DD.[23–25] The myocardial ECM is composed of three important constituents:[26] (1) fibrillar protein, such as collagen type I, collagen type III, and elastin; (2) proteoglycans; and (3) basement membrane proteins, such as collagen type IV, laminin, and fibronectin. Alterations in ECM fibrillar collagen, including the amount, geometry, distribution, degree of cross-linking, and ratio of collagen type I versus collagen type III, contribute to the development and reversal of DD. Major regulators of collagen synthesis include those that are mechanical (eg, relating to ventricular load, including preload and afterload) and neurohumoral (eg, the RAAS and the sympathetic nervous system) as well as numerous growth factors and cytokines (eg, transforming growth factor, connective tissue growth factor, platelet-derived growth factor, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor, interleukin 1, and tumor necrosis factor).[19,27] Collagen

degradation is under the control of proteolytic enzymes, which include a family of zinc-dependent enzymes, the matrix metalloproteinases.[26,28] In hypertension and aging, the rate of collagen turnover increases greatly, and although both synthesis and degradation are increased, the disequilibrium primarily is the result of a rapid increase in collagen synthesis.[19] These structural changes in the ECM result in fibrosis of the myocardium, leading to increased ventricular stiffness, impaired relaxation, and DD.

Age-related formation of advanced glycation end products results in increased collagen cross-linking, which is further aggravated by hypertension and diabetes, resulting in increases of ventricular and vascular stiffness.[19] The advanced glycation end products have been shown to be responsible for increases in proinflammatory activity, increased production of superoxide anions and oxidative stress, and the inducement of premature senescence of endothelial cells,[29] contributing to increased ventricular fibrosis and DD.

Cytoskeleton and cardiac myocyte

Restoration of diastolic calcium ion levels in the cytosol governs the active phase of diastolic relaxation of the cardiac myocyte. Abnormalities of calcium reuptake in the cardiac myocyte may cause LV diastolic abnormalities and impaired relaxation. Phosphorylation of phospholamban, a sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA2a) inhibitor, by protein kinase A or Ca^{2+}/calmodulin-dependent kinase attenuates inhibition of SERCA2a, thus accelerating relaxation. The energy-dependent reuptake of the cytosolic calcium back into the sarcoplasmic reticulum may explain why DD develops earlier than myocardial contraction abnormality. Abnormal sarcoplasmic reticulum calcium reuptake can be caused by a decrease in SERCA2a, abnormalities in the sarcolemmal channels, and changes in the phosphorylation state of the proteins that modify SERCA2a function.[26] Interference with the rapid uptake of the cytosolic calcium results in a slower rate of LV relaxation as the result of decreased elastic recoil from the energy stored during systole,[9] leading to delayed mitral valve opening, a lower early transmitral gradient, and a shift to a LV filling pattern that has a greater proportion of filling at atrial contraction, causing increased left atrial pressure.[30] With aging, SERCA2a receptor concentration declines[31] and hypertension causes a predisposition to prolonged calcium-decay time, elevated diastolic calcium ion levels in response to force-frequency stimulation, and decreased SERCA2a receptor concentration, as shown in animal models with DD, causing excessively slow diastolic relaxation time.[32] Excessively slow diastolic relaxation causes a predisposition to elevated diastolic pressures, more so at high heart rates and with exercise.

Changes in the cytoskeletal proteins may alter diastolic function.[33,34] These changes could be in the microtubule architecture, and increased network density and distribution could contribute to altered viscosity and increased myocardial and cardiomyocyte stiffness.[35] Similarly, changes in the titin isotypes could alter relaxation and viscoelastic stiffness in pressure overload situations.[26] An increased collagen volume fraction, higher cardiomyocyte diameter, and higher resting cardiomyocyte tension have been correlated with LV diastolic stiffness and HFPEF.[36,37] Administration of protein kinase A to cardiomyocytes from subjects in a diastolic heart failure group lowered resting cardiomyocyte tension to control values, suggesting that reduced phosphorylation of sarcomeric proteins is involved in HFPEF.[36,37]

Endothelial and neurohormonal function

The endothelium plays a major role in the regulation of vascular tone, and disruption in the endothelial function and neurohormonal activation is present in people who have

hypertension before overt vascular changes.[38] Endothelial dysfunction has been shown to adversely impact coronary reserve flow and ventricular diastolic and systolic function.[38,39] Acute activation or inhibition of neurohumoral and cardiac endothelial systems has been shown to alter relaxation and stiffness.[39] Chronic activation of the RAAS increases ECM fibrillar collagen content, promotes hypertrophy of the cardiac myocytes, causes a marked increase in tissue aldosterone, causes an increase in perivascular interstitial fibrosis,[40] and has been associated with increased ventricular stiffness.[26] Inhibition of the RAAS prevents or reverses this increase in fibrillar collagen and generally but not consistently reduces myocardial stiffness.[26] Aldosterone may be a mediator of adverse vascular and myocardial remodeling and contribute to increased inhibition of nitric oxide synthesis, endothelial dysfunction, and myocardial stiffness. A high level of angiotensin II in cardiac tissue activates an increase in local cardiac endothelin-1 synthesis, which via ETB receptors stimulates aldosterone release, and this in turn may increase collagen production.[41] Administration of spironolactone, an aldosterone blocker and inhibitor of the rennin angiotensin and aldosterone system, to patients who have HFPEF has been shown to relieve symptoms and decrease left atrial area (size), suggesting a beneficial effect on diastolic function.[42]

Left Ventricular Hypertrophy and Cardiac Remodeling in Hypertension

The prevalence of LVH is closely associated with advancing age and the severity of hypertension, ranging from 6% in people younger than 30 years of age to 43% in those older than age 69,[43] and from 20% to 50% in people who have mild to severe hypertension.[44] An increase in protein synthesis and deposition by protein and collagen in the ECM and an increase in the size and heightened organization of force-generating units (sarcomeres) within individual myocytes are the hallmarks of LVH in hypertensive hearts.[45] Pathologic hypertrophy occurs in response not only to increased hemodynamic load but also to neurohumoral activation and altered genotypes, leading to an increase in cardiac myocyte size and heightened organization of the sarcomeres (indicated by bold, parallel bands of sarcomeric proteins on microscopic examination).[45] LVH undoubtedly reflects the progressive sequelae of hypertension on the heart and is associated with abnormalities of diastolic function.

Changes induced by volume and pressure overload or a combination of both cause different LV geometric adaptations in patients who have hypertension, including changes in normal geometry, concentric ventricular remodeling, or eccentric or concentric hypertrophy; these adaptations can be used to identify groups with distinctive pathophysiologic patterns (Fig. 2). Increased LV mass (LVM) and LVH are powerful and independent predictors of conditions that can cause CV morbidity and mortality, including sudden death, ventricular dysrhythmias, heart failure, and coronary artery disease.[46,47]

In the general population, left atrial enlargement is associated both with the duration of elevated blood pressure and with the level of systolic blood pressure that is present in severe hypertension,[48] and it is a finding that is frequently associated with hypertension and may signify LV dysfunction even before clinical evidence of LVH can be found.[49,50] Left atrial size increases with increasing LV filling pressure and correlates with Doppler evidence of DD and with increasing severity of DD as defined by invasive hemodynamic study.[51] Increased left atrial volumes are increasingly viewed as a chronic marker for DD, and atrial dilation frequently occurs with aging, which can contribute to alterations in left atrial pressure and therefore with reduced early diastolic filling.[52]
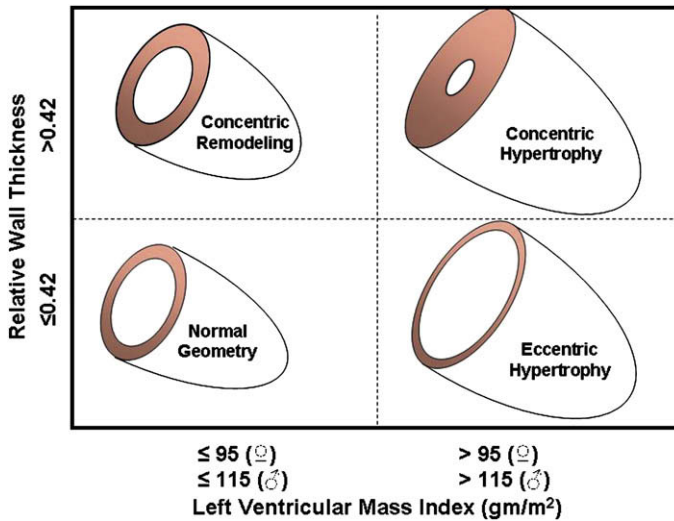
Fig. 2. Patients with hypertension can either have normal LV geometry (normal LV mass and relative wall thickness (RWT) $\leq$ 0.42), concentric remodeling (normal LV mass with RWT $\geq$ 0.42), increased LV mass with either concentric (RWT $\geq$ 0.42) or eccentric (RWT $\leq$ 0.42) hypertrophy.

Vascular and Ventricular Interaction in the Pathogenesis of Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction

Ventricular and vascular stiffness increase with advancing age, and they are further amplified by the presence of hypertension and diabetes. Vascular stiffening results secondary to arterial remodeling from collagen cross-linking, from geometric changes, and from alterations in endothelial function, structural protein composition, and neurohumoral signaling.[53] Increased central arterial stiffness contributes directly to the generation of wide pulse pressure and elevated systolic pressure. With widening pulse pressure and increased central arterial stiffness, the primary reflected waves arrive back at the aortic root during the late systole, where they interact with the incident wave and add to the central pulse pressure and the LV afterload. An increase in the net and late-systolic afterload alters ventricular systolic and diastolic function, increasing the myocardial work load and myocardial oxygen consumption, which leads to impairment of CV reserve function and labile systemic blood pressures, diminished coronary flow reserve, impaired diastolic relaxation, and increased diastolic filling pressures.[54,55] Recently, investigators demonstrated that early myocardial velocities as assessed using Doppler tissue imaging were inversely related to vascular stiffness and net afterload and directly related to total arterial compliance and that myocardial relaxation was strongly related to the pulsatile component, particularly late-systolic load.[54,56] Parallel increases in ventricular and vascular stiffening associated with advancing age and female gender may contribute to the enhanced prevalence of DD and HFPEF among the elderly, and elderly women in particular.[4]

ASSESSMENT OF DIASTOLIC FUNCTION

DD is characterized by impairment of isovolumetric ventricular relaxation, decreased ventricular compliance, and an abnormally increased LV end diastolic pressure. Impaired relaxation can be assessed by measurement of the peak instantaneous

rate of LV pressure decline (–dP/dt) using a high-fidelity micromanometer catheter, increased τ (time constant of relaxation), or prolonged isovolumetric relaxation time (IVRT), which is the period of time between aortic valve closure and mitral valve opening. LV end diastolic pressure can be reliably estimated during cardiac catheterization and has been considered as a gold standard for assessment of LV filling pressure.[57] Given that cardiac catheterization is invasive and impractical for daily practice, echocardiography is the most commonly used tool to assess diastolic function and LV filling pressure noninvasively and to differentiate between systolic and diastolic LV dysfunction.

Images showing mitral inflow velocities produced on pulse wave Doppler (**Fig. 3**) are used to initially characterize LV filling. The early mitral inflow (E wave) velocity represents the dynamics of the pressure gradient between the left atrium and the left ventricle and is influenced by LV compliance and left atrial pressure at the end of the LV systole. The second part of the mitral inflow velocity (A wave) is impacted by atrial contractility and LV compliance. The deceleration time of the E wave velocity correlates with the length of time it takes to reach a point of equal pressure between the left atrium and left ventricle, and the IVRT is the time interval between aortic valve closure and mitral valve opening. In young people who do not have cardiac disorders of any kind, most of the inflow occurs in the early diastole, with an E/A ratio greater than 1.5, along with a short E-wave deceleration time of <180 milliseconds and an IVRT of<80 milliseconds. Early DD (grade I DD) is characterized by delayed LV relaxation, increased early diastolic pressures, and a reduced transmitral pressure gradient; it is accompanied by vigorous atrial contraction, and accordingly the E/A ratio becomes less than 0.9, with prolongation of the deceleration time (>240 ms) and IVRT (>90 ms).[58] With further worsening of diastolic function and impedance to atrial emptying (grade II DD), the left atrial pressure increases, leading to a higher E velocity and E/A ratio (0.9–1.5), a deceleration time of 160 to 240 milliseconds, and an IVRT of less than 90 milliseconds; this state has sometimes been referred to a pseudonormal filling pattern. With a restrictive filling pattern (grade III DD), the E/A ratio becomes greater than 2, with a reduction in deceleration time to less than 150 milliseconds, and an IVRT of less than 70 milliseconds. Patients who have a restrictive filling pattern but show improvement using maneuvers that reduce preload, such as using the Valsalva maneuver for impaired relaxation, have less severe DD and a better prognosis than those who have an irreversible restrictive pattern (grade IV DD).[58] These
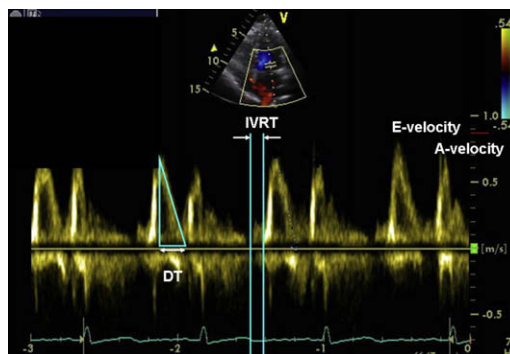
Fig. 3. Mitral inflow velocities profile on pulse wave Doppler. A-velocity, atrial component of mitral filling; DT, deceleration time; E-velocity, early diastolic mitral inflow velocity.

measures are limited by higher heart rates and atrial fibrillation. and they are highly preload dependent.

Pulmonary venous flow Doppler images recorded in the apical four-chamber view can provide an estimate of late diastolic LV pressure but are difficult to obtain.[59] An increase in early diastolic LV filling pressure is associated with a decrease in forward systolic flow (S velocity) and a more prominent diastolic velocity (D velocity). As left atrial afterload increases, there is more resistance to forward flow across the mitral valve, and flow reversal into the pulmonary veins (Ar velocity) increases both in duration (usually >35 ms) and amplitude (Ar velocity >30 cm/s).[59]

Using the color M mode in Doppler imaging, the flow propagation velocity (Vp) in the early diastole can be readily recorded using high temporal and spatial resolution.[58] The Vp (normal >50 cm/s) has a significant correlation with the intraventricular pressure gradient and LV relaxation.[60] The Vp was shown in earlier studies to be insensitive to preload changes; the ratio of mitral E velocity to Vp was used to correct for the influence of LV relaxation on E velocity, and thus to predict filling pressures, with an E/Vp ratio greater than 1.5 suggestive of a pulmonary capillary wedge pressure of greater than 15 mm Hg.[58,61] Again, these measures are highly preload dependent.

Given the limitations of the above measures, impaired LV relaxation may be better characterized through the evaluation of mitral annular motion using pulsed-wave tissue Doppler imaging (TDI). Pulsed-wave TDI is used to measure peak myocardial velocities and is particularly well suited to the measurement of long-axis ventricular motion because the longitudinally oriented endocardial fibers are most parallel to the ultrasound beam in the apical views and are less load dependent.[62] Because the apex remains relatively stationary throughout the cardiac cycle, mitral annular motion is a good surrogate measure of overall longitudinal LV contraction and relaxation.[62] During the diastole in patients with sinus rhythm, velocities can be recorded during the isovolumetric relaxation period and the early (Ea) and late (Aa) diastole (**Fig. 4**). When validated against invasive hemodynamic measures, TDI can be correlated with the time constant of isovolumetric relaxation. In adults older than 30 years of age, a lateral Ea velocity greater than 12 cm/s is associated with normal LV diastolic function. Reductions in lateral Ea velocity to 8 cm/s in middle-aged to older adults indicate impaired LV relaxation and can assist in differentiating a normal from a pseudonormal mitral inflow pattern.[58,62] A ratio of Ea velocity to mitral E velocity (E/Ea) can be used to reliably predict left ventricular filling pressure and has been shown to correlate to LV filling pressure obtained at cardiac catheterization.[63,64]
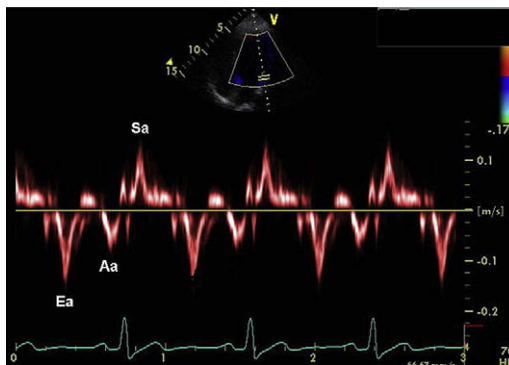
Fig. 4. Pulsed-wave TDI of the mitral annulus. Aa, atrial contraction; Ea, early diastolic motion; Sa, systolic myocardial motion.

The use of two-dimensional speckle tracking technology is a relatively new echocardiographic technique that can characterize myocardial function in terms of deformation or strain and by the rate of deformation or strain, and unlike velocity, it is not affected by tethering and translation. The global diastolic strain rate during the isovolumetric relaxation phase of the cardiac cycle (SRivr) behaves as a load-independent index of LV relaxation, relates well with the time constant of LV relaxation, and is less influenced by annular and valvular pathology and by preload. The relationship of the mitral E-wave velocity to the SRivr appears to relate well to an elevation in mean pulmonary capillary wedge pressure when compared with the E/Ea ratio.[65]

In the evaluation for DD, an echocardiographic assessment of left atrial volume and the LV mass index is imperative and cannot be ignored. The left atrial volume provides insight into the chronicity of elevation of LV filling pressure and is regarded as a barometer of the chronicity of DD, and to make an analogy, left atrial volume is to diastolic function and to all forms of heart disease as HbA_{1c} is to diabetes.[58] During ventricular diastole, the left atrium is directly exposed to LV pressure through the open mitral valve, and as an adaptation to the decreased ventricular compliance, left atrial pressure rises, increasing left atrial wall tension and stretching the atrial myocardium. Thus, increased left atrial volume and enlargement usually reflect elevated ventricular filling pressure,[58] are common findings in hypertension,[49] and provide useful criteria for classifying functional impairment in hypertensive heart disease.[50]

CURRENT THERAPEUTIC STRATEGIES FOR DIASTOLIC DYSFUNCTION AND HEART FAILURE WITH PRESERVED EJECTION FRACTION

Currently, the best evidence for improving structural abnormalities comes from clinical trials to date that have focused exclusively on patients who have systolic heart failure, postmyocardial infarction, or hypertension in which pharmacologic therapy using beta-blockers and inhibitors of RAAS has been shown to improve morbidity and mortality. Above all, DD has not been defined as a therapeutic target for prevention or treatment of HFPEF. Thus, the treatment recommendations are based upon empiric therapies and expert opinions.

Regular exercise and endurance training has been shown to reduce arterial pressure, improve endothelial function[39,66] in the vasculature, reduce ventricular and vascular stiffness, and even to prevent age-related increases in ventricular stiffness and development of DD,[67] which in turn could prevent increases in LV filling pressure during exercise and subsequent development of heart failure. Reduction in dietary salt lowers arterial pressure and could reduce arterial stiffness, improve diastolic function, and attenuate adverse CV effects of aging in patients who have hypertension.[20] Thus, lifestyle modification with regular exercise and dietary salt restriction should be encouraged in patients who have hypertension.

Optimal blood pressure reduction using agents such as diuretics, calcium antagonists, and RAAS antagonists can reduce CV-related morbidity and mortality and is associated with enhanced myocardial relaxation,[15,68] reduced central aortic stiffness,[69] and a dramatic reduction in the incidence of heart failure.[70] Blood pressure reduction using a combination of the angiotensin-converting enzyme inhibitor (ACEI) benazepril and the calcium-channel blocker amlodipine was found to be superior to the combination of the ACEI benazepril and the thiazide diuretic hydrochlorothiazide in reducing CV events (hazard ratio, 0.80 for the benazepril–amlodipine combination; 95% confidence interval, 0.72 to 0.90; *P*<.001) in the recently concluded Avoiding CV Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial.[71] The reduction in the central arterial systolic pressure is

believed to account for the greater effectiveness of the ACEI, angiotensin receptor blockers (ARBs), and calcium blocker compared with conventional diuretics and beta-blocking drugs in reducing adverse CV events in people who have hypertension.[69,72] The ACEI and ARBs inhibit the RAAS and prevent neurohormonal activation, reducing fibrillar collagen deposition[73] and myocardial stiffness and reversing LVH.[74] Some of these actions are thought to be load-independent mechanisms related to a blockade of angiotensin II-mediated myocyte hypertrophy, a reduction in the cardiac extracellular collagen matrix, and decreases in aldosterone release and bradykinin-mediated actions.[75,76] Long-term therapy with the ACEI ramipril in the Heart Outcomes Prevention Evaluation (HOPE)[77] study revealed favorable effects on LV structure and function by reducing LVM and LV volumes and the reduction loss in LVEF in high-risk patients who had vascular disease while controlling blood pressure and reducing CV mortality, myocardial infarction, and stroke.[78] Similarly, the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study demonstrated that treatment with the ARB losartan was associated with greater reduction in LV mass compared with the use of β-beta-blocker therapy, with a significant reduction in CV mortality and the number of heart failure–relatedhospitalizations.[74,79]

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Preserved trial did not show any beneficial effect for the ARB candesartan on CV death in patients who had heart failure and LVEF above 40%, but it showed a significantly reduced number of hospitalizations for heart failure (230 versus 279, $P = .017$), and there was a nonsignificant trend to reduction in the composite primary endpoint of CV death or heart failure–related hospitalizations (covariate-adjusted hazard ratio 0.86 for candesartan versus placebo, $P = .051$).[80] Similarly, in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial,[81] the ACEI perindopril failed to show any beneficial impact on the primary outcome, with a composite of all-cause mortality and unplanned heart failure–related hospitalizations secondary to insufficient power, but at the end of the first year, patients treated with perindopril were less likely to experienced the primary outcome (10.8% versus 15.3%, hazard ratio, 0.69; 95% CI, 0.47–1.01; $P = .055$) and hospitalization for heart failure (hazard ratio, 0.63; 95% CI, 0.41–0.97; $P = .03$) and they showed an improvement in functional class and a six-minute walk distance. Thus, there is a growing rational for use of inhibitors of the RAAS for the treatment of DD and the prevention of heart failure due to the additional cardioprotection achieved from these agents in patients who have a variety of CV disorders.

Despite evidence from the above studies, the recently published Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) study,[82] which was designed to evaluate the effect of the ARB irbesartan in patients who have HFPEF, failed to demonstrate a beneficial effect for irbesartan in reducing the primary outcome of death from any cause or hospitalization for a CV cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke) (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; $P = .35$).[82]

Even though no pharmacologic therapy has been shown to be effective in improving outcomes in patients who have HFPEF, reduction in arterial pressure has proven to be effective in improving diastolic function. The VALIDD trial was designed to test the hypothesis that lowering blood pressure using the ARB valsartan would improve diastolic function to a greater extent than lowering blood pressure using non-RAAS approaches in patients who have Stage 1 or 2 hypertension.[15] At the primary end point of the trial, diastolic function was evaluated using TDI of mitral annular relaxation velocities at baseline and after 38 weeks of therapy. The difference in blood pressure reduction between the two groups was not significant. The diastolic relaxation velocity increased by 0.60 cm/s from baseline in the valsartan group ($P<0.0001$) and by

0.44 cm/s from baseline in the placebo group (P<0·0001) by week 38 (**Fig. 5**). However, there was no significant difference in the change in diastolic relaxation velocity between the groups (P = 0.29).[15] Reduction in blood pressure was associated with increases in annular relaxation velocity, even after adjusting for baseline relaxation velocity, blood pressure, age, and study treatment group (P = 0·01), with a blood pressure reduction of 10 mm Hg or greater demonstrating the greatest degree of improvement in relaxation velocity (**Fig. 6**).[15] The investigators in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), in their analysis on the effect of the initial drug used to treat hypertension on the subsequent risk of heart failure requiring hospitalization stratified by ejection fraction, concluded that treatment of hypertension with the thiazide diuretic chlorthalidone reduced the risk of HFPEF compared with other therapies using amlodipine, lisinopril, or doxazosin; the hazard ratios were 0.69 (95% CI, 0.53 to 0.91; P = .009), 0.74 (95% CI, 0.56 to 0.97; P = .032), and 0.53 (95% CI, 0.38 to 0.73; P<.001), respectively.[83] Lowering arterial pressure and treating hypertension could be effective in improving diastolic function and reducing the risk of developing heart failure irrespective of the type of antihypertensive agent used, as supported by analysis of the VALIDD and ALLHAT studies.

In addition to adequate control of hypertension, therapies should be directed at controlling the heart rate and restoring the sinus rhythm in patients who have supraventricular tachyarrhythmias, reducing the congestive state, and avoiding coronary ischemia.[84] There are several ongoing studies of DD that may further add to our understanding of the pathophysiology and treatment of diastolic dysfunction. The EXforge Aggressive Control of Hypertension to Evaluate Efficacy in Diastolic Dysfunction trial is an investigator-initiated, randomized, open-label, blinded endpoint–design trial to test the effects of standard versus intensive blood pressure lowering using a combination of the calcium-channel blocker amlodipine plus the ARB valsartan on diastolic function and vascular stiffness in patients who have uncontrolled type II hypertension with preserved systolic function and echocardiographic evidence of DD. The National Institutes of Health–sponsored Treatment of Preserved Systolic Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, which is based on the observation that aldosterone-related myocardial fibrosis may play a similar role in the pathogenesis of age- and hypertension-related DD, is evaluating the effectiveness of aldosterone
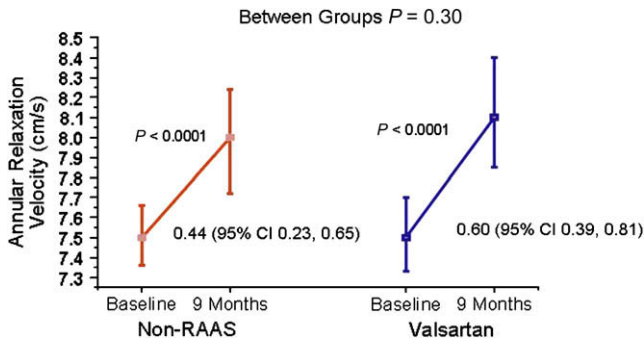
Fig. 5. Graph of the change in mitral annular relaxation velocity from baseline to follow-up in the VALIDD trial (non-RAAS, non–renin-angiotensin-aldosterone system). (*From* Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 2007;369:2079–87; with permission.)

Fig. 6. Graph of the change in diastolic function for each quartile of systolic blood pressure reduction in the VALIDD trial. Error bars are standard error. (*From* Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. Lancet 2007;369:2079–87; with permission.)
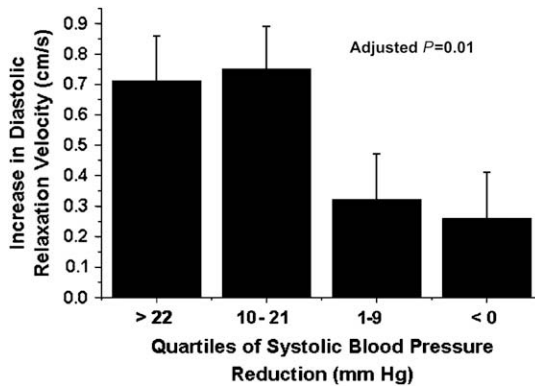
antagonist therapy in reducing all-cause mortality in patients who have HFPEF. The ongoing Effect of Losartan and Amlodipine on Left Ventricular Diastolic Function in Patients with Mild-to-Moderate Hypertension (J-ELAN) study is a multicenter, prospective, randomized trial designed to assess the effects of losartan and amlodipine on LV diastolic function in patients who have hypertension and DD in the absence of systolic dysfunction.[85] Novel therapeutic targets focusing on disease mechanism that have been identified and are under investigation include regression of hypertrophy by inhibition of rho-kinase[86] and phase II trials evaluating MCC-135 (Mitsubishi Pharma Corp. Compound, or Caldaret) in subjects who have chronic heart failure.[87]

SUMMARY

LVDD as an early measure of myocardial end-organ damage is commonly associated with hypertension and may well precede development of LVH in hypertension. About half of the patients presenting with heart failure have a normal ejection fraction, a clinical syndrome that is commonly referred to as HFPEF or diastolic heart failure and is commonly associated with impaired LV relaxation and increased diastolic stiffness. DD and HFPEF are commonly associated with advancing age and hypertension and increase in prevalence in association with these conditions, but there is a paucity of data on any specific therapeutic regimen. Hypertension control appears to be the most effective strategy in improving diastolic function and possibly for reducing the morbidity and mortality associated with HFPEF.

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