Contractile Behavior of the Left Ventricle in Diastolic Heart Failure
With Emphasis on Regional Systolic Function

Gerard P. Aurigemma, MD; Michael R. Zile, MD; William H. Gaasch, MD

In diastolic heart failure, the left ventricular (LV) ejection fraction (EF) is normal and there is increased passive stiffness with impaired relaxation of the ventricle, resulting in disturbances in the pattern of filling and elevated diastolic pressure.1–3 The mechanism underlying such failure has been thought to be principally diastolic because LV diastolic function is universally abnormal and systolic performance, function, and contractility are normal.4 However, several reports suggest that abnormalities in regional shortening are present in diastolic heart failure.5–9 The significance of these findings, especially their relation to the syndrome of heart failure, remains uncertain. Accordingly, we will review some of the structural and functional differences between systolic and diastolic heart failure, and, emphasizing the systolic or contractile behavior of the left ventricle, we will attempt to reconcile what appear to be disparate conclusions about LV systolic function in patients with diastolic heart failure.

Structural Remodeling
The hearts of patients with systolic heart failure differ dramatically from those of patients with diastolic heart failure in regard to both gross and microscopic anatomic features. As will be seen, these anatomic differences tend to parallel physiological and functional differences in systolic and diastolic heart failure10,11 (Table 1).

LV Chamber Remodeling
Patients with diastolic heart failure generally exhibit a concentric pattern of LV remodeling and a hypertrophic process that is characterized by a normal or near-normal end-diastolic volume, increased wall thickness, and a high ratio of mass to volume with a high ratio of wall thickness to chamber radius.12 By contrast, patients with systolic heart failure exhibit a pattern of eccentric remodeling with an increase in end-diastolic volume, little increase in wall thickness, and a substantial decrease in the ratio of mass to volume and thickness to radius.13 These differences are highlighted in Figure 1.

The Cardiomyocyte and Extracellular Matrix
The aforementioned dramatic differences in organ morphology and geometry are paralleled by anatomic differences at the microscopic level. As shown in Figure 2, in diastolic heart failure the cardiomyocyte exhibits an increased diameter, and there is an increase in the amount of collagen with a corresponding increment in the width and continuity of the fibrillar components of the extracellular matrix.13–16 By contrast, in systolic heart failure, the cardiomyocytes are elongated, and there is degradation and disruption of the fibrillar collagen.13,14,17

Diastolic Dysfunction and Heart Failure
The term diastolic dysfunction indicates an abnormality of diastolic distensibility, filling, or relaxation of the left ventricle, regardless of whether the EF is normal or abnormal and whether the patient is symptomatic or asymptomatic. Thus, diastolic dysfunction refers to abnormal mechanical (diastolic) properties of the ventricle and is present in virtually all patients with heart failure. The term diastolic heart failure is used to describe patients with the signs and symptoms of heart failure, a normal EF, and LV diastolic dysfunction.

The structural remodeling of the heart that is seen in patients with heart failure is associated with substantial alterations in the systolic and diastolic function of the left ventricle. In systolic heart failure, the dominant abnormality is a contractile dysfunction with LV enlargement, afterload excess, and reduced EF. In diastolic heart failure, the dominant abnormality is diastolic dysfunction with normal or near-normal LV volume, increased relative wall thickness, normal EF, and elevated filling pressures. It should be recognized that not all patients with heart failure exhibit the gross structural changes shown in Figure 1. Indeed, some patients meet the criteria for diastolic heart failure with little or no evidence of LV hypertrophy or concentric remodeling. A minority exhibit relatively balanced systolic and diastolic dysfunction with a normal end-diastolic volume and a high LV mass to volume ratio but low EF.
Diastolic function is determined by the passive elastic properties of the left ventricle interacting with the active process of relaxation. Abnormalities of the passive elastic properties are largely caused by alterations in the extramyocardial collagen network, but changes within the cardiomyocyte as well as geometric remodeling of the whole ventricle also contribute to an increase in passive stiffness. Impaired relaxation caused by hypertrophy or ischemia can effect further stiffening of the ventricle. As a result, the LV diastolic pressure-volume relationship is shifted up and to the left, chamber compliance is reduced (stiffness is increased), the time course of filling is altered, and the diastolic pressure is elevated.3,10–12,18,19

LV diastolic pressure-volume data from a group of patients with diastolic heart failure and a group with systolic heart failure are shown in Figure 3. In diastolic heart failure, the diastolic pressure-volume curve indicates an increase in LV passive stiffness. Thus, compared with a normal ventricle, the diastolic pressure is increased at any common volume. Under these circumstances, an increase in venous and/or arterial tone in association with a relatively small increase in central blood volume can produce a substantial increase in LV diastolic and pulmonary venous pressure, which may result in acute pulmonary edema.20 By contrast, patients with systolic heart failure exhibit a diastolic pressure-volume relationship that is displaced to the right (decreased chamber stiffness) (Figure 4).

The structural remodeling and functional disturbances described above are essential to the development of diastolic heart failure, but acute or subacute decompensation with congestive failure generally requires a precipitant or trigger. Thus, the underlying substrate for diastolic heart failure is often a hypertrophic or concentric remodeling of the ventricle with LV diastolic dysfunction. If the substrate is present, triggers acting alone or in combination can lead to decompensation and heart failure. In the absence of substrate, the triggers are generally well tolerated. The triggers (including dietary indiscretion with excessive sodium intake, medication noncompliance, hypertension, renal insufficiency, atrial fi-

**TABLE 1. LV Structure and Function in Chronic Heart Failure**

<table>
<thead>
<tr>
<th>Remodeling</th>
<th>Systolic Failure</th>
<th>Diastolic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-diastolic volume</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>End-systolic volume</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>Mass</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Geometry</td>
<td>Eccentric</td>
<td>Concentric</td>
</tr>
<tr>
<td>Cardiomyocyte</td>
<td>↑ Length</td>
<td>↑ Diameter</td>
</tr>
<tr>
<td>Extracellular matrix</td>
<td>↓ Collagen</td>
<td>↑ Collagen</td>
</tr>
</tbody>
</table>

**LV systolic properties**

<table>
<thead>
<tr>
<th>Performance</th>
<th>Stroke volume</th>
<th>Stroke work</th>
<th>Function</th>
<th>PR stroke work</th>
<th>Ejection fraction</th>
<th>Contractility</th>
<th>(+)dP/dt</th>
<th>End-systolic elastance</th>
<th>Stress shortening</th>
<th>Preload reserve</th>
<th>LV diastolic properties</th>
<th>EDP</th>
<th>Tau</th>
<th>Chamber stiffness</th>
<th>Myocardial stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(or normal)</td>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal (or ↑)</td>
<td>Normal</td>
<td>Exhausted</td>
<td>Normal (or ↑)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

PR indicates preload recruitable.

Figure 1. Autopsy (left) and echocardiographic (right) examples of the left ventricle imaged at the midventricular cross section in systolic heart failure (top), a normal heart (middle), and diastolic heart failure (bottom). Diastolic heart failure is characterized by a pattern of concentric LV remodeling with a normal or near-normal end-diastolic volume, increased wall thickness and mass, and a high ratio of mass to volume. By contrast, patients with systolic heart failure exhibit eccentric remodeling with an increased end-diastolic volume, little change in wall thickness, and a low ratio of mass to volume. (Cardiac specimen photographs courtesy of Dr Marvin Konstam. Reprinted from Journal of Cardiac Failure, volume 9, Konstam MA, “‘Systolic and diastolic dysfunction’ in heart failure? Time for a new paradigm,” pp 1–3, Copyright 2003, with permission from Elsevier.)
brillation) are similar to those that precipitate decompensation in systolic heart failure.21

The prevalence of diastolic heart failure and the prognosis of patients with the syndrome are well described,10,22 diagnostic criteria have been developed,23,24 and a variety of therapeutic trials are under way.2 However, questions and controversy about the contractile behavior of the left ventricle persist in part because of basic and important issues concerning terminology and definitions.

**Contractile Behavior: Definitions**

The most commonly used index of LV contractile function is the EF, which represents volume strain (change in volume divided by initial volume). It is, by definition, normalized and does not require consideration of body size. A large published body of literature supports the clinical utility of this parameter.25,26,27 However, the EF is influenced by acute or short-term as well as chronic alterations in preload, afterload, and contractility. A full assessment of the contractile behavior of the ventricle requires the combined use of indices that reflect LV systolic performance, function, and contractility, as well as a consideration of global and regional function.26 The definitions of these indices of contractile behavior are provided below.

*Ventricular performance* is a term that is used to describe the pumping ability of the left ventricle. The performance of...
curve suggests “depressed ventricular function.” Recognizing the difference in the diastolic pressure-volume curve relations in the 2 hearts (Figure 5, bottom) and plotting performance against end-diastolic volume lead to a distinctly different conclusion, namely, that the relation between systolic performance and end-diastolic volume is normal (Figure 5, top right). Thus, during acute interventions, end-diastolic volume provides a more direct reflection of end-diastolic fiber stretch than does end-diastolic pressure; when Frank-Starling ventricular curves are constructed, the use of end-diastolic pressure can be misleading. The appropriate analysis relates systolic performance to end-diastolic volume (eg, preload recruitable stroke work).

The term ventricular function has been generalized to include a variety of shortening parameters including EF and fractional shortening of the minor axis dimension. Midwall shortening has been used particularly in the study of hypertensive heart disease and concentric hypertrophic remodeling. Regional shortening has also been studied noninvasively by the technique of MRI tagging. Echocardiographic parameters that describe apex to base shortening include fractional shortening of the long axis and mitral annular systolic velocity, which is an approximation of the long-axis shortening velocity; these parameters as well as mitral annular displacement (measured in centimeters) are not normalized and therefore must be considered limited indices of function. Developments in Doppler technology allow measurement of regional LV systolic strain and strain rate, both of which are normalized/dimensionless and do not require correction for LV size (or body size), as will be discussed below.

The term ventricular contractility refers to the contractile or inotropic state of the whole ventricle. Indices of ventricular contractility have conventionally been divided into isovolumic phase indices (eg, peak positive dP/dt), ejection phase indices (eg, systolic wall stress versus endocardial shortening), and indices determined at the end of ejection (eg, end-systolic elastance). The concept of ventricular contractility is similar to that of myocardial contractility, but all indices of ventricular contractility are inextricably linked to and influenced by loading conditions and ventricular remodeling. Only if loading conditions and ventricular remodeling are considered or incorporated in the analysis can these parameters of “function” reflect changes in ventricular “contractility.” For example, peak positive dP/dt can be altered by an acute change in preload, but the influence of chronic geometric changes and remodeling on dP/dt is not well defined. By contrast, systolic elastance is not affected by acute changes in preload (it is determined by altering load); however, systolic elastance is affected by chronic changes in LV volume and mass.

Myocardial contractility refers to the basic property of heart muscle that reflects the intensity of cross bridge activity and is manifested as the extent and velocity of force development and fiber shortening. The contractile or inotropic state of the myocardium is therefore independent of loading and remodeling. Whereas myocardial contractility can be assessed in isolated cardiac muscle cells, muscle strips, or Langendorff-perfused hearts, its assessment in humans in vivo presents a continuing challenge.

The effect of diastolic dysfunction on the relation between LV systolic performance and preload. Classic ventricular function curves relating stroke work to end-diastolic pressure are shown in the top left panel; stroke work is related to end-diastolic volume in the top right panel; diastolic pressure-volume curves are shown below. When the LV end-diastolic pressure is used as an index of preload, ventricular systolic function in diastolic heart failure (D1, D2) appears to be less than normal (N1, N2). See text for details.

A classic ventricular function curve is constructed by plotting coordinates of performance (eg, stroke work) against an index of preload (eg, end-diastolic pressure or volume). When contractility is increased, the stroke work versus preload relationship is shifted upward, and when contractility is decreased, the relationship is shifted downward. A family of such ventricular function curves credits the ventricle for pressure and stroke volume multiplied by the mean arterial pressure. A limitation of the noninvasive method is that total pressure development and ejection, and, importantly, it incorporates load and contractility. Thus, stroke work calculated as the product of developed pressure and stroke volume credits the ventricle for pressure and shortening work in a single integrated index.

In Figure 5, systolic performance is plotted against end-diastolic pressure (top left), and a normal relation is illustrated (solid line). If this heart were subjected to a volume load, the coordinates of systolic performance and end-diastolic pressure would move up the curve (from point N1 to N2). If a similar volume load were applied to a noncompliant heart from a patient with diastolic heart failure, the coordinates would move up along a “depressed” curve, from point D1 to D2. In this case, the downward position of the Frank-Starling ven}

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**Figure 5.** The effect of diastolic dysfunction on the relation between LV systolic performance and preload. Classic ventricular function curves relating stroke work to end-diastolic pressure are shown in the top left panel; stroke work is related to end-diastolic volume in the top right panel; diastolic pressure-volume curves are shown below. When the LV end-diastolic pressure is used as an index of preload, ventricular systolic function in diastolic heart failure (D1, D2) appears to be less than normal (N1, N2). See text for details.
A description of LV contractile behavior requires measurement of the ability of the ventricle to develop force (pressure) and to shorten (stroke volume). A complete description requires measurement of both force and shortening and calculation of several indices of contractile behavior. There is, however, relatively little published information on LV contractile behavior in diastolic heart failure. The available data are reviewed below.

**Standard Techniques**

Using data derived from echocardiographic and catheterization studies, Baicu et al found that LV systolic performance, function, and contractility were normal in patients meeting published criteria for “definite” diastolic heart failure (Figure 6). In that study, stroke work and preload recruitable stroke work were normal and consonant with data published by others. Baicu et al also found values for LV maximum systolic elastance that were higher than normal. Others have made similar observations, but it is doubtful that this reflects a true increase in contractility because some chronic structural changes (eg, hypertrophy) can increase systolic elastance. If elastance is normalized for the LV mass/volume ratio, thereby adjusting for chronic remodeling, the result indicates normal contractility, a result that is more consistent with the data indicating normal performance and function.

Baicu et al found normal stress-shortening relations at the endocardial surface in patients with diastolic heart failure, but one third of the patients had depressed midwall stress-shortening relations (Figure 7). This has previously been described in hypertrophic hearts with normal shortening at the endocardium and no evidence of heart failure. For example, midwall indices of function are depressed in approximately one third of patients with hypertensive remodeling (either concentric LV hypertrophy or concentric LV hypertrophy).
remodeling),30,35 in a substantial number of patients with aortic stenosis,36 and even in some elderly individuals with concentric remodeling, in the absence of hypertension.37 The work of Baicu et al indicates, however, that despite a reduction in midwall shortening, the pumping function of the whole ventricle appears to be normal in diastolic heart failure.

**Tissue Doppler Techniques**

Methods used to evaluate regional systolic myocardial function have evolved from invasive and experimental tools (such as radiopaque markers and sonomicrometry crystals) to widely available noninvasive clinical methods, such as MRI, echocardiography, and tissue Doppler imaging (TDI). Fundamentally, each technique is based on measurements of regional length and velocity, which, when normalized to initial length, can be used to derive strain and strain rate. The advances in TDI technology have made it relatively easy to measure regional strain and strain rate. However, interpretation of these quantitative indices remains dependent on knowledge of both the engineering principles used to develop them and the basic mechanical laws governing LV and myocardial function.

**Methodology**

Given the wealth of recent studies utilizing TDI in various cardiac diseases and its recent application to the study of systolic function in diastolic heart failure, this technique will be reviewed in some detail. The general principle involved in TDI is the same that is involved in the measurement of blood flow velocity by conventional Doppler. Modifications in the image acquisition process permit direct measurement of tissue velocities. Ultrasound reflections from the fast-moving blood pool are high frequency and low amplitude, whereas those from slower-moving tissue are low frequency and high amplitude. The TDI technique requires filtering of the high-frequency, low-amplitude echoes originating from the blood pool, enabling measurement of the velocity of myocardial tissue. The velocity profile thus recorded is displayed either as a color or spectral display (Figure 8). Details concerning the mathematical derivation of strain and strain rate methods can be found in the online-only Data Supplement.

Standard TDI allows a Doppler sample volume (region of interest) to be placed in any myocardial structure (eg, interventricular septum; anterior, posterior, inferior, lateral wall of the left ventricle; or mitral anulus) from LV apex to base. Therefore, regional shortening and lengthening can be measured in the longitudinal direction. To date, most of the studies have measured velocity in the long-axis direction from the echocardiographic apical 4-chamber view. Standard TDI examination of a single region of interest will yield values of myocardial velocity in centimeters per second. If this velocity signal is integrated with respect to time, displacement (in centimeters) is derived.

Myocardial strain rate imaging, utilizing a newer generation of TDI technology, examines the velocity gradient between 2 points along the ultrasound beam separated by a selected distance, generally 5 to 10 mm. This velocity gradient is used to calculate myocardial strain rate in units of inverse seconds. If strain rate is integrated, myocardial strain, expressed as a percentage, can be derived. Systolic strain represents the normalized extent of deformation of a region of the LV in systole; strain rate represents the rate of this systolic deformation.

**Advantages/Disadvantages of Myocardial TDI**

Velocity and/or displacement measurements obtained by standard TDI have difficulty discriminating between actively contracting and “tethered” myocardium, wherein an akinetic segment may demonstrate motion if it is pulled by an adjacent segment that is functioning normally. In addition, the velocity and displacement parameters are not normalized for length or size. As a result, systolic displacement and velocity of a given
region would likely be greater in the heart of a larger subject than a smaller subject. Some of these limitations are avoided by using TDI measurements of myocardial systolic strain and strain rate. Because strain rate imaging measures a vector component of regional contraction, and the 2 points are equally affected by tethering and translation, the result is independent of the effect of tethering and translation. Strain and strain rate measurements are also appropriately normalized for length and are therefore more appropriate than standard TDI velocity measurements in assessing regional myocardial function. Strain and strain rate derived from myocardial TDI velocity gradient imaging have been validated in gel phantoms and in an animal model in which sonomicrometric crystals were used, and results agree closely with those obtained by MRI tissue tagging.

Indices of systolic function such as the extent and velocity of long-axis shortening, mitral annular systolic velocity, systolic atrioventricular plane displacement, and myocardial systolic strain and strain rate are not inherently less “load sensitive” than EF and fractional shortening. In fact, since all shortening or displacement indices are affected by loading conditions, it is not possible to conceive of a load-independent index of LV systolic function. For example, some investigators have confirmed a decline in myocardial strain and strain rate as afterload is increased in the normal heart. When the myocardium was injured by hypoxia, the slope of the inverse relationship between strain or strain rate and afterload decreased, so that a relatively large change in load caused a small change in strain or strain rate. These data imply that TDI indices are not independent of or insensitive to load, but they can be interpreted to mean that shortening may be less load dependent in depressed than in normal myocardium. Therefore, to determine whether a change in any measurement represents a specific change in LV function or contractility, factors such as preload, afterload, and remodeling must be either held constant or considered in the analysis.

**Clinical Data**

The emerging interest in these new technologies has led to an expansion of our understanding of regional ventricular function in a wide variety of clinical conditions, primarily systolic heart failure and LV hypertrophy. There are, however, relatively few such studies in patients with diastolic heart failure—2—4; the principal findings of these 5 studies are summarized in Table 2. These studies indicate that systolic displacement or motion of the atrioventricular plane or mitral annulus (as well as some myocardial velocities) can be abnormal in some patients with diastolic heart failure. These results have been taken as evidence that heart failure is caused by “subtle” systolic dysfunction,5—7 that diastolic heart failure exhibits a “coexistence” of or a “continuum” with systolic dysfunction,5—8 and that “long-axis function” can be impaired in diastolic heart failure.5—8 The implication is that the heart failure syndrome is related to, if not caused by, these regional disturbances in long-axis function. In our judgment, there are several reasons why this notion is problematic.

First, more than half of the patients in these 5 studies did not exhibit abnormalities in the functional parameters that were utilized. The mechanism underlying heart failure in these patients is unlikely to be a disturbance of long-axis function when only a minority of the patients exhibit this abnormality. By contrast, the diastolic properties of the ventricle are virtually always abnormal in these patients.3—4

Thus, it is more likely that the underlying mechanism(s) of the heart failure resides in diastole, especially when one considers the fact that patients with diastolic heart failure virtually always exhibit normal indices of LV systolic performance, function, and contractility.4

Second, abnormalities in shortening of the long axis have long been known to occur in patients with LV hypertrophy, in the absence of heart failure.30—32 Because many, if not most, patients with diastolic heart failure exhibit some degree of hypertrophy and/or concentric remodeling, the confirmation of abnormal long-axis shortening is not unexpected. These abnormalities likely represent markers of a hypertrophic heart that may have prognostic value or other significance, but it would seem unlikely that they are the dominant cause of failure in patients with diastolic heart failure.

Third, variations in long-axis shortening have relatively little impact on the EF or stroke volume; most of the stroke volume is produced by shortening of the minor axis dimension.42 For example, a ventricle with an ellipsoidal geometry...
and a normal EF (eg, 65%) and a normal circumferential fractional shortening (eg, 33%) will exhibit a relatively small decline in EF (≈6 to 7 percentage units) when long-axis shortening falls by one third. If long-axis shortening approaches zero, the EF can fall by as much as 10 percentage units, but the EF still remains >50%. This is seen, for example, after mitral valve replacement when the mitral chordae are transected.\(^4\) Therefore, isolated abnormalities in long-axis function such as those presented in Table 2 are unlikely to be responsible for a clinically significant decrement in LV systolic performance or function and therefore are unlikely to be responsible for heart failure.

Fourth, appropriate normalization methods were not used in any of the studies that are summarized in Table 2. The principles of normalization, first published a century ago, have been applied in a variety of clinical and experimental studies\(^5,44,45\); normalized indices of function (ie, those expressed in dimensionless terms) provide more consistent and reliable functional information than nonnormalized data (ie, those expressed in centimeters or centimeters per second). For example, some investigators have concluded that myocardial velocities at the base of the heart are substantially increased stiffness, we conclude that the dominant abnormality resides in systole and that the appropriate term for this form of heart failure is systolic heart failure.

In patients with diastolic heart failure, an abnormal and concentrically remodelled LV geometry is generally seen and the contractile behavior of the whole ventricle is normal, despite the presence of abnormal regional function in some patients. Parameters that reflect the diastolic properties of the ventricle are virtually always abnormal.\(^3,4\) For these reasons we have concluded that (1) the dominant functional abnormality resides in diastole and (2) “subtle” abnormalities in regional systolic function are unlikely to be responsible for heart failure in patients with diastolic heart failure.

**Acknowledgment**
The authors are indebted to Catalin Baicu, PhD, for contributions to the mathematical derivation as well as help with the illustrations, to Jacqueline Jolie for assistance with the preparation of the manuscript, and to Jeffrey Hill, RDMS, for assistance with the strain imaging data.

**Disclosures**
None.

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KEY WORDS: diastole ■ echocardiography ■ ventricles
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Circulation. 2006;113:296-304
doi: 10.1161/CIRCULATIONAHA.104.481465
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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