

New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part I

Diagnosis, Prognosis, and Measurements of Diastolic Function

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There is growing recognition that congestive heart failure (CHF) caused by a predominant abnormality in diastolic function (ie, diastolic heart failure) is both common and causes significant morbidity and mortality. However, there is continued controversy surrounding the definition of diastolic dysfunction and the diagnostic criteria for diastolic heart failure. As a result, clinical therapeutic trials have been slow to develop and difficult to design. Fortunately, these controversies are yielding to an emerging consensus. Recent clinical studies have provided sufficient data to develop standardized diagnostic criteria to define diastolic heart failure.¹⁻⁴ Experimental studies have provided increased insight into the mechanisms that cause diastolic heart failure.⁵⁻²² Together, these clinical and experimental studies are being used to design targeted clinical trials to test effective treatments for diastolic heart failure. The purpose of this 2-part article is to provide a perspective on these issues, highlight new research, and introduce emerging ideas. Part 1 will focus on the criteria used to diagnose diastolic heart failure, the effects of diastolic heart failure on prognosis, and measurements used to assess diastolic function. Part 2 will describe the mechanisms that cause diastolic heart failure and discuss approaches to treatment.

Definitions

Differentiating Diastolic Dysfunction From Diastolic Heart Failure

Heart failure is a clinical syndrome characterized by symptoms and signs of increased tissue/organ water and decreased tissue/organ perfusion. Standardized criteria to diagnose heart failure have been developed, perhaps the best validated of which come from the Framingham Study.²³ Definition of the mechanisms that cause this clinical syndrome requires measurement of both systolic and diastolic function. When heart failure is accompanied by a predominant or isolated abnormality in diastolic function, this clinical syndrome is called diastolic heart failure.

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. Abnormalities in diastolic function can occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome.

Definition of Diastolic Heart Failure

Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction (EF), and abnormal diastolic function. From a conceptual perspective, diastolic heart failure occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole, at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume. These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness. Diastolic heart failure can produce symptoms that occur at rest (New York Heart Association [NYHA] class IV), symptoms that occur with less than ordinary physical activity (NYHA class III), or symptoms that occur with ordinary physical activity (NYHA class II).

Definition of Diastolic Dysfunction

Conceptually, diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force. By extension, diastolic dysfunction occurs when these processes are prolonged, slowed, or incomplete. Whether this time period is defined by the classic concepts of Wiggers or the constructs of Brutsaert,²⁴ the measurements that reflect changes in this normal function generally depend on the onset, rate, and extent of ventricular pressure decline and filling and the relationship between pressure and volume or stress and strain during diastole. Moreover, if diastolic function is truly normal, these measurements must remain normal both at rest and during the stress of a variable heart rate, stroke volume, end-diastolic volume, and blood pressure.

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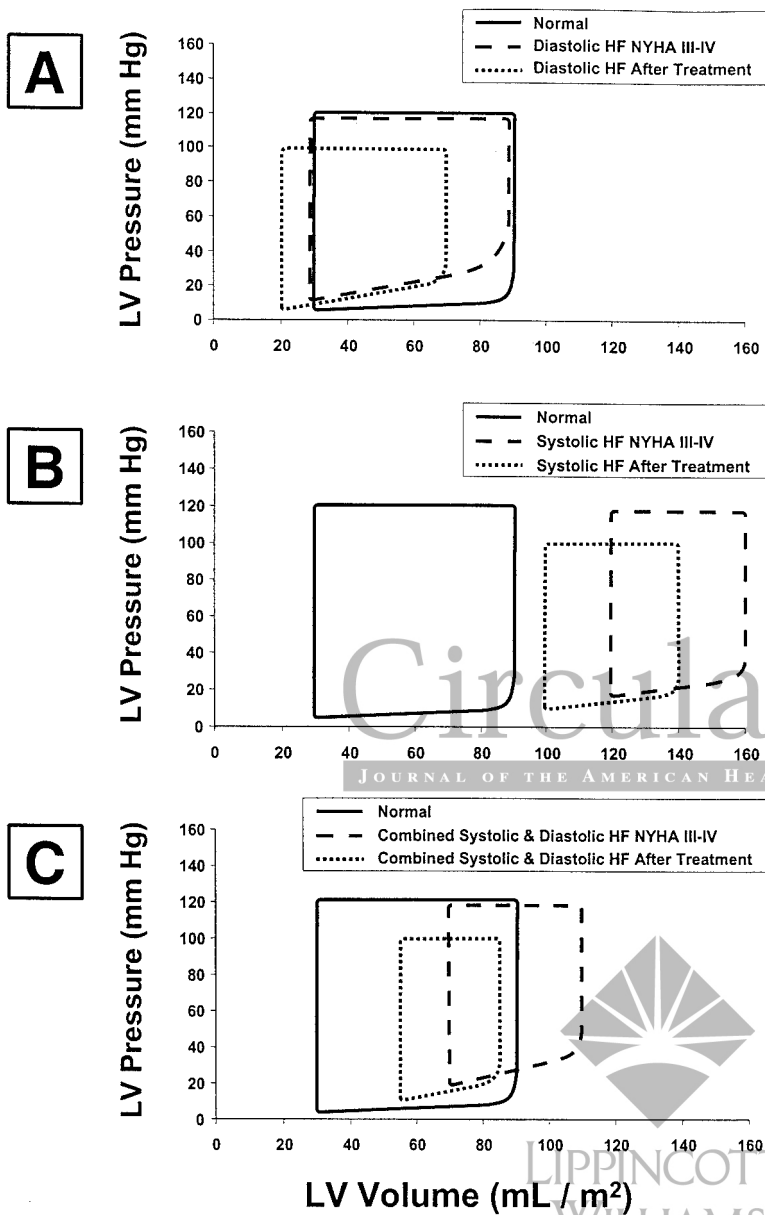


Figure 1. Pressure-volume loops contrasting isolated diastolic heart failure (A) with systolic heart failure (B) and combined systolic and diastolic heart failure (C). A normal patient (solid line) is compared with a patient with heart failure before (dashed line) and after (dotted line) treatment. HF indicates heart failure.

Definition of Combined Systolic and Diastolic Heart Failure

Diastolic heart failure can occur alone (Figure 1A) or in combination with systolic heart failure (Figure 1, B and C). In patients with isolated diastolic heart failure (Figure 1A), the only abnormality in the pressure-volume relationship occurs during diastole, when there are increased diastolic pressures with normal diastolic volumes. When diastolic pressure is markedly elevated, patients are symptomatic at rest or with minimal exertion (NYHA class III to IV). With treatment, diastolic volume and pressure can be reduced, and the patient becomes less symptomatic (NYHA class II), but the diastolic pressure-volume relationship remains abnormal.

In patients with systolic heart failure (Figure 1B), there are abnormalities in the pressure-volume relationship during systole that include decreased EF, stroke volume, and stroke work. In addition, there are changes in the diastolic portion of the pressure-volume relationship. These changes result in

increased diastolic pressures in symptomatic patients, which indicate the presence of combined systolic and diastolic heart failure. Whereas the diastolic pressure-volume relationship may reflect a more compliant chamber, increased diastolic pressure and abnormal relaxation reflect the presence of abnormal diastolic function. Thus, all patients with systolic heart failure and elevated diastolic pressures in fact have combined systolic and diastolic heart failure.

Another form of combined systolic and diastolic heart failure is also possible (Figure 1C). Patients may have only a modest decrease in EF and a modest increase in end-diastolic volume but a marked increase in end-diastolic pressure and a diastolic pressure-volume relationship that reflects decreased chamber compliance. Therefore, virtually all patients with symptomatic heart failure have abnormalities in diastolic function, those with a normal EF have isolated diastolic heart failure, and those with a decreased EF have combined systolic and diastolic heart failure.

TABLE 1. Prevalence of Specific Symptoms and Signs in Systolic vs Diastolic Heart Failure

	Diastolic Heart Failure (EF>50%)	Systolic Heart Failure (EF<50%)
Symptoms		
Dyspnea on exertion	85	96
Paroxysmal nocturnal dyspnea	55	50
Orthopnea	60	73
Physical examination		
Jugular venous distension	35	46
Rales	72	70
Displaced apical impulse	50	60
S ₃	45	65
S ₄	45	66
Hepatomegaly	15	16
Edema	30	40
Chest radiograph		
Cardiomegaly	90	96
Pulmonary venous hypertension	75	80

Data are presented as percent of patients in each group with the listed symptom or sign of heart failure.^{25,26} There were no statistically significant differences between patients with an EF >50% vs <50%.

Diagnosis

The diagnosis of diastolic heart failure cannot be made “at the bedside.” Differentiation between systolic and diastolic heart failure cannot be made on the basis of history, physical examination, ECG, or chest radiograph alone, because markers from these examinations occur with the same relative frequency in both systolic and diastolic heart failure (Table 1).^{25,26} It is for this reason that diagnostic criteria based on measurements of systolic and diastolic function have been developed.

The Working Group for the European Society of Cardiology proposed that “[a] diagnosis of primary diastolic heart failure requires three obligatory conditions to be simultaneously satisfied: 1) presence of signs or symptoms of congestive heart failure (CHF); 2) presence of normal or only mildly abnormal left ventricular (LV) systolic function; 3) evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness.”¹ These diagnostic criteria have been criticized for 3 reasons. The first obligatory condition requires the presence of signs “or” symptoms of CHF; however, it is well recognized that the mere presence of breathlessness and fatigue is not specific for the presence of CHF. It would be more prudent to include the term signs “and” symptoms of CHF or to use specific diagnostic criteria such as the Framingham criteria. The second criticism revolves around the term “systolic function.” The working group defined systolic function as being normal when LV EF is $\geq 45\%$. Because EF is not a measure of contractility or a load-independent measurement of systolic function, the second requirement would be more precise if stated simply as a normal EF. The third difficulty is the requirement that a measurable abnormality in diastolic function be present. Similar to measurements of systolic function, measurements

of ventricular relaxation, filling, and compliance are load dependent. Therefore, their poor specificity, sensitivity, and predictive accuracy, as well as the difficult practical aspects of making measurements of diastolic function, limit the application of this requirement in the clinical setting.

Vasan and Levy² proposed an expansion and refinement of these diagnostic criteria by suggesting that they be divided into definite, probable, and possible diastolic heart failure. Definite diastolic heart failure requires definitive evidence of CHF; objective evidence of normal systolic function, with an EF >50% within 72 hours of the CHF event; and objective evidence of diastolic dysfunction on cardiac catheterization. If objective evidence of diastolic dysfunction is lacking but the first 2 criteria are present, this fulfills the criteria for probable diastolic heart failure. If the first criterion is present and EF is >50% but not assessed within 72 hours of the CHF event, this fulfills the criteria for possible diastolic heart failure. Possible diastolic heart failure can be upgraded to probable diastolic heart failure if one of a number of additional criteria is present.

The clinical application of these guidelines is limited both because they are complex and because they are empiric. However, subsequent studies suggested methods to simplify the diagnostic criteria and provided objective data to validate them.^{3,4} Studies by Gandi et al³ addressed the requirement for the presence of an EF $\geq 50\%$ within 72 hours of the CHF event. This study demonstrated that in patients presenting to the emergency room with acute pulmonary edema and systolic hypertension (systolic blood pressure >160 mm Hg), there were no significant differences between EF measured echocardiographically at the time of presentation to the emergency room, when patients had active CHF, and 72 hours after the event, at a time at which patients were clinically stable and no longer in symptomatic heart failure. Therefore, under most circumstances, EF does not need to be measured coincident with the heart failure event. Measurement of EF within 72 hours is sufficient to meet diagnostic criteria for diastolic heart failure. The one possible exception to the use of this approach may be the presence of acute ischemia. However, >50% of the patients studied by Gandi et al³ had segmental wall-motion abnormalities on echocardiogram consistent with ischemic heart disease. Two patients had transient segmental wall-motion abnormalities that normalized with resolution of the pulmonary edema. None of these patients had a significant change in EF after 72 hours. It is possible that patients with pulmonary edema caused by acute ischemia are unable to generate high systolic pressure and/or have resolution of the ischemia before echocardiographic study; however, although it is unknown how often this occurs, it is likely to be infrequent. Thus, based on this study, to meet the diagnostic criteria for diastolic heart failure, EF must be >50% within 72 hours of the heart failure event. Whether this measurement can be delayed beyond 72 hours remains to be determined.

Zile et al⁴ examined the necessity of obtaining objective evidence of diastolic dysfunction. In this study, patients with a history of CHF who fulfilled the Framingham criteria and had an EF $\geq 50\%$ underwent diagnostic left heart catheterization and simultaneous Doppler echocardiography. None of

TABLE 2. Diastolic Heart Failure: Effects of Age on Prevalence and Prognosis

	Age, y		
	<50	50–70	>70
Prevalence	15	33	50
Mortality	15	33	50
Morbidity	25	50	50

All values are percentages.

Prevalence indicates percentage of all heart failure patients presenting with diastolic heart failure; Mortality, 5-year mortality rate; and Morbidity, 1-year rate of hospital admission for heart failure. The percentage values given in this table are approximate and rounded figures based on multiple studies.^{24,27–40}

these patients had evidence of coronary heart disease. Fewer than half of the patients had LV hypertrophy (defined as LV mass ≥ 125 g/m²). In this group of patients, 92% had at least 1 pressure-derived abnormality in diastolic function (including an LV end-diastolic pressure >16 mm Hg), 94% had at least 1 Doppler echocardiography–derived abnormality in diastolic function (including a deceleration time >250 ms), and 100% had at least 1 pressure or Doppler abnormality in diastolic function. Therefore, objective measurements of LV diastolic function serve to confirm rather than establish the diagnosis of diastolic heart failure. These authors concluded that the diagnosis of diastolic heart failure can be made without measurement of diastolic function if 2 criteria are present: (1) symptoms and signs of heart failure (Framingham criteria) and (2) LV EF $>50\%$.

Prognosis

Prevalence

The prevalence of diastolic dysfunction without diastolic heart failure and the prevalence of mild diastolic heart failure (NYHA class II) are not known. Early studies suggested that as many as one third of patients presenting with overt CHF have a normal EF and, therefore, isolated diastolic heart failure.^{27–29} However, more recent studies have made it clear that both the prevalence and prognosis (discussed below) of diastolic heart failure are dependent on age, sex, methods used to diagnose diastolic heart failure, study design, the value of EF that is used as a cutoff value, and the underlying clinical disease process that caused the diastolic heart failure.^{30–37} Whereas these determinants are largely interdependent, the most important determinant is likely to be age (Table 2). Studies examining prevalence of diastolic heart failure in hospitalized patients or in patients undergoing outpatient diagnostic screening and prospective community-based studies have shown that in patients >70 years old, the prevalence of diastolic heart failure approaches 50%.^{30–37}

Mortality

The prognosis of patients with diastolic heart failure, although less ominous than that for patients with systolic heart failure, does exceed that for age-matched control patients.^{38–40} The annual mortality rate for patients with diastolic heart failure approximates 5% to 8%. In comparison, the annual mortality rate for patients with systolic heart failure approximates 10% to 15%, whereas that for age-

matched controls approaches 1%. In patients with diastolic heart failure, the prognosis is also affected by the pathological origin of the disease. Thus, when patients with coronary artery disease are excluded, the annual mortality rate for isolated diastolic heart failure approximates 2% to 3%.^{39,40} The other determinants of mortality include age, EF cutoff, and study design. Like prevalence, these are interactive, with the most important determinant being age (Table 2). In fact, an increasing amount of data suggests that in patients >70 years old, the mortality rates for systolic and diastolic heart failure are nearly equivalent.^{30–37}

Morbidity

Morbidity from diastolic heart failure is quite high, which necessitates frequent outpatient visits, hospital admissions, and the expenditure of significant healthcare resources. The 1-year readmission rate approaches 50% in patients with diastolic heart failure. This morbidity rate is nearly identical to that for patients with systolic heart failure.^{30–37}

Measurement of Diastolic Function

Measurements of diastolic function can be divided into those that reflect the process of active relaxation and those that reflect passive stiffness. This division is in some ways arbitrary, because structures and processes that alter relaxation can also result in measurable abnormalities in stiffness. However, this division is pragmatic and provides a necessary scaffold on which to develop methods of measurement.

Relaxation

Diastole encompasses the period during which the myocardium loses its ability to generate force and shorten and then returns to resting force and length. Relaxation occurs in a series of energy-consuming steps beginning with the release of calcium from troponin C, detachment of the actin-myosin cross-bridge, phosphorylation of phospholamban, sarcoplasmic reticulum calcium ATPase–induced calcium sequestration into the sarcoplasmic reticulum, sodium/calcium exchanger–induced extrusion of calcium from the cytoplasm, slowing of cross-bridge cycling rate, and extension of the sarcomere to its rest length.^{5–9} Adequate energy supplies and the mechanisms to regenerate them must be present for this process to occur at a sufficient rate and extent.^{6,8,9} The rate of and extent to which these cellular processes occur determine the rate and extent of active ventricular relaxation. At the chamber level, this process results in LV pressure decline at constant volume (isovolumic relaxation), then LV chamber filling, which occurs with variable LV pressures (auxotonic relaxation). Measurements made during auxotonic relaxation are affected both by active relaxation and by passive stiffness.

Isovolumic relaxation can be quantified by measurement of LV pressure with a high-fidelity micromanometer catheter and calculation of the peak instantaneous rate of LV pressure decline, peak (–) dP/dt, and the time constant of isovolumic LV pressure decline, τ .^{41–43} When the natural log of LV diastolic pressure is plotted versus time, τ equals the inverse slope of this linear relation. Stated in more conceptual terms, τ is the time that it takes for LV pressure to fall by approximately two thirds of its initial value. When isovol-

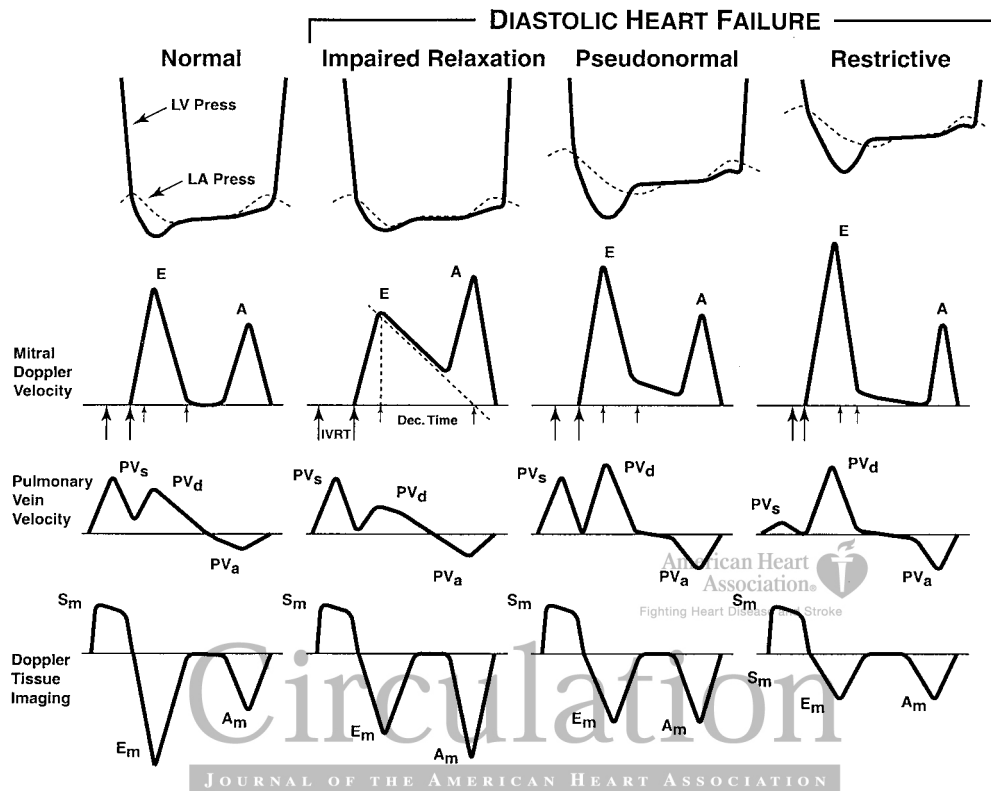


Figure 2. LV and left atrial (LA) pressures during diastole, transmitral Doppler LV inflow velocity, pulmonary vein Doppler velocity, and Doppler tissue velocity. IVRT indicates isovolumic relaxation time; Dec. Time, e-wave deceleration time; E, early LV filling velocity; A, velocity of LV filling contributed by atrial contraction; PVs, systolic pulmonary vein velocity; PVd, diastolic pulmonary vein velocity; PVa, pulmonary vein velocity resulting from atrial contraction; S_m , myocardial velocity during systole; E_m , myocardial velocity during early filling; and A_m , myocardial velocity during filling produced by atrial contraction.

mic pressure decline is slowed, τ is prolonged and the numerical value of τ increases. Noninvasive estimates of total isovolumic relaxation time can be made by echocardiographic techniques. No index of relaxation (isovolumic or auxotonic) can be considered an index of “intrinsic” relaxation rate unless loading conditions (and other modulators) are held constant or are at least specified. One practical way to overcome this limitation is to examine indices of relaxation over a range of loads. Afterload can be altered acutely by mechanical or pharmacological methods. Abnormal relaxation is indicated by the shift in the position of the relaxation rate-versus-afterload relationship, where relaxation is slowed at any equivalent systolic stress.⁴⁴

Whereas active relaxation may be regarded in the strictest sense as an early diastolic event, the time of onset of this process depends, at least in part, on systolic events such as the duration of contraction.²⁴ Conversely, the time of onset of relaxation can modify systolic events. Therefore, the rate and extent of relaxation, in addition to being dependent on ventricular load, are also dependent on the duration of systole, the time of onset of relaxation, and the time during systole in which load is altered.^{24,44,45} If the onset of relaxation is delayed (for example, by an increase in load early in systole), this may prolong the duration of systole, increase cardiac work during systole, and prolong relaxation. Conversely, if the onset of relaxation occurs earlier (for example, because of an increase in load late in systole), this may

shorten the duration of systole and may abbreviate relaxation. Thus, a complex interaction between events traditionally considered to occur during systole can affect the measurement and interpretation of active relaxation.

The auxotonic LV filling phases of diastole can be characterized by Doppler echocardiography or by radionuclide, conductance, or MRI techniques. Whereas each technique has advantages and disadvantages, all assess diastolic function by measuring indices of volume transients during ventricular filling. However, like all relaxation indices, auxotonic indices must be interpreted in light of simultaneous changes in load, both afterload and filling load (load present during filling).^{24,44,46} For example, the precise pattern of early and late diastolic transmitral flow velocities will depend on factors that govern instantaneous atrial and LV pressures before and after mitral valve opening and the resultant atrial-ventricular pressure gradient (filling load). Thus, it is not surprising that interventions or pathological conditions that increase left atrial pressure increase early transmitral flow velocities, whereas interventions that reduce left atrial pressure reduce early filling velocities. To correctly interpret changes in transmitral flow velocities, concomitant changes in filling load must be considered. Additional indices that may be less sensitive to and may indicate changes in load are currently under investigation.^{47–52} These include pulmonary venous flow rates, transmitral propagation velocity, and tissue Doppler velocity (Figure 2).

Stiffness

In addition to active relaxation, passive viscoelastic properties contribute to the process that returns the myocardium to its resting force and length. These passive viscoelastic properties are dependent on both intracellular and extracellular structures (see "Mechanisms" in part 2 of this report⁵³). Changes in the stiffness of the ventricular chamber can be assessed by examination of the pressure and volume relationship during diastole. Chamber stiffness is determined both by the stiffness of the constituent myocardium and by LV mass and the LV mass/volume ratio. Changes in myocardial stiffness can be assessed by examination of the myocardial stress, strain, and strain-rate relationships during diastole.

Chamber stiffness can be quantified by examination of the relationship between diastolic pressure and volume. The operating stiffness at any point along a given pressure-volume curve is equal to the slope of a tangent drawn to the curve at that point (dP/dV). Operating stiffness changes throughout filling; stiffness is lower at smaller volumes and higher at larger volumes (volume-dependent change in diastolic pressure and stiffness). Because the diastolic pressure-volume relationship is curvilinear and generally exponential, the relationship between dP/dV and pressure is linear; the slope (K_c), is called the modulus of chamber stiffness (or chamber stiffness constant) and can be used as a single numerical value to quantify chamber stiffness. When overall chamber stiffness is increased, the pressure-volume curve shifts to the left, the slope of the dP/dV -versus-pressure relationship becomes steeper, and K_c is increased (volume-independent change in diastolic pressure and stiffness). Thus, diastolic pressure can be changed either by a volume-dependent change in operating stiffness or by a volume-independent change in chamber stiffness.

Cardiac muscle behaves as a viscoelastic material, developing a resisting force (stress, σ) as myocardial length is increased (strain, ϵ) by ventricular filling. Strain is the deformation (increased length) of the muscle produced by the application of a force (increased stress). Myocardial stiffness can be quantified by examination of the relationship between myocardial stress and strain during diastole. At any given strain, myocardial stiffness is equal to the slope ($d\sigma/d\epsilon$) of a tangent drawn to the stress-strain relationship at that strain. Because the stress-strain relationship is curvilinear and exponential, the relationship between $d\sigma/d\epsilon$ and stress is linear, and the slope of this relation, K_m , is the modulus of myocardial stiffness (or myocardial stiffness constant). When myocardial stiffness is increased, the stress-strain relationship shifts to the left, so that for any given change in myocardial length (strain), there is a greater increase in force (wall stress) that develops to resist this deformation. In addition, the slope of the $d\sigma/d\epsilon$ -versus-stress relationship becomes steeper and K_m increases when myocardial stiffness is increased.

Thus, these measurements can be used to quantify changes in diastolic function that occur during the development of diastolic heart failure. These measurement techniques can also be used in experiments designed to identify the mecha-

nisms that cause diastolic heart failure. Finally, these measurement techniques can be used to evaluate the effectiveness of therapeutic strategies to treat diastolic heart failure. Part 2 of this article⁵³ will describe the mechanisms that have thus far been identified as playing a causal role in the development of diastolic heart failure and will discuss the efforts being made to develop clinical therapeutic trials that target these mechanisms.

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