Is echocardiographic evaluation of diastolic function useful in determining clinical care?

Echocardiographic Evaluation of Diastolic Function Can Be Used to Guide Clinical Care

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For normal cardiac performance, the left ventricle (LV) must be able to eject an adequate stroke volume at arterial pressure (systolic function) and fill without requiring an elevated left atrial (LA) pressure (diastolic function). These systolic and diastolic functions must be adequate to meet the needs of the body both at rest and during stress.

Response by Tschöpe and Paulus on p 809

Systolic function is conveniently (although not always accurately) measured as the ejection fraction (EF), calculated as stroke volume divided by end-diastolic volume. The LV EF is easily interpreted. The lower limit of normal is 50%. The lower the EF is, the greater the reduction in systolic function. Diastolic function has been more difficult to evaluate. Traditionally, invasive measures of LV diastolic pressure-volume relations and the rate of LV pressure fall during isovolumetric relaxation have been used. However, these methods are not practical for routine clinical use and do not adequately evaluate all aspects of diastolic filling.

Comprehensive echocardiographic evaluation of the dynamics of LV filling using blood pool and tissue Doppler has now progressed so that it provides clinically important information that can be used to direct patient care. We present data that support the use of echocardiographic evaluation of diastolic function to recognize cardiac dysfunction in patients with heart failure, especially those with preserved EF; to guide the management of patients by identifying those with and without elevated left filling pressures regardless of underlying EF; and to determine prognosis in a wide variety of patient populations.

LV Filling

Although the LV end-diastolic pressure-volume relation describes the passive properties of the LV, LV filling is not a passive or slow process. In fact, the peak flow rate across the mitral valve is equal to or greater than the peak flow rate across the aortic valve. Understanding the physiological basis of LV filling provides the basis for the interpretation of the information available from a comprehensive echocardiographic evaluation of LV filling dynamics.

During LV ejection, energy is stored as the myocytes are compressed and the elastic elements in the myocardial wall are compressed and twisted. Relaxation of myocardial contraction allows this energy to be released as the elastic elements recoil. This causes LV pressure to fall rapidly during isovolumetric relaxation. Furthermore, for the first 30 to 40 milliseconds after mitral valve opening, relaxation of LV wall tension is normally rapid enough to cause the LV pressure to continue to decline despite an increase in LV volume. This fall in LV pressure produces an early diastolic pressure gradient from the LA that extends to the LV apex (Figure 1). This accelerates blood out of the LA and...
produces rapid early diastolic flow that quickly propagates to the apex. Because the diastolic intraventricular pressure gradient pulls blood to the apex, it can be considered a measure of LV suction. It is reduced in experimental models of heart failure and ischemia and in patients with ischemia, hypertrophic cardiomyopathy, and heart failure.

The rate of early LV filling is determined by the pressure gradient from the LA to the LV apex (Figure 1). Although peak filling occurs after the peak pressure gradient, the 2 are closely related. The lower the early diastolic LV pressure is, the greater the gradient for filling, allowing the heart to fill without requiring elevated LA pressure. Furthermore, the ability to decrease LV early diastolic pressure in response to stress allows an increase in LV stroke volume without much increase in LA pressure. LV relaxation is very sensitive to myocardial dysfunction, and the ability to increase LV filling without an increase in LA pressure is reduced or absent in heart failure.

After filling of the LV begins, the pressure gradient from the LA to the LV apex decreases and then transiently reverses (Figure 1). The reversed mitral valve pressure gradient decelerates and then stops the rapid flow of blood into the LV early in diastole. The time for flow deceleration is determined predominantly by the functional LV chamber stiffness and provides a noninvasive indication of LV diastolic operating stiffness.

During the midportion of diastole (diastasis), the pressure in the LA and LV equilibrates and mitral flow nearly ceases. Late in diastole, atrial contraction produces a second LA-to-LV pressure gradient that again propels blood into the LV. After atrial systole, as the LA relaxes, its pressure decreases below LV pressure, causing the mitral valve to begin closing. The onset of ventricular systole produces a rapid increase in LV pressure that seals the mitral valve and ends diastole.

The dynamics of LV filling and their alteration with diastolic dysfunction are noninvasively assessed from Doppler measurement of mitral inflow velocity and tissue Doppler assessment of mitral annular velocity. Under normal circumstances, the peak early mitral inflow velocity (E) substantially exceeds the peak velocity during atrial contraction (A). Thus, the E/A ratio is >1.

Because the LV apex remains fixed during the cardiac cycle, the mitral annular velocity provides a measure of long-axis shortening rate. Under normal conditions, peak early diastolic mitral annular velocity (e', which has also been called Ea, E'a, and EM) occurs coincidently with the mitral E (Figures 2 and 3). This is a manifestation of the symmetrical expansion of the LV in early diastole as blood moves rapidly to the LV apex in response to a progressive pressure gradient from the left atrium to the LV apex. Under normal
circumstances, both E and e’ respond to changes in the LA-to-LV pressure gradient. For example, both E and e’ normally increase in response to volume load and exercise.

In the presence of mild diastolic dysfunction with slow LV relaxation but without an increase in LA pressure, the early diastolic pressure gradient that accelerates flow is decreased as a result of a higher LV pressure (Figure 2). This results in a decrease in both the E and e’ with an increase in the importance of atrial contraction, producing an E/A ratio <1 (Figures 2 and 3). The delayed relaxation results in a prolongation of E-wave deceleration time (DT) and may be associated with a mid-diastolic peak of mitral flow (L wave). With increased flow from the LA to LV with atrial contraction, the LA is relatively empty at the beginning of systole, which results in increased systolic velocities in the pulmonary veins toward the LA. This filling pattern has been called an impaired relaxation pattern or grade 1 diastolic dysfunction. In most patients with impaired relaxation pattern, the mean LA pressure is not elevated despite an increased LV end-diastolic pressure that is maintained by a vigorous atrial contraction.

With progressive worsening of diastolic dysfunction associated with an increase in LA pressure, the early diastolic pressure gradient is restored despite increased diastolic LV pressures, resulting in a return of the E wave to the normal range (pseudonormal mitral inflow pattern or grade 2 diastolic dysfunction). Displacement of the LV onto a steeper slope of diastolic filling results in increased systolic velocities in the pulmonary veins toward the LA. This filling pattern has been called a pseudonormal mitral inflow pattern or grade 3 diastolic dysfunction. With slower relaxation, the e’ is delayed, occurring after the E. This indicates that the LV is not expanding symmetrically in diastole but that propagation of filling to the apex and longitudinal expansion occur slowly after the LV is filled by movement of blood from the LA into the LV inflow tract. In the presence of slow relaxation, e’ does not occur during the time of the LA-to-LV pressure gradient, so e’ is reduced and becomes almost independent of LA pressure. Both the mitral annular e’ and the delay in e’ relative to E correlate with the time constant of LV isovolumetric pressure decline. Thus, the pseudonormal mitral inflow pattern is distinguished from normal by a reduced and delayed e’ and increase in the E/e’ ratio (Figures 2 and 3).

With even more severe diastolic dysfunction with markedly slowed relaxation and elevated LA pressure, the E increases further, DT becomes very short, and e’ is further reduced and delayed, resulting in a marked elevation of E/e’ (Figures 2 and 3). With severe diastolic dysfunction, the late diastolic annular velocity (a’max) decreases, and pulmonary venous systolic forward flow velocity is reduced and less than diastolic forward flow velocity. Other indicators of diastolic dysfunction can be obtained from color M-mode imaging, Doppler echocardiography, and strain-rate imaging.

The presence of pseudonormalized and restricted filling patterns with elevated E/e’ indicates the presence of both diastolic dysfunction (impaired relaxation and elevated LV early diastolic pressures) and elevated LA pressure. In contrast, the impaired relaxation pattern indicates diastolic dysfunction without a marked elevation in mean LA pressure.

Evaluation of Patients With Heart Failure
A comprehensive echocardiographic examination (including imaging and Doppler evaluation) is an important part of the evaluation of all patients with heart failure. Echocardiography provides assessment of the size of the cardiac chambers, LV regional wall motion, and EF, as well as evaluation of valvular function, assessment of the presence of pericardial disease, and an estimation of pulmonary artery pressure. This information should be obtained in all patients being evaluated for heart failure. The comprehensive evaluation of diastolic function is also an essential part of an echocardiographic evaluation of the patient with possible heart failure that provides additional clinically important information.

The presence of a reduced EF in a patient with the clinical picture consistent with heart failure objectively confirms the presence of a cardiac abnormality, increasing the probability that the patient actually has heart failure. As such, a reduced EF has been used as an entry criterion for most of the large randomized trials that guide our therapy of heart failure. However, it is now recognized that many patients have real heart failure without a clear reduction in the LV EF below 50%. Such heart failure with preserved EF is most common in elderly patients, particularly women, who may make up the majority of patients with heart failure. It is possible that signs and symptoms of heart failure in a patient with a preserved EF (or even a reduced EF) may not actually be due to heart failure. For example, the clinical picture might be due to obesity, lung disease, and/or deconditioning. Thus, it is important to demonstrate objectively that these patients have cardiac dysfunction. Almost all patients with heart failure, regardless of EF, have diastolic dysfunction. In contrast, a normal e’ (>8 cm/s medial or >10 cm/s lateral) is very unusual in a patient with heart failure (unless the patient has pericardial constriction) and indicates the need to look for other causes of the patient’s symptoms.

Lam et al. found that e’ was reduced and E/e’ was increased in patients with heart failure and a normal EF compared with both normal subjects and patients with hypertension without heart failure. Similarly, Kasner et al. observed that an elevated E/e’ ratio was the best noninvasive measure of diastolic dysfunction for distinguishing patients with heart failure and a preserved EF with invasively proven diastolic dysfunction from normal subjects. Consistent with these observations, the European Society of Cardiology consensus statement on how to diagnose diastolic heart failure suggests that an E/e’ ratio >15 alone or an E/e’ >8 in combination with an elevated B-type natriuretic peptide (BNP) >200 pg/mL can be used as the simplest noninvasive
Two-dimensional echocardiography also provides clinical clues about diastolic function. The extent of mitral annular motion from the parasternal and apical views provides visual assessment of myocardial relaxation. LA volume is an important structure for the assessment of diastolic function and LV filling pressure. It is unlikely for a patient to have abnormal diastolic dysfunction with normal LA volume. However, not all increased LA volumes indicate diastolic dysfunction and can be seen in patients with mitral regurgitation. In this situation, the e’ velocity is usually normal.

The 2-dimensional echocardiography features may be able to identify an underlying cause of diastolic dysfunction. Examples include cardiac amyloid with increased wall thickness and low QRS voltage on ECG, hypertrophic cardiomyopathy with dynamic LV outflow tract obstruction, and thick ventricular septum, noncompaction with increased trabeculation, primary restrictive cardiomyopathy, constrictive pericarditis, or hypertensive heart disease.

**Determination of LV Filling Pressure**

The mean LA pressure is the source pressure for LV filling. Determining the LV filling pressure is a key element in the diagnosis and management of patients with suspected decompensated heart failure.3,5 Measurement of the pulmonary capillary wedge pressure with the Swan-Ganz catheter has become the gold standard for determining LV filling pressure. This invasive procedure can produce complications, especially in critically ill patients. Two randomized clinical studies found no benefit from the use of the Swan-Ganz catheter to manage critically ill patients.3,6,7 Thus, efforts to find a noninvasive method of determining LV filling pressure have continued.

Several diastolic parameters obtained from a comprehensive echocardiographic examination provide information on whether LA pressure is elevated.8 For example, enlargement of the LA correlates with chronic elevations of the LA pressure. A restricted filling pattern with a short DT indicates elevated LA pressure. An abnormal pulmonary venous flow pattern also is seen with an elevated LA pressure. Furthermore, elevated LA pressure usually is associated with some degree of pulmonary hypertension.9 The systolic pulmonary artery pressure can be estimated by calculating the tricuspid valve gradient from the Doppler measurement of the velocity of the tricuspid regurgitation jet. The most common cause of increased pulmonary artery systolic pressure in adults is elevated LA pressure, and the echocardiographic parameters best correlated with pulmonary artery systolic pressure are DT and E/e’.

All of the measures discussed above are useful in identifying patients with or without elevations of LA pressure. However, the most commonly used and easiest-to-interpret parameter to estimate LA pressure is the E/e’ ratio. As discussed, the mitral E wave is augmented when there is an increased LA-to-LV pressure gradient. The e’ velocity is reduced and delayed in the presence of slow relaxation. Thus, a high E and a low e’ (ie, increased E/e’ ratio) indicates that the increased E was due to an elevation of LA pressure, not a fall in LV diastolic pressure. E/e’ has been found to correlate with pulmonary capillary wedge pressures in a wide range of patients studied in multiple laboratories.23 It has a stronger correlation with pulmonary capillary wedge pressure than B-type natriuretic peptide.41 An E/e’ >15 has been found to clearly indicate elevated pulmonary capillary wedge pressure, whereas an E/e’ <8 is associated with normal LA pressure (Figure 4).42 In the intermediate range, an assessment of LA pressure should include the evaluation of other echo Doppler parameters associated with increased LA pressure (ie, LA size, LV filling pattern, DT, isovolumetric relaxation time, and presence of pulmonary hypertension).23

The cutoff value of E/e’ of 15 to recognize elevated LA pressure was obtained using e’ velocity from the medial mitral annulus. Because e’ velocity from the lateral annulus is usually higher than the medial e’ velocity, the cutoff should be adjusted to 12 if the lateral annular velocity is used. An average of the medial and lateral annular velocities has been recommended,23 but as long as there is no basal regional LV wall motion abnormalities, the consistent use of 1 annular velocity should be adequate in clinical practice. We prefer using the medial annular velocity because it is helpful in differentiating myocardial disease from constrictive pericarditis.

There are several situations when E/e’ may not provide an accurate assessment of pulmonary capillary wedge pressure. First, in a normal heart, e’ occurs coincidentally with E and responds to changes in LA pressure. For example, E/e’ was not increased but actually decreased in response to massive fluid loading in normal experimental animals.17 However, because LA pressure is rarely elevated in patients with a normal heart,18 the failure of E/e’ to recognize elevated LA pressures in normal subjects is of little clinical importance. Furthermore, E/e’ can distinguish an overfilled normal LV (decreased E/e’) from...
elevated LA pressure associated with cardiac dysfunction (elevated E/e'). Second, E/e' does not increase in patients with constrictive pericarditis despite elevated pulmonary capillary wedge pressures. In fact, the medial e' increases as constriction becomes worse, which results in a decrease in E/e' as constriction gets more severe and diastolic filling pressure increases (annulus paradoxus). The lateral annular velocity may be decreased and often is lower than the medial annular velocity in constriction. If a patient has clinical signs of heart failure, especially with increased jugular venous pressure, a normal or increased medial e' velocity strongly suggests constrictive pericarditis. Third, E/e' may not provide an estimate of LA pressure in patients with mitral stenosis or mitral regurgitation, especially without a reduction in EF. Intuitively, the mitral annular velocity should not work as well in patients with aortic or mitral valve replacement and in patients with mitral annulus calcification. However, this issue has not been systematically evaluated. Fourth, although E/e' correlates with LA pressure in patients with hypertrophic cardiomyopathy, there is substantial scatter limiting its use alone in an individual patient.

**Recent Concerns**

A recent publication and associated editorial in *Circulation* raised concerns about the accuracy of the use of E/e' for patient management. Mullens and colleagues from The Cleveland Clinic assessed the reliability of E/e' as a predictor of pulmonary capillary wedge pressure in 106 patients with advanced decompensated heart failure. These patients underwent simultaneous Swan-Ganz catheterization and Doppler echocardiography after admission for clinical decompensation. In these patients, E/e' correlated poorly with pulmonary capillary wedge pressure. Overall, the E/e' ratio was similar among patients with pulmonary capillary wedge pressure >18 and <18 mm Hg. Finally, there was no direct association of changes in pulmonary capillary pressure and changes in the E/e' ratio.

The failure of E/e' to perform adequately as a measure of LA pressure in these patients may result at least partially from the characteristics of the patients studied. Significant mitral regurgitation was present in nearly a quarter of the patients. Significant mitral regurgitation was present in nearly a quarter of the patients. Significant mitral regurgitation was present in nearly a quarter of the patients. Second, half of the patients had undergone cardiac resynchronization therapy, and most had a prolonged QRS with variable degrees of mechanical dyssynchrony. There are also potential questions about the measurement of the filling pressure in these patients. This was accomplished by use of the pulmonary capillary wedge pressure, which may not accurately reflect LA pressure in all situations and is prone to error in patients with pulmonary arterial hypertension.

In addition, the technical quality of the mitral inflow and mitral annular velocity recordings in the figures included in the publication is not optimal. It is surprising that so many of the patients had nearly normal pulmonary capillary wedge pressures within 12 hours of admission for decompensated heart failure so severe that it required invasive monitoring. Finally, E/e' was used in isolation to characterize the LV filling pressure in these patients. In contrast, E/e' should be used as part of a comprehensive echocardiographic evaluation of patients with heart failure.

**Echocardiographic Diastolic Assessment to Guide Heart Failure Treatment**

Comprehensive echocardiographic assessment of diastolic function can help guide the management of patients with heart failure. Optimally, heart failure therapy should maximize diastolic reserve. Correction of the underlying myocardial problem can improve myocardial relaxation, which will be apparent as an increase in e'. However, in most patients with heart failure, e' remains depressed. In these patients, the most optimal filling pattern achievable is usually an impaired relaxation pattern, with E/A <1 indicating relatively normal LA pressure. Once this is achieved, there is little to be gained from further diuresis. It may be helpful to maintain sinus rhythm in this situation so that the important atrial contribution to LV filling is not compromised.

In patients with echocardiographic evidence of increased filling pressure, diuresis and preload reduction may improve diastolic reserve and symptoms. If a restrictive LV filling pattern persists after optimal treatment of heart failure, a poor prognosis is indicated. Because stroke volume is limited in this situation, bradycardia should be avoided. The LV filling pattern also helps in the programming of the atrial-ventricular interval in patients with pacemakers.

Although medical therapy improves heart failure symptoms, it is often difficult to assess clinically whether an optimal filling pressure is achieved. If a patient continues to have increased filling pressure with a minimal diastolic reserve, development of recurrent heart failure symptoms and hospitalization are frequent. Documentation of normal filling pressure or the pattern of impaired relaxation without increased filling pressure is very helpful to know that a patient’s treatment is optimized (Figure 5).

**Prognosis**

Echocardiographic findings of diastolic function provide important prognostic information in a wide variety of patients. A normal filling pattern in community-dwelling subjects indicates an excellent prognosis (Figure 6). In contrast, an abnormal filling pattern and progressively greater abnormalities of LV filling pattern (impaired relaxation versus pseudonormalized and restricted filling) indicate subjects with a progressively increased risk of subsequent mortality. The stage of diastolic dysfunction correlates with the impairment of exercise capacity in patients without myocardial ischemia; LV EF does not. In patients with heart failure, the
stage of diastolic dysfunction is a stronger predictor of mortality than EF.29

A short DT indicates an increased LV operating stiffness, is a hallmark of restrictive filling pattern, and denotes poor prognosis in patients after myocardial infarction, dilated cardiomyopathy, and heart transplantation; in those with hypertrophic cardiomyopathy; and in patients with restrictive cardiomyopathy (Figure 7).23 Both pseudonormalized and restricted filling patterns indicate a 4-fold increase in the risk of death in patients with heart failure and coronary artery disease.51 Similarly, an elevated E/e’ indicates a poor prognosis in a wide variety of patients.23

Conclusions

Comprehensive echocardiographic evaluation, including blood flow Doppler and tissue Doppler, provides essential information in patients with heart failure. In addition to assessing cardiac structure and systolic LV function, the diastolic filling dynamics provide prognostic information and can help guide therapy. Patients with myocardial dysfunction have a reduced and delayed e’ indicating slowed relaxation. An increased E wave in the presence of a reduced e’ (ie, E/e’ >15) indicates elevated LA pressure. In patients with borderline increased E/e’ (>8, <15), the entire echocardiographic picture should be assessed, including LA size, mitral filling pattern, DT, pulmonary vein velocities, and pulmonary artery systolic pressure. This information is particularly helpful in establishing the diagnosis in patients with the clinical picture of heart failure when the LV EF is preserved. It provides prognostic information and can help guide therapy in patients with heart failure regardless of the EF.

Disclosures

None.

References


Response to Little and Oh
Carsten Tschöpe, MD; Walter J. Paulus, MD, PhD

Little and Oh summarize the arguments supporting the clinical use of echocardiography for the evaluation of diastolic left ventricular (LV) function. In their view, the E/e’ ratio provides diagnostic evidence in heart failure with normal LV ejection fraction and therapeutic guidance in heart failure with reduced LV ejection fraction. The diagnostic use of E/e’ in heart failure with normal LV ejection fraction is in line with recent European and American consensus statements on diastolic LV dysfunction. Concentric LV remodeling explains why E/e’ is a reliable estimate of left atrial pressure in heart failure with normal LV ejection fraction. In a concentrically remodeled LV, early diastolic myocardial lengthening loads are low because of small LV cavity size and thick LV walls. With low early diastolic lengthening loads, e’ reflects only LV relaxation kinetics; therefore, E/e’ corresponds to left atrial pressure. Similar pathophysiological reasoning, however, compromises the use of E/e’ for therapeutic guidance in heart failure with reduced LV ejection fraction. In heart failure with reduced LV ejection fraction, the LV is eccentrically remodeled, so early diastolic myocardial lengthening loads are high as a result of large LV cavity size and thin LV walls. With elevated early diastolic lengthening loads, e’ no longer exclusively reflects LV relaxation kinetics; therefore, E/e’ fails to correlate with left atrial pressure. Hence, the poor performance of E/e’ as a measure of left atrial pressure during treatment of heart failure with reduced LV ejection fraction relates to the pathophysiology of eccentric LV remodeling and not to technical issues involving resynchronization therapy, comparison with pulmonary wedge capillary pressure, or quality of Doppler recordings. The search for a widely applicable and reliable noninvasive estimate of left atrial pressure is therefore far from over.
Is echocardiographic evaluation of diastolic function useful in determining clinical care?

Doppler Echocardiography Yields Dubious Estimates of Left Ventricular Diastolic Pressures

Carsten Tschöpe, MD; Walter J. Paulus, MD, PhD

Quantification of left ventricular (LV) diastolic function is necessary to diagnose heart failure (HF) when LV systolic function is normal. Furthermore, repetitive assessment of LV filling pressures is an important guide for titration of diuretic treatment and can predict survival of HF patients. Because of patient discomfort and the risks involved in invasive procedures, a noninvasive estimate of diastolic LV function and pressures is highly desirable. In current cardiological practice, noninvasive evaluation of diastolic LV function is based on Doppler echocardiographic visualization of LV inflow and/or LV tissue reextension. LV inflow and LV tissue reextension, however, are only indirectly related to LV filling pressures through laws of physics such as the Bernoulli principle and Laplace law. Noninvasive estimates of LV filling pressures can therefore be offset not only by limitations of the imaging technique but also by shortcomings inherent to derivation of pressures from inflow or reextension signals. As a result of these problems with noninvasive estimates of LV diastolic function and pressures, the cardiological community has witnessed over the past 20 years repetitive cycles in which a Doppler echocardiographic index was first proposed as robust and shortly thereafter discredited by contradictory evidence. The latest of such cycles involved the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/E'). The value of the E/E' ratio as a reliable estimate of LV filling pressures was demonstrated in a variety of cardiac diseases and endorsed by European and American consensus statements on diastolic HF and diastolic LV dysfunction before being seriously questioned both in hypertrophic cardiomyopathy. This continuing uncertainty surrounding the value of noninvasive estimates of LV filling pressures and diastolic LV dysfunction asks for a reappraisal of physiological assumptions linking LV filling pressures to myocardial reextension kinetics, of pitfalls of diastolic LV dysfunction indices, and of limitations of current Doppler echocardiographic imaging techniques.

Response by Little and Oh on p 820

From Myocardial Lengthening to Ventricular Filling Pressure

The original experimental and clinical studies establishing the E/E' ratio as a reliable estimate of LA pressure emphasized the importance of LV relaxation kinetics for E'. These studies suggested E' to be strongly associated with LV relaxation kinetics and minimally affected by LA pressure. Hence, because E' corresponded with LV relaxation kinetics and E depended on both LV relaxation kinetics and LA pressure, the E/E' ratio could serve as a reliable measure of LA pressure. In view of the recent controversy surrounding E/E' as an estimate of LA pressure, the relative importance...
for early diastolic myocardial lengthening of residual LV relaxation pressure, myocardial restoring forces, and lengthening loads needs to be reassessed.

Residual LV relaxation pressure after mitral valve opening has been extrapolated from an exponential curve fit to isovolumic LV pressure decay used to determine \( r \). By subtracting this residual “active” LV relaxation pressure from measured early diastolic LV pressure, a “passive” early diastolic LV pressure could be calculated. In ischemic heart disease\(^{21-23}\) and in diastolic HF,\(^{24}\) these calculations revealed substantial residual LV relaxation pressure after mitral valve opening. In isolated papillary muscle experiments with physiological sequence relaxation, residual LV relaxation forces also were observed even at a time when muscle lengthening was completed.\(^{25,26}\) Furthermore, in occasional patients with LV hypertrophy caused by hypertrophic cardiomyopathy or aortic stenosis, measured early diastolic LV pressure almost resembled residual LV relaxation pressure, with a continuous decline throughout early diastole and a minimum diastolic LV pressure observed just before atrial contraction (Figure 1).\(^{27}\) Involvement of cardiomyocyte calcium handling in this early diastolic LV pressure decline was supported by its appearance after postextrasystolic potentiation and by its disappearance after calcium channel blockers.\(^{27,28}\) Throughout this early diastolic LV pressure decline, the mitral valve was open with minimal LV filling (Figure 1). This suggested a near equilibrium in these patients within the LV wall between residual LV relaxation force, which opposes LV filling, and forces that promote LV filling. The latter consist of restoring forces within the cardiomyocytes resulting from end-systolic compression and of lengthening loads imposed by left atrial (LA) pressure. Taken together, these observations support residual LV relaxation pressure after mitral valve opening as important for early diastolic myocardial lengthening or for \( E' \) but do not suggest that restoring forces and lengthening loads can be overlooked.

When peak diastolic lengthening velocity of an isolated papillary muscle strip was plotted against systolic shortening, a relation appeared between peak diastolic lengthening velocity and systolic shortening (Figure 2).\(^{29}\) A higher lengthening load shifted the relation upward, but a higher calcium concentration had no effect. These findings imply that during diastolic lengthening, normal cardiac muscle behaves like a spring: When the spring is more forcefully compressed during systole or when a heavier load is suspended on the spring, diastolic lengthening velocity is higher. The cardiomyocyte protein responsible for this spring-like behavior of cardiac muscle has meanwhile been identified as the giant cytoskeletal protein titin.\(^{30}\) Titin acts as a bidirectional spring affecting early diastolic muscle lengthening kinetics and late diastolic muscle extension. Its spring properties are altered by transcriptional (ie, isoform shifts) and posttranslational (ie, phosphorylation, oxidation) modifications.\(^{31}\) Higher expression of the compliant N2BA titin isoform is observed in patients with HF and reduced LV ejection fraction (HREF)\(^{32-34}\) but not in patients with HF and normal LV ejection fraction (HFNEF).\(^{35}\) Furthermore, in both HREF and HFNEF patients, reduced overall phosphorylation of titin\(^{36}\) and reduced phosphorylation of the noncompliant N2B titin isoform\(^{37}\) have just been reported. Lower phosphorylation of titin, especially of its noncompliant N2B isoform, stiffens its spring characteristics.\(^{38}\) These titin-related restoring forces within the cardiomyocyte affect LV filling kinetics, as evident from associations in HREF patients between titin isoform shifts and E/A ratio, exercise tolerance, or symptom-
HFNEF, restoring forces will fall especially in HFREF. Reduction in myocardial systolic shortening in HFREF than in HFNEF as determinants of myocardial reextension, and use of E/E\(_{\text{a}}\) ratio as a reliable estimate of LV filling pressures.

As nicely illustrated by the continuous early diastolic LV pressure decline in the occasional patient with LV hypertrophy (Figure 1), E′ is determined by a balance between forces opposing LV filling such as residual LV relaxation pressure and forces promoting LV filling such as restoring forces and external lengthening loads (Figure 3). In HF, this balance between forces shifts. Slower LV isovolumic relaxation raises residual LV relaxation pressures in early diastole; this occurs regardless of HF phenotype.\(^4^{,}^{13}^{,}^{40}^{,}^{41}\) Because of a larger reduction in myocardial systolic shortening in HFREF than in HFNEF,\(^4^{,}^{42}\) restoring forces will fall especially in HFREF.\(^4^{,}^{44}\) LA pressure at mitral valve opening rises, but the resultant elevation of early diastolic lengthening load will be smaller in concentrically remodeled LV of HFREF than in an eccentrically remodeled LV of HFREF. Moreover, a normal LVEF has recently been shown to protect cardiomyocytes against the excessive late systolic load imposed by arterial wave reflection.\(^4^{,}^{46}\) Similarly, a normal LVEF also could protect cardiomyocytes against excessive isovolumic relaxation or early diastolic loads.

Because HFNEF and HFREF have unequal effects on early diastolic forces that control cardiomyocyte lengthening, it is not surprising that the reliability of E/E′ as an estimate of diastolic LV dysfunction or LV filling pressures also differs in both conditions. In 86% of patients with HFNEF, E/E′ detected diastolic LV dysfunction evident from conductance catheter pressure-volume loop analysis,\(^4^{,}^{46}\) whereas in only 53% of patients with HFREF, E/E′ correctly identified a pulmonary capillary wedge pressure (PCWP) \(>18\) mm Hg.\(^1^{3}\) This divergence is explained by lengthening load, which is more important for early diastolic myocardial extension and E′ in HFREF. In HFREF, dividing E by E′ no longer simply corrects for residual LV relaxation pressure, and the E/E′ ratio becomes unreliable as an estimate of LV filling pressure.

In HFREF, residual LV relaxation pressure probably remains the dominant determinant of early diastolic myocardial extension and E′. Hence, in HFNEF, dividing E by E′ continues to correct for the effect of residual LV relaxation pressure on mitral E velocity, and the E/E′ ratio still yields a reliable estimate of LV filling pressures. The prominent control of early diastolic LV filling by LA pressure also explains why a simple mitral E velocity measurement also is reliable as an estimate of LV filling pressures in HFREF but correlates poorly with LV filling pressures in patients with LVEF \(>50\%\).\(^4^{,}^{47}^{,}^{48}\) Even in the recent critical study on the mitral E/E′ ratio in decompensated HFREF patients with advanced HF and resynchronization therapy, a significant but weak correlation was observed between mean PCWP and mitral E velocity.\(^1^{3}\)

From these pathophysiological insights, it becomes evident that current Doppler echocardiographic techniques for estimation of LV filling pressures or diastolic LV dysfunction cannot be used as a “1 size fits all” tool but that a “tailored” approach is needed. Such a tailored approach with different strategies in HFREF and HFNEF is indeed proposed in the recent recommendations for the echocardiographic evaluation of LV diastolic function issued by the American Society of Echocardiography and the European Association of Echocardiography.\(^1^{1}\) Their recommendations for the echocardiographic diagnosis of diastolic LV dysfunction in HFNEF also correspond to earlier guidelines published in a consensus document for the diagnosis of diastolic HF written by the Heart Failure and Echocardiography associations of the European Society of Cardiology.\(^7\) Finally, different noninvasive diagnostic strategies for diastolic LV dysfunction in HFNEF and HFREF provide support for HFNEF and HFREF as distinct HF phenotypes, with LV remodeling in both conditions driven by dissimilar gene programs.\(^4^{,}^{35}\) This unique course of LV remodeling in HFNEF and HFREF is further endorsed by recent large multicenter trials or registries in which treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or \(\beta\)-blockers.
yields positive outcome in HFREF but neutral outcome in HFNEF.

**Pitfalls of Diastolic Dysfunction Indexes**

Diastolic LV function can be assessed in each of the 4 phases of diastole: isovolumic relaxation, rapid filling, slow filling, and atrial contraction. Each of these 4 phases uniquely reflects cardiomyocyte, myocardial, or LV physiology and is variably accessible to invasive or noninvasive evaluation. Indexes of diastolic LV dysfunction derived from each of these 4 phases therefore have different clinical implications, have to meet specific clinical or scientific needs, and often have specific pitfalls frequently overlooked when noninvasive surrogate measures are proposed.

Isovolumic relaxation time, which corresponds to the time interval from aortic valve closure to mitral valve opening, is difficult to appreciate from simultaneous LV pressure, aortic pressure, and PCWP recordings but is easily measured by continuous-wave Doppler from the simultaneous display of the end of aortic ejection and the onset of mitral inflow. Its clinical value as an index of diastolic LV function is limited because it depends on arterial or mitral valve opening pressures and therefore is not uniquely related to LV isovolumic relaxation rate. An invasively determined time constant of an exponential curve fit to LV pressure fall ($\tau$) is a better approximation of LV isovolumic relaxation rate. Three potential pitfalls should be addressed when calculating $\tau$. First, does a monoexponential curve fit adequately describe LV pressure decay? Second, which start and end points have to be used for the curve fitting procedure? 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obstructed mitral inflow to deviate significantly from diastolic LV pressure predicted from isovolumic LV pressure decay. The third approach was already being heavily criticized 30 years ago because it requires long extrapolations to achieve a common diastolic LV pressure level. Despite these critiques, a variant of this approach has recently been introduced to noninvasively compare diastolic LV stiffness in patient populations with arterial hypertension and HFNEF. This variant uses not only a single-beat but also a single-measurement approach because it noninvasively assesses a single value of LVEDP and LV end-diastolic volume. It subsequently derives the entire LVEDP–end-diastolic volume relation from this single value of LVEDP and LV end-diastolic volume under the assumption that volume-normalized LVEDP–LV end-diastolic volume relations always have a similar shape regardless of animal species or heart size. These assumptions, however, have been tested only ex vivo in explanted HFREF hearts and in vivo in control subjects and HFNEF patients. The current use of this approach to clinically assess LV stiffness therefore seems premature, and its noninvasive application has to await further invasive in vivo validation against conductance catheter–derived LVEDP–LV end-diastolic volume relations.

Limitations of Current Doppler Echocardiographic Techniques

Mitral Inflow Patterns

Mitral inflow patterns have a U-shaped relation with diastolic LV dysfunction. Thus, patterns in normal subjects and HF patients at an intermediate stage of decompensation are similar. This made the use of mitral inflow patterns cumbersome and inspired many investigators to find other methods to measure LV filling pressures noninvasively. Especially in HFNEF patients, the use of mitral inflow as an estimate of diastolic LV dysfunction is limited. In these patients, who frequently have LV hypertrophy related to arterial hypertension, diabetes, and obesity, residual LV relaxation pressures are prominent, and myocardial lengthening load increased only slightly despite elevated mitral valve opening pressure because of a favorable Laplace relationship with small end-systolic LV cavity size and thick LV walls. In HFNEF patients, elevated mean PCWP or LA pressure will therefore not change the predominant control of early diastolic LV filling by residual LV relaxation pressure, so a slow LV relaxation pattern can coexist with elevated mean PCWP or LA pressure. Because of this limited reliability of mitral

Figure 4. Simultaneous recordings of mean PCWP, phasic PCWP, and diastolic LV pressure (LVP) in a patient with large V waves. Pressure values corresponding with LV minimum diastolic pressure (LVMDP), Y trough, LVEDP, and X trough differ from mean PCWP. Approximate positions of mitral flow velocity E wave and of tissue Doppler mitral annular E' wave are also indicated at peak PCWP-LV pressure gradient and just before the second PCWP-LV pressure crossover, respectively. The phasic PCWP values corresponding to E and E' also differ from mean PCWP and from LVEDP.
inflow patterns, mitral flow velocity Doppler is no longer withheld as an adequate diagnostic method for diastolic LV dysfunction in HFNEF, as evident from 2 recent consensus statements, in contrast to earlier guidelines in which it was still proposed to be of value. In patients with HFREF, myocardial lengthening load is the predominant control mechanism of early diastolic filling and easily overrides the influence of residual relaxation pressure. In these patients, mitral inflow pattern will track mean PCWP or LA pressure; therefore, a high mitral E/A ratio was proposed as first-line diagnostic evidence for diastolic dysfunction in HFREF. A major drawback for the use of mitral inflow pattern will track mean PCWP or LA pressure; therefore, a high mitral E/A ratio was proposed as first-line diagnostic evidence for diastolic dysfunction in HFREF. Therefore, a high mitral E/A ratio was proposed as first-line diagnostic evidence for diastolic dysfunction in HFREF.

**Tissue Doppler Annular Velocities**

Diastolic tissue velocities measured at the mitral annulus show low-velocity deflections during early filling (E’) and with atrial contraction (A’). E’ is presumed to correlate closely with LV relaxation indexes such as τ and to be relatively preload insensitive. These initial assumptions about E’, however, have recently been refuted by E’ measurements in instrumented dogs, which revealed close correlations of E’ with mitral valve opening pressure but weak correlations with LV relaxation rate under a variety of experimental conditions. Moreover, similar to mitral E flow, E’ appears to be age dependent. This age dependence also could detract from its prognostic value. The E/E’ ratio has been proposed as a reliable estimate of LV filling pressure. Because E depends on LA pressure, residual LV relaxation pressure, and age and because E’ is presumed to depend only on LV relaxation pressure, dividing E by E’ eliminates LV relaxation pressure and age, so the E/E’ ratio becomes a noninvasive estimate of LA pressure. Similar to E’, the value of the E/E’ ratio as a reliable estimate of LA pressure has recently been questioned both in patients with hypertrophic cardiomyopathy and in decompensated patients with resynchronization therapy.

Apart from conceptual problems involving E’, some practical issues detract from its usefulness. Septal and lateral mitral annular E’ velocities differ. Recent guidelines for the diagnosis of diastolic HF therefore recommend use of an E/E’ value that is the average of septal and lateral mitral annular E’. Furthermore, a value of E/E’ >15 is usually proposed as evidence for elevated LV filling pressure and a value of E/E’ <8 as evidence for normal LV filling pressure. As a consequence, there is a wide range of E/E’ values (8<E/E’>15) for which additional investigations are required to obtain a LV filling pressure estimate. Further technical limitations include angle dependency, signal noise, signal shifting, spatial resolution, sample volume, and tethering artifacts. E’ also can be reduced erroneously by mitral annular calcification, surgical rings, or prosthetic valves.

**Deformation Analysis**

Myocardial deformation (strain) is an important consequence of LV contraction. Myocardial strain and strain rate used to be measured with magnetic resonance imaging but recently have also been determined by speckle-tracking echocardiography, in which patterns of echocardiographic pixel intensity are identified and tracked throughout the cardiac cycle. Assessment of myocardial diastolic strain and diastolic strain rate avoids tissue Doppler–associated angulation errors and tethering artifacts. It has recently been used experimentally to evaluate diastolic LV stiffness or myocardial fibrosis and clinically to estimate LV filling pressures, especially in patients with inconclusive E/E’ ratio or with HFNEF.

Diastolic strain rates derived from the isovolumic relaxation period are measured using tissue Doppler or strain imaging. The strain rate is defined as the rate of change of strain over time, and it quantifies the rate at which the myocardium is being stretched. In HF patients, high mitral E/A ratio was proposed as first-line diagnostic evidence for diastolic dysfunction in HFREF. Therefore, a high mitral E/A ratio was proposed as first-line diagnostic evidence for diastolic dysfunction in HFREF.
period (SR\textsubscript{VR}) could be especially useful because they are unaffected by LA pressure and are solely related to LV relaxation kinetics. A recent report indeed confirmed that E/SR\textsubscript{VR} has higher predictive value for elevated LV filling pressures than E/E′ in patients with 8<E/E′>5 or with HFNEF. A similar result was also observed, however, for diastolic strain rates measured during early diastolic filling. Prospective studies in a wide variety of patients are needed to validate these promising novel techniques to estimate LV filling pressures noninvasively.

**Stepwise and Tailored Doppler Echocardiographic Strategies**

Both the consensus statement of the HF and echocardiography associations of the European Society of Cardiology and the joint recommendations of the European Association of Echocardiography and the American Society of Echocardiography suggest a stepwise approach to the Doppler echocardiographic diagnosis of HFNEF. Only patients with an E/E′ >15 are considered to have diagnostic evidence of diastolic LV dysfunction, whereas patients with an 8<E/E′<15 also need to satisfy criteria from other investigations. These investigations include measurements of LA size, mitral flow Doppler at rest or during Valsalva, pulmonary venous flow Doppler, LV wall mass, pulmonary artery systolic pressure, or isovolumic relaxation time divided by the time interval between the onset of E and E′. This approach corresponds to the initial observations validating E/E′ ratio as a reliable estimate of LV filling pressures. In this study, elevated LVEDP was predicted by an E/E′ >15 and 8<E/E′<15 in the presence of an abnormal pulmonary venous Ar-A and an abnormal response of mitral flow Doppler to Valsalva. Recently, this stepwise approach was evaluated in a practical scenario. LA size >40 mL/m\textsuperscript{2} provided diagnostic information additive to E/E′ ratio, but mitral and pulmonary venous flow velocity Doppler failed to do so. A more appropriate diagnostic strategy could therefore consist of performing invasive mean PCWP measurements in patients with dubious outcome of E/E′ ratio and LA size rather than pursuing further sequential noninvasive testing. Furthermore, stepwise positioning of tests increases diagnostic specificity at the expense of sensitivity and creates a gray zone of patients who score positively on 1 test but negatively on another. Adding exercise or dobutamine stress to a single test could circumvent this stepwise use of several tests and preserve diagnostic sensitivity (Figure 5).

Apart from a stepwise approach, the joint recommendations of the European Association of Echocardiography and the American Society of Echocardiography also propose a tailored diagnostic strategy for diastolic LV dysfunction depending on LVEF. In patients with depressed LVEF, first-line evidence of diastolic LV dysfunction is derived from mitral flow Doppler, whereas in patients with normal LVEF, it is derived from E/E′ ratio. Such a dichotomous approach depends on an LVEF cutoff value separating normal from depressed LVEF. In this respect, diagnostic guidelines for HFNEF propose an LVEF <50% as a lower limit for LVEF, whereas HFREF trials frequently use an LVEF <40% as an upper limit for LVEF. It obviously remains uncertain which diagnostic algorithm to apply in patients with LVEF between 40% and 50%. Clinical and hemodynamic characteristics of patients with LVEF between 40% and 50% have recently been described. These patients often have a previous myocardial infarction and eccentric LV remodeling and therefore differ from HFNEF patients, who usually suffer from arterial hypertension and concentric LV remodeling. A tailored strategy with preferential use of the E/E′ ratio to diagnose diastolic LV dysfunction in HFNEF11
also consists of circular reasoning because it implies preexisting knowledge of the diagnosis of HFNEF, which precisely requires evidence of diastolic LV dysfunction. Moreover, patients labeled as having HFNEF frequently suffer from noncardiac conditions. The very initial studies on HFNEF already observed that only one third of the recruited patients with HF and normal systolic function had significant diastolic LV dysfunction.80,81 More than 2 decennia later, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Echocardiographic Substudy (CHARM) again confirmed these findings.82 Only one half of the CHARM-preserved patients, who had been recruited because of signs and symptoms of HF and an LVEF >40%, had diastolic LV dysfunction evident from a pseudonormal or restrictive LV filling pattern on mitral flow Doppler. Patients presenting with HF, normal systolic LV function, and no diastolic LV dysfunction frequently appear to suffer from volume overload caused by renal insufficiency or anemia. A recent study again confirmed the high prevalence of volume overload in a population with HF and normal systolic LV function.83 In the absence of cardiac disease, E’ was demonstrated to be sensitive to volume overload.15 This could seriously jeopardize the tailored strategy with preferential use of a Doppler echocardiographic index in a specific clinical setting involves circular reasoning because it requires pretest knowledge of a diagnosis, which precisely depends on evidence of diastolic LV dysfunction. Because of these persistent shortcomings, clinicians should continue to make critical use of current Doppler echocardiographic estimates of LV filling pressures and should not hesitate to implement invasive investigations to confirm their clinical suspicions.

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None.

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Response to Tschöpe and Paulus

William C. Little, MD; Jae K. Oh, MD

Tschöpe and Paulus review potential limitations of the assessment of left ventricular (LV) diastolic pressures by Doppler echocardiography. Their elegant review of myocardial muscle physiology does not alter the demonstrated clinical utility of Doppler echocardiography. They remind us that in normal subjects, e' is not a pure measure of LV relaxation and that E/e' does not reflect increases in left atrial pressures. However, normal subjects rarely have markedly elevated left atrial pressures. When LV relaxation is impaired, e' is reduced and delayed, occurring after termination of the pressure gradient that drives filling. Thus, reductions in e' reflect impaired LV relaxation, and increased E/e' indicates elevated left atrial pressure. LV filling dynamics are altered in many elderly subjects without apparent cardiac disease. However, abnormal filling indicates a high risk of subsequently developing heart failure. Tschöpe and Paulus consider it a weakness that the optimal evaluation of left atrial pressure requires integration of multiple echocardiographic Doppler parameters, especially when the E/e' ratio is intermediate. However, as in all clinical practice, the best diagnosis is made from all of the available information. They propose a low threshold for the invasive measurement of LV filling pressure, but this has been found to be of no benefit in randomized trials. In contrast, echocardiography provides important information noninvasively. The excellent review by Tschöpe and Paulus provides balance but does not change the fact that echocardiographic Doppler evaluation of LV filling determines whether a cardiac abnormality is present in patients who may have heart failure, can guide therapy, and assesses prognosis.
Echocardiographic Evaluation of Diastolic Function Can Be Used to Guide Clinical Care
William C. Little and Jae K. Oh

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