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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This is Part I of a 2-part article. Part II will be published in the March 26, 2002, issue of *Circulation*.

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(*Circulation*. 2002;105:1387–1393.)

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/hc1102.105289**

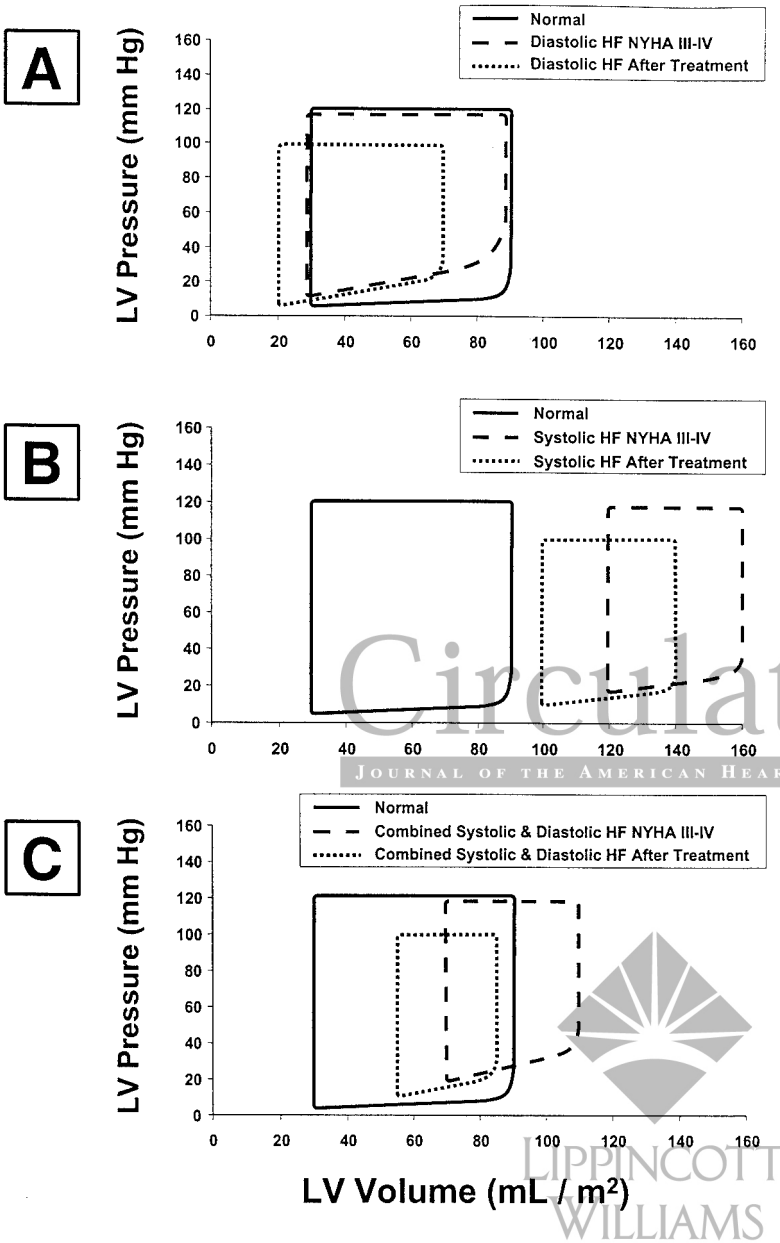

Figure 1. Pressure-volume loops contrasting isolated diastolic heart failure (A) with systolic heart failure (B) and combined systolic and diastolic heart failure (C). A normal patient (solid line) is compared with a patient with heart failure before (dashed line) and after (dotted line) treatment. HF 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 ≥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 Levy[2] 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 al[3] addressed the requirement for the presence of an EF ≥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 al[3] 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 al[4] 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 ≥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/m^2). 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 isovolu-

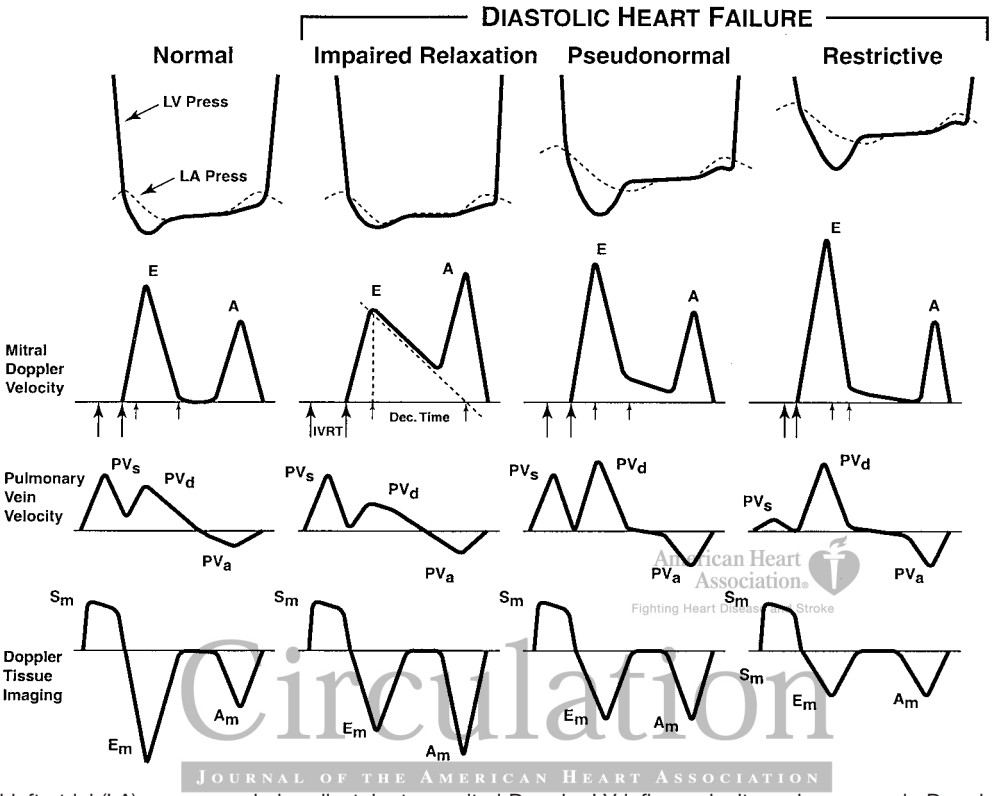

Figure 2. LV and left atrial (LA) pressures during diastole, transmitral Doppler LV inflow velocity, pulmonary vein Doppler velocity, and Doppler tissue velocity. IVRT indicates isovolumic relaxation time; Dec. Time, e-wave deceleration time; E, early LV filling velocity; A, velocity of LV filling contributed 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 report[53]). 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 ($d\sigma/d\varepsilon$) of a tangent drawn to the stress-strain relationship at that strain. Because the stress-strain relationship is curvilinear and exponential, the relationship between $d\sigma/d\varepsilon$ 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 $d\sigma/d\varepsilon$-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 mechanisms 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 article[53] 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.

Acknowledgments

The authors thank Bev Ksenzak for her help in the preparation of this manuscript. In addition, the authors thank William H. Gaasch, MD, for his critique of this review. Many of the concepts discussed in this review were originally formulated and later validated by Dr Gaasch, his collaborators, and his students. The authors are grateful for his unique insights and his ability to explain complex ideas in easily understood terms.

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KEY WORDS: heart failure ■ diastole ■ systole

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

Causal Mechanisms and Treatment

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As described in Part I of this 2-part article,[1] diastolic heart failure is common and causes significant alterations in prognosis. In Part II, experimental studies that have provided insight into the mechanisms that cause diastolic heart failure will be described.[2–19] In addition, current treatment strategies and the design of future clinical trials of diastolic heart failure will be discussed. The development of truly effective therapy for diastolic heart failure depends on gaining a clear understanding of the basic mechanisms that alter diastolic function and the ability to efficiently target these mechanisms to correct these abnormalities in diastolic function.

Mechanisms That Cause Diastolic Dysfunction

Conceptually, the mechanisms that cause abnormalities in diastolic function that lead to the development of diastolic heart failure can be divided into factors intrinsic to the myocardium itself (myocardial) and factors that are extrinsic to the myocardium (extramyocardial; Table 1). Myocardial factors can be divided into structures and processes within the cardiac muscle cell (cardiomyocyte), within the extracellular matrix (ECM) that surrounds the cardiac muscle cell, and that activate the autocrine or paracrine production of neurohormones. Each of these mechanisms are active in the major pathological processes that result in diastolic dysfunction and heart failure. Myocardial and extramyocardial mechanisms, cellular and extracellular mechanisms, and neurohumoral activation each play a role in the development of diastolic heart failure caused by ischemia, pressure-overload hypertrophy, and restrictive and hypertrophic cardiomyopathy.

Cardiomyocyte

Diastolic dysfunction can be caused by mechanisms that are intrinsic to the cardiac muscle cells themselves. These include changes in calcium homeostasis caused by (1) abnormalities in the sarcolemmal channels responsible for short- and long-term extrusion of calcium from the cytosol, such as the sodium calcium exchanger and the calcium pump; (2) abnormal sarcoplasmic reticulum calcium (SR Ca^{2+}) reuptake caused by a decrease in SR Ca^{2+} ATPase; and (3) changes in the phosphorylation state of the proteins that modify SR Ca^{2+} ATPase function, such as phospholamban, calmodulin, and calsequestrin. Changes in any of these processes can result in increased cytosolic diastolic calcium concentration, prolongation in the calcium transient, and delayed and slowed diastolic decline in cytosolic calcium concentration. These changes have been shown to occur in cardiac disease and cause abnormalities in both active relaxation and passive stiffness.[2]

The myofilament contractile proteins consist of thick-filament myosin and thin-filament actin proteins. Bound to actin are a complex of regulatory proteins that include tropomyosin and troponin (Tn) T, C, and I. During relaxation, ATP hydrolysis is required for myosin detachment from actin, calcium dissociation from Tn-C, and active sequestration of calcium by the SR. Modification of any of these steps, the myofilament proteins involved in these steps, or the ATPase that catalyzes them can alter diastolic function.[2–6] Thus, relaxation is an energy-consuming process. Energetic factors necessary to maintain normal diastolic function include the requirement that the concentration of the products of ATP hydrolysis (ADP and inorganic phosphate [Pi]) must remain low and produce the appropriate relative ADP/ATP ratio.[3–6] Diastolic dysfunction will occur if the absolute concentration of ADP or Pi increases or if the relative ratio of ADP/ATP rises. Abnormalities in these energetics factors may be caused by a limited ability to recycle ADP to ATP because of a decrease in phosphocreatine.

The cardiomyocyte cytoskeleton is composed of microtubules, intermediate filaments (desmin), microfilaments (actin), and endosarcomeric proteins (titin, nebulin, α-actinin, myomesin, and M-protein).[8] Changes in some of these cytoskeletal proteins have been shown to alter diastolic function.[7,8,20–25] Changes in titin isotypes have been shown to alter relaxation and viscoelastic stiffness. During contraction, potential energy is gained when titin is compressed, and during diastole, titin acts like viscoelastic springs, expends this stored potential energy, and provides a recoiling force to restore the myocardium to its resting length.[20,21] In addition,

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This is Part II of a 2-part article. Part I was published in the March 19, 2002, issue of *Circulation* (*Circulation*. 2002;105:1387–1393).

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(*Circulation*. 2002;105:1503-1508.)

***Circulation* is available at http://www.circulationaha.org** **DOI: 10.1161/hc1202.105290**

TABLE 1. Diastolic Heart Failure: Mechanisms

- Extramyocardial
  - Hemodynamic load: early diastolic load, afterload
  - Heterogeneity
  - Pericardium
- Myocardial
  - Cardiomyocyte
    - Calcium homeostasis
      - Calcium concentration
      - Sarcolemmal and SR calcium transport function
      - Modifying proteins (phospholamban, calmodulin, calsequestran)
    - Myofilaments
      - Tn-C calcium binding
      - Tn-I phosphorylation
      - Myofilament calcium sensitivity
      - α/β-myosin heavy chain ATPase ratio
    - Energetics
      - ADP/ATP ratio
      - ADP and Pi concentration
    - Cytoskeleton
      - Microtubules
      - Intermediate filaments (desmin)
      - Microfilaments (actin)
      - Endosarcomeric skeleton (titin, nebulin)
  - Extracellular matrix
    - Fibrillar collagen
    - Basement membrane proteins
    - Proteoglycans
    - MMP/TIMP
  - Neurohormonal activation
    - Renin-angiotensin-aldosterone
    - Sympathetic nervous system
    - Endothelin
    - Nitric oxide
    - Naturetic peptides

MMP indicates matrix metalloproteinase; TIMP, tissue inhibitor of matrix metalloproteinase.

titin extension during diastole is limited and protects the myocardium from being stretched too far beyond resting length. In experimental end-stage dilated cardiomyopathy, titin isoforms and distribution have been shown to change in a manner that confers an increase in stiffness.[21] Likewise, an increase in microtubule density and distribution has been shown in some forms of pressure overload to act as a viscous load and increase myocardial and cardiomyocyte viscoelastic stiffness.[7,22–25] This change in diastolic function is reversible when microtubules are acutely depolymerized by chemical or physical agents.[7,22–25]

Extracellular Matrix

Changes in the structures within the ECM can also affect diastolic function. The myocardial ECM is composed of 3 important constituents: (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. It has been hypothesized that the most important component within the ECM that contributes to the development of diastolic heart failure is fibrillar collagen.[11–15] The evidence that suggests that changes in ECM fibrillar collagen play an important role in the development of diastolic dysfunction and diastolic heart failure follows 3 lines. First, disease processes that alter diastolic function also alter ECM fibrillar collagen, particularly in terms of its amount, geometry, distribution, degree of cross-linking, and ratio of collagen type I versus collagen type III. Second, treatment of these disease processes, which is successful in correcting diastolic function, is associated with normalization of fibrillar collagen. Third, experiments in which a chronic alteration in collagen metabolism is accomplished result in an alteration of diastolic function.[26–31] The role played by other fibrillar proteins, the basement membrane proteins, and the proteoglycans remains largely unexplored.

The regulatory control of collagen biosynthesis and degradation has at least 3 major determinants: transcriptional regulation by physical, neurohumoral, and growth factors; posttranslational regulation, including collagen cross-linking; and enzymatic degradation.[17–19] Collagen synthesis is altered by load, including preload and afterload; neurohumoral activation, including the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system; and growth factors. Collagen degradation is under the control of proteolytic enzymes, which includes a family of zinc-dependent enzymes, the matrix metalloproteinases (MMPs).[17–19] The balance between synthesis and degradation results in the total collagen present in a given pathological state at a specific time. Changes in either synthesis or degradation and their regulatory processes have been shown to alter diastolic function and lead to the development of diastolic heart failure.

Neurohumoral and Cardiac Endothelial Activation

Both acutely and chronically, neurohumoral and cardiac endothelial activation and/or inhibition have been shown to alter diastolic function. Chronic activation of the RAAS has been shown to increase ECM fibrillar collagen and to be associated with increased stiffness. Inhibition of RAAS prevents or reverses this increase in fibrillar collagen and generally but not consistently reduces myocardial stiffness. In addition, acute activation or inhibition of neurohumoral and cardiac endothelial systems has been shown to alter relaxation and stiffness.[32] These acute pharmacological interventions act in a time frame too short to alter the ECM; therefore, their effect on diastolic function must be caused by direct action on the cardiomyocyte to alter 1 or more cellular determinants of diastolic function. For example, acute treatment of patients with pressure overload with an ACE inhibitor, a direct NO donor, or an indirect endothelin-dependent NO donor caused left ventricular (LV) pressure decline and LV filling to be more rapid and complete and caused the LV pressure-versus-volume relationship to shift to the right,

TABLE 2. Diastolic Heart Failure: Treatment

Symptom-targeted treatment
Decrease pulmonary venous pressure
Reduce LV volume
Maintain atrial contraction
Prevent tachycardia
Improve exercise tolerance
Use positive inotropic agents with caution
Nonpharmacological treatment
Restrict sodium to prevent volume overload
Restrict fluid to prevent volume overload
Perform moderate aerobic exercise to improve cardiovascular conditioning, decrease heart rate, and maintain skeletal muscle function
Pharmacological treatment
Diuretics, including loop diuretics, thiazides, spironolactone
Long-acting nitrates
β-Adrenergic blockers
Calcium channel blockers
Renin-angiotensin-aldosterone antagonists, including ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists
Disease-targeted treatment
Prevent/treat myocardial ischemia
Prevent/regress ventricular hypertrophy
Mechanism-targeted treatment
Modify myocardial and extramyocardial mechanisms
Modify intracellular and extracellular mechanisms

decreasing stiffness.[10] In addition, there is a cyclical release of NO in the heart that is most marked subendocardially and that peaks at the time of relaxation and filling. These brief bursts of NO release provide a beat-to-beat modulation of relaxation and stiffness.[9]

Treatment

General Approach

Unfortunately, there have been no randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic heart failure. Consequently, the guidelines for the management of diastolic heart failure are based on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on pathophysiological mechanisms.[33–36] The treatment regimen outlined below and in Table 2 applies to those patients with symptomatic diastolic heart failure. Whether treatment of asymptomatic diastolic dysfunction confers any benefit has not been examined.

Treatment of diastolic heart failure can be framed in 3 steps. First, treatment should target symptom reduction, principally by decreasing pulmonary venous pressure at rest and during exertion. Both nonpharmacological and pharmacological approaches proposed but not proven to be effective in targeting symptoms are listed in Table 2. Second, treatment should target the pathological disease that caused the diastolic heart failure. For example, coronary artery disease, hypertensive heart disease, and aortic stenosis provide relatively specific therapeutic targets, such as lowering of blood pressure, induction of hypertrophy regression, performance of aortic valve replacement, and treatment of ischemia by increasing myocardial blood flow and reducing myocardial oxygen demand. Third, treatment should target the underlying mechanisms that are altered by the disease processes.

Symptom-Targeted Treatment

Decrease Diastolic Pressure

The initial step in treating patients presenting with diastolic heart failure is to reduce pulmonary congestion by decreasing LV volume, maintaining synchronous atrial contraction, and increasing the duration of diastole by reducing heart rate. By decreasing LV diastolic volumes, LV pressures "slide" down the curvilinear diastolic pressure-volume relationship toward a lower, less steep portion of this curve. LV diastolic pressures can be decreased by reducing total blood volume (eg, through fluid and sodium restriction or use of diuretics), decreasing central blood volume (nitrates), and blunting neurohumoral activation. Treatment with diuretics and nitrates should be initiated at low doses to avoid hypotension and fatigue. Hypotension can be a significant problem, because these patients have a very steep diastolic pressure-volume curve such that a small change in diastolic volume causes a large change in pressure and cardiac output.

Both basic and clinical studies suggest that hypertrophy is associated with activation of neurohumoral systems such as the RAAS.[11,12] One mechanism that causes fluid retention and an increase in central and systemic volume is activation of these neurohumoral systems. Therefore, treatment for diastolic heart failure might include agents such as ACE inhibitors, AT_1 receptor antagonists, and aldosterone antagonists. In addition to promoting fluid retention, neurohumoral activation can have direct effects on cellular and extracellular mechanisms that contribute to the development of diastolic heart failure. Modulation of neurohumoral activation may also affect fibroblast activity, interstitial fibrosis, intracellular calcium handling, and myocardial stiffness.

Tachycardia is poorly tolerated in patients with diastolic heart failure for several reasons. First, rapid heart rates cause an increase in myocardial oxygen demand and a decrease in coronary perfusion time, which can promote ischemic diastolic dysfunction even in the absence of epicardial coronary disease, especially in patients with LV hypertrophy. Second, a shortened diastole may cause incomplete relaxation between beats, resulting in an increase in diastolic pressure relative to volume. Third, hearts with diastolic dysfunction exhibit a flat or even negative relaxation velocity–versus–heart rate relationship, so that as heart rate increases, relaxation rate does not increase or may even decrease, which can then cause diastolic pressures to increase.[37–39] β-Blockers and some calcium channel blockers can thus be used to prevent excessive tachycardia and produce a relative bradycardia. Although the optimal heart rate must be individualized, an initial goal might be a resting heart rate of ≈60 to 70 bpm with a blunted exercise-induced increase in heart rate.[40]

Improve Exercise Tolerance

Patients with diastolic heart failure have a marked limitation in exercise tolerance. There are a number of mechanisms

TABLE 3. Randomized Clinical Trials for Diastolic Heart Failure

Trial	Inclusion	End Points	Duration	Drug	Sponsor
CHARM	CHF; EF>40%	Mortality; hospitalization	3 y	Candesartan; placebo	AstraZeneca LP
Wake Forest	Hypertension; EF>50%	Exercise tolerance; Vo_2 max	6 mo	Losartan; hydrochlorothiazide	Merck
MCC-135	CHF; EF>40%	Exercise tolerance; remodeling	6 mo	MCC-135; placebo	Mitsubishi-Tokyo

CHARM indicates Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHF, congestive heart failure; EF, ejection fraction; Wake Forest, the effect of losartan versus hydrochlorothiazide on exercise tolerance in patients with exercise-induced hypertension and asymptomatic diastolic dysfunction; Vo_2max, maximum oxygen consumption; and MCC-135, a phase II, double-blind, randomized, placebo-controlled, dose-comparative study of the efficacy, tolerability, and safety of MCC-135 in subjects with chronic heart failure, New York Heart Association class II/III.

responsible for this limitation. In patients with diastolic heart failure, the ability to use the Frank-Starling mechanism is limited despite the increased filling pressures because increased diastolic stiffness prevents the increase in LV end-diastolic volume that normally accompanies exercise.[41–44] The abnormal relaxation velocity–versus–heart rate relationship that exists in patients with diastolic heart failure prevents augmentation of relaxation velocity as heart rate increases during exercise.[37–39] As a result, during exercise, diastolic pressure increases, the stroke volume fails to rise, and patients experience dyspnea and fatigue. In patients with diastolic heart failure, there is frequently an exaggerated rise in blood pressure in response to exercise that increases LV load and in turn further impairs myocardial relaxation and filling.[45]

β-Blockers, calcium channel blockers, and AT_1 antagonists may have a salutary effect on symptoms and exercise capacity in many patients with diastolic heart failure. However, the beneficial effect of these agents on exercise tolerance is not always paralleled by improved LV diastolic function or increased relaxation rate. Nonetheless, a number of small clinical trials have shown that the use of these agents results in improvement in exercise capacity in patients with diastolic heart failure.[46–48]

Use Positive Inotropic Drugs With Caution

Positive inotropic agents are generally not used in the treatment of patients with isolated diastolic heart failure because the ejection fraction is preserved, and there appears to be little potential benefit. Moreover, such drugs have the potential to worsen the pathophysiological processes that cause diastolic heart failure. In contrast to long-term use, positive inotropic drugs may be beneficial in the short-term treatment of pulmonary edema associated with diastolic heart failure because they enhance SR function, promote more rapid and complete relaxation, increase splanchnic blood flow, increase venous capacitance, and facilitate diuresis.[49–52] However, even short-term treatment with these agents may adversely affect energetics, induce ischemia, raise heart rate, and induce arrhythmias. Therefore, these agents should be used with caution, if they are used at all.

Results of the Digitalis Investigation Group trial[53] suggested that patients with heart failure and a normal ejection fraction may have fewer symptoms and fewer hospitalizations if they are treated with digitalis. However, a detailed analysis of these data in patients with a preserved ejection fraction has not been published, and a beneficial effect has not been proved. Digitalis may produce an increase in systolic energy demands while adding to a relative calcium overload in diastole. These effects may not be clinically apparent under many circumstances, but during hemodynamic stress or ischemia, digitalis may promote or contribute to diastolic dysfunction.[53] Therefore, the utility of digitalis in the treatment of diastolic heart failure remains unclear.

Differences Between Pharmacological Treatment of Systolic and Diastolic Heart Failure

With a number of notable exceptions, many of the drugs used to treat diastolic heart failure are in fact the same as those used to treat systolic heart failure. However, the rationale for their use, the pathophysiological process that is being altered by the drug, and the dosing regimen may be entirely different depending on whether the patient has systolic or diastolic heart failure. For example, β-blockers are now recommended for the treatment of both systolic and diastolic heart failure. In diastolic heart failure, however, β-blockers are used to decrease heart rate, increase the duration of diastole, and modify the hemodynamic response to exercise. In systolic heart failure, β-blockers are used chronically to increase inotropic state and modify LV remodeling. In systolic heart failure, β-blockers must be titrated slowly and carefully over an extended time period. This is generally not necessary in diastolic heart failure. Diuretics are used in the treatment of both systolic and diastolic heart failure. However, the doses of diuretics used to treat diastolic heart failure are generally smaller than the doses used in systolic heart failure. Some drugs are used only to treat either systolic or diastolic heart failure but not both. For example, calcium channel blockers such as diltiazem, nifedipine, and verapamil have no place in the treatment of systolic heart failure. By contrast, each of these has been proposed as being useful in the treatment of diastolic heart failure.

Mechanism-Targeted Treatment (Future Directions)

Conceptually, an ideal therapeutic agent should target the underlying mechanisms that cause diastolic heart failure. Therefore, a therapeutic agent might improve calcium ho-

meostasis and energetics, blunt neurohumoral activation, or prevent and regress fibrosis. Fortunately, some pharmaceutical agents that fit these design characteristics are already in existence, and many more are under development. Unfortunately, randomized, double-blind, placebo-controlled, multicenter trials that examine the efficacy of these agents used either singly or in combination have been slow to develop. Difficulties that have prevented these kinds of studies have included a lack of recognition of the importance of diastolic heart failure, an inability to define a homogeneous study population, a lack of agreement on the definition and diagnostic criteria for diastolic heart failure, and a perception that there would be a marginal return on investment for funding these kinds of studies. There is now, however, reason for a great deal of optimism. Diastolic heart failure is now recognized as an important problem, guidelines for diagnosis have been developed, and the pharmaceutical industry has supported (and it is hoped that in the near future, government agencies will support) randomized, double-blind, placebo-controlled, multicenter trials. Three such trials are now under way (Table 3). Two of these trials target neurohumoral activation in the RAAS by inhibiting the angiotensin II receptor (Candesartan cilexetil in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM] and Wake Forest). The third study targets intracellular calcium homeostasis using an agent that is proposed to improve SR calcium reuptake (MCC-135). With these 3 studies, and others that are currently under development, an effective treatment for diastolic heart failure will be more completely defined.

Acknowledgments

The authors thank Bev Ksenzak for her help in the preparation of this manuscript. In addition, the authors thank William H. Gaasch, MD, for his critique of this review. Many of the concepts discussed in this review were originally formulated and later validated by Dr Gaasch, his collaborators, and his students. The authors are grateful for his unique insights and his ability to explain complex ideas in easily understood terms.

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KEY WORDS: heart failure ■ diastole ■ systole