Diastology 2010: clinical approach to diastolic heart failure

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Received: 27 May 2010 / Revised: 9 June 2010 / Accepted: 9 June 2010
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Abstract The role of echocardiography in the evaluation of left ventricular diastolic function is increasingly important in both systolic and diastolic heart failure. In routine clinical practice, the diastolic dysfunction associated with diastolic heart failure can mainly be evaluated by Doppler echocardiography. In order to use echocardiographic techniques for this purpose, one should recognize the definition, terminology, epidemiology, and pathophysiology of diastolic dysfunction and diastolic heart failure. There are various echocardiographic parameters for this purpose, including transmitral flow velocity, pulmonary venous flow velocity, mitral annular velocity, flow propagation velocity, left atrial size, strain, strain rate, twist, and so on. However, no single Doppler echocardiographic index has yielded a robust criterion for diastolic dysfunction and elevated left ventricular filling pressure. Thus, multiple indices are required to increase the sensitivity of the diagnosis. Clinicians who take care of heart failure patients should continue to make critical use of a current Doppler echocardiographic evaluation and utilize this information to improve survival and quality of life in these patients.

Keywords Diastole · Heart failure · Echocardiography · Tissue Doppler · LV filling pressures · Prognosis

Introduction

The role of echocardiography in the management of congestive heart failure (HF) is increasingly important in both systolic and diastolic HF. Every patient with HF, regardless of systolic or diastolic HF, has evidence of diastolic dysfunction, and approximately half of patients with overt HF have diastolic dysfunction with preserved left ventricular (LV) ejection fraction (EF) or diastolic HF. The diastolic
Dysfunction associated with diastolic HF can mainly be evaluated by Doppler echocardiography in routine clinical practice. Estimation of LV filling pressure is most important for managing both systolic and diastolic HF, and reliable estimation of filling pressure is the most useful information derived from the echocardiographic assessment of diastole. This article reviews a state-of-the-art practical approach to assessing diastolic dysfunction and diastolic HF using echocardiography, beginning with an overview of the background, clinical significance as well as new methods in evaluating diastolic function in clinical practice.

**Definition and terminology**

Diastolic dysfunction is a functional abnormality of myocardial relaxation, filling, or distensibility in the diastolic phase. Diastolic dysfunction occurs regardless of whether the EF is normal or abnormal, or patients are symptomatic or asymptomatic. Thus, diastolic dysfunction refers to abnormal mechanical diastolic properties of the ventricle and is present in virtually all patients with HF. If diastolic function is truly normal then relaxation, filling, and distensibility must remain normal both at rest and during stress of a variable heart rate, stroke volume, end-diastolic volume, and blood pressure [1, 2].

In contrast, diastolic HF is defined as a clinical syndrome characterized by the symptoms and signs of HF, a preserved EF, and abnormal diastolic function [1]. Diastolic HF 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. In other words, it is the situation with impaired capacity of the ventricles to fill without a compensatory increase in left atrial (LA) pressure. Diastolic HF can produce symptoms that occur at rest or with ordinary physical activity. The terms “diastolic HF” and “systolic HF” are often used instead of “HF with preserved EF” or “HF with reduced EF”, respectively but this is controversial. Recently “HF with preserved EF” has become the more accepted term used by the American Heart Association and the American College of Cardiology rather than “diastolic HF” [3]. However, “diastolic HF” is still familiar to the clinician and describes patients with symptoms and signs of HF with a normal pump function and abnormal diastolic function. For the purpose of this review, we will use the “diastolic HF” term.

Virtually all patients with HF, whether the diastolic or systolic type, will have some degree of diastolic abnormalities and elevated LV filling pressures. From this point of view, evaluation of diastolic function is needed in any case of congestive HF regardless of whether the EF is normal or reduced.

Many clinical conditions cause HF with preserved EF. These include not only diastolic dysfunction but also valvular disease, pericardial disease, arrhythmias, intracardiac mass, as well as others. However, diastolic dysfunction is the most common cause of HF with preserved EF and is associated with decreased LV distensibility, delayed relaxation, and abnormal filling. It is important to recognize that preserved EF does not mean that the contractile function is normal. Indeed, patients with diastolic HF often have some abnormality of systolic dysfunction which cannot be expressed by an EF. In addition, comorbidities such as hypertension, renal dysfunction, tachycardia, and anemia are commonly associated with the development of diastolic HF in these patients.

**Epidemiology and prognosis of diastolic dysfunction**

We retrospectively evaluated diastolic filling patterns obtained by using Doppler echocardiography in 520 consecutive patients referred to our laboratory for transthoracic echocardiograms and applied the standard guidelines used to characterize LV diastolic function [4]. Patients were classified by the Canadian consensus guidelines using transmitral and pulmonary venous Doppler echocardiographic parameters to have normal diastolic function or mild (abnormal relaxation), mild-to-moderate, moderate (pseudonormal), or severe (restrictive) diastolic dysfunction. LV diastolic dysfunction was present in 290 (56%) patients, whereas 167 (45%) patients with a normal LV EF had abnormal diastolic function. Patients with progressively more abnormal diastolic patterns had greater structural abnormalities with larger LA and LV size and lower LV EF. In the subset of patients with clinical evidence of congestive HF (99 patients), the prevalence of primary diastolic HF was 38% and most patients had underlying coronary or hypertensive heart disease.

Diastolic HF can occur alone (isolated diastolic HF) or in combination with systolic HF. Frequency of diastolic HF in overt HF and that of diastolic HF in the community varies widely, probably because of the differences in definitions of diastolic HF among the studies. Owan et al. [5] reported that the prevalence of HF with preserved EF among patients with a discharge diagnosis of HF increased significantly from 1987 to 2001. Their data showed that the number of admissions for HF with preserved EF increased during the study period, whereas the number of admissions for HF with reduced EF did not change (Fig. 1). This is partly because treating clinicians are more aware of diastolic HF, and because many people live...
longer. More recently, Redfield et al. [6] investigated the prevalence of diastolic dysfunction assessed by Doppler echocardiography including tissue Doppler imaging in 2042 randomly sampled subjects in Olmsted County, Minnesota. Overall, 20.8% of the population had mild diastolic dysfunction, 6.6% had moderate diastolic dysfunction, and 0.7% had severe diastolic dysfunction. 5.6% of the population had moderate or severe diastolic dysfunction with normal EF. A similar study was performed in Augsburg, Germany by Fischer et al. [7]. The overall prevalence of diastolic abnormalities, as defined by the European Study Group on Diastolic HF [i.e., age-dependent isovolumic relaxation time (92–105 ms) and ratio of early diastolic transmitral flow velocity to atrial systolic transmitral flow velocity (E/A ratio 1–0.5)], was 11.1%. The prevalence was 3.1% when only subjects treated with diuretics or with LA enlargement were considered (suggesting diastolic dysfunction). Significantly higher rates of diastolic abnormalities were observed in men as compared to women. Independent predictors of diastolic abnormalities were arterial hypertension, evidence of LV hypertrophy, and coronary artery disease. Interestingly, in the absence of these predisposing conditions, diastolic abnormalities (4.3%) or diastolic dysfunction (1.1%) were rare, even in subjects older than 50 years of age (4.6%) and (1.2%), respectively. The prevalence of diastolic abnormalities and diastolic dysfunction is higher than that of systolic dysfunction and is increased (despite age-dependent diagnostic criteria) in the elderly. However, in the absence of risk factors for diastolic abnormalities or diastolic dysfunction, namely LV hypertrophy, arterial hypertension, coronary artery disease, obesity, and diabetes, the condition is rare even in elderly subjects. These observations suggest that diastolic dysfunction is more common than systolic dysfunction in community-dwelling patients.

Whether diastolic HF leads to a similar or better outcome than systolic HF is still unknown. Earlier data from the 1980s and 1990s suggested that diastolic HF carries a better prognosis than systolic HF [8]. Participants in the Framingham Heart Study, for example, were followed for 6 years: those with diastolic HF were found to have an annual mortality of 9% as compared with 18% among those with systolic HF [8]. More recent investigations suggest that mortality for the 2 conditions may be similar (Fig. 2) [5, 9].

It has been well known that the mitral restrictive filling pattern (RFP) is an important prognostic indicator in patients with HF. The Meta-analysis Research Group in Echocardiography (MeRGE) has been established to determine whether the RFP is predictive of mortality independently of EF in patients with congestive HF [10]. Overall, RFP was associated with higher all-cause mortality than the non-RFP: hazard ratio 2.42 (95% CI 2.06, 2.83). The RFP was associated with higher mortality compared with the non-RFP group regardless of EF (Fig. 3). In multivariable analysis the RFP, EF, New York Heart Association class, and age were independent predictors of mortality. The prevalence of the RFP was inversely related to EF but remained a predictor of mortality even in those patients with preserved EF.

In the observation by Redfield et al. [6], mild, moderate, or severe diastolic dysfunctions were predictive of all-cause mortality during a median of 3.5 person-years of follow-up (Fig. 4). The percentage of participants with recognized congestive HF increased according to the severity of systolic or diastolic dysfunction, clearly indicating that diastolic as well as systolic dysfunction is associated with congestive HF. The diastolic dysfunction was predictive of all-cause mortality even when controlling for age, sex, and EF.

These observations suggest that diastolic dysfunction, particularly of a moderate or severe degree, is a powerful predictor of mortality in patients with HF. Whether diastolic HF leads to a similar or better outcome than systolic HF is still unknown.

**Fig. 1** Secular trends in the prevalence of heart failure with preserved ejection fraction. Left panel shows the increase during the study in the percentage of patients with heart failure who had preserved ejection fraction. Right panel shows that the number of admissions for heart failure with preserved ejection fraction increased during the study period, whereas the number of admissions for heart failure with reduced ejection fraction did not change. Adapted from Owan et al. [5]
predictor for increased morbidity and mortality in the community. Some studies also suggest that patients with diastolic HF are older and more likely to be female than those with systolic HF (Fig. 5) [11]. The observation that 22–29% of patients with diastolic HF die within 1 year of hospital discharge and 65% die within 5 years is a reminder that we are dealing with a lethal condition [12]. Owan et al. also showed that there has been little improvement in
the survival rate among patients with diastolic HF compared to the survival rate improvement among patients with systolic HF.

### Diseases and cardiac remodeling with diastolic HF

Among the various underlying diseases causing diastolic HF (Table 1), hypertensive heart disease is the most common and ischemic heart disease is the second most common in clinical practice. Diastolic HF is typically associated with significant remodeling that affects the LV and LA chambers, the cardiomyocytes, and the extracellular matrix. The structural remodeling that occurs in diastolic HF differs dramatically from that in systolic HF (Fig. 6). In diastolic HF, the diameter of cardiomyocyte increases with little or no change in length; this corresponds to the increase in LV wall thickness with no change in LV volume. By contrast, in systolic HF, the cardiomyocytes are elongated with little or no change in diameter which corresponds to the increase in LV volume with no change in LV wall thickness. In diastolic HF, the amount of collagen increases with a corresponding increment in the width and continuity of the fibrillar components of the extracellular matrix. In systolic HF, there is degradation and disruption of the fibrillar collagen. In end-stage systolic HF, replacement fibrosis and ischemic scarring may result in an overall increase in fibrillar collagen within the extracellular matrix.

### Assessment of diastolic function

Clinical assessment of diastolic function is made by clinical examination, cardiac catheterization, radionuclide angiography, echocardiography, magnetic resonance imaging or computed topographic scanning, and exercise testing. Echocardiography is a powerful tool that enables the clinician to noninvasively obtain parameters of flow, pressure, and resistance and thus evaluate intracardiac hemodynamics in the diastolic phase of the cardiac cycle. Regardless of the etiology, abnormalities in diastolic function can result in an increase in LV end-diastolic pressure (LVEDP), mean LA pressure, and pulmonary capillary wedge pressure. All these pressures are commonly referred to as LV filling pressure. During diastole, there is a continuum between the pulmonary capillary bed, pulmonary veins, LA, and the LV. An initial increase in LV end-diastolic pressure followed by an increase in LA and pulmonary capillary pressure can subsequently contribute to pulmonary congestion and HF symptoms. Consequently, assessment of diastolic function can be used to grade the degree of diastolic function and provide an estimate of LV filling pressure. The current assessment of diastolic function by echocardiography is accomplished by the evaluation of multiple Doppler parameters including (1) transmitral flow velocities, (2) pulmonary venous flow velocities, (3) tissue Doppler mitral annular velocities, and (4) propagation velocity of mitral inflow by color M-mode (Table 2; Fig. 7). Other echocardiographic parameters that sometimes add useful information for the evaluation include Tei index, pulmonary valve regurgitant flow velocity, estimated pulmonary artery pressure from tricuspid regurgitant flow velocity, B bump on the mitral valve M-mode echocardiogram, LA volume index, and size and respiratory change of the inferior vena cava. However, there is not one parameter that clearly defines diastolic dysfunction and predicts elevated filling pressure.
Echocardiographic evaluation

Transmitral flow velocity

The initial primary assessment of diastolic function is an evaluation of the transmitral flow velocity pattern and the grade of diastolic dysfunction is classically categorized into four abnormal grades according to this flow velocity pattern. The pattern is typically obtained using pulsed Doppler echocardiography at the tips of the mitral valve leaflet in the apical 4-chamber view. Usually, the peak early diastolic transmitral flow velocity \( E \) and atrial systolic transmitral flow velocity \( A \), the \( E/A \) ratio, and the deceleration time of the \( E \) wave \( (DT) \) are measured from the flow velocity pattern. The diastolic dysfunction is classified into mild or grade 1 (impaired relaxation pattern); moderate or grade 2 (pseudonormal); severe or grade 3 (restrictive filling); and grade 4 (irreversible restriction) (Figs. 8, 9). Table 2 illustrates which parameters help define each diastolic filling pattern [4, 13, 14]. Normal

Fig. 6 Isolated cardiac muscle cells (left) and scanning electron micrographs (right) taken from an animal model of dilated cardiomyopathy that produces systolic heart failure (bottom), a normal heart (middle), and an animal model of pressure-overload hypertrophy that produces diastolic heart failure (top). Arrows indicate fibrillar components of the extracellular matrix. Adapted from Aurigemma et al. [2]

Diastolic Heart Failure

Normal

Systolic Heart Failure

Table 2 Criteria used to define the grade of diastolic dysfunction

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Normal young</th>
<th>Normal adult</th>
<th>Impaired relaxation (grade 1)</th>
<th>Pseudonormal (grade 2)</th>
<th>Restrictive reversible (grade 3)</th>
<th>Restrictive irreversible (grade 4)</th>
</tr>
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<tbody>
<tr>
<td>( E/A ) ratio</td>
<td>1–2</td>
<td>1–2</td>
<td>&lt;1.0</td>
<td>1–1.5 (reverses with Valsalva maneuver)</td>
<td>&gt;1.5</td>
<td>1.5–2.0 (Doppler values similar to grade 3 except no change with Valsalva maneuver)</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IVRT (ms)</td>
<td>&lt;240</td>
<td>150–240</td>
<td>≥240</td>
<td>150–200</td>
<td>&lt;150</td>
<td>&lt;150</td>
</tr>
<tr>
<td>PVS(_2)/PVD ratio</td>
<td>&lt;1</td>
<td>≥1</td>
<td>≥1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PV AR—MV A wave duration (ms)</td>
<td>≥30</td>
<td>≤0</td>
<td>≤0 or ≥30</td>
<td>≥30</td>
<td>≥30</td>
<td>≥30</td>
</tr>
<tr>
<td>AR velocity (cm/s)</td>
<td>&lt;35</td>
<td>&lt;35</td>
<td>≥35</td>
<td>≥35</td>
<td>≥35</td>
<td>≥35</td>
</tr>
<tr>
<td>Propagation velocity (cm/s)</td>
<td>&gt;55</td>
<td>&gt;55</td>
<td>&gt;45</td>
<td>&lt;45</td>
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<td>Mitral e(^{+}) velocity (cm/s)</td>
<td>&gt;10</td>
<td>&gt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
<td>&lt;8</td>
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<tr>
<td>Left atrium</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or mildly enlarged LA</td>
<td>Mild to moderate LA enlargement</td>
<td>Severe LA enlargement</td>
<td>Severe LA enlargement</td>
</tr>
</tbody>
</table>

AR atrial reversal, \( D \) diastolic wave, \( E/A \) ratio of early to late diastolic filling velocities, IVRT isovolumic relaxation time, LA left atrial, \( MV \) mitral valve, \( PV \) pulmonary vein, \( S \) systolic wave (adapted from Garcia et al. [13], Bursi et al. [14], and Yamada et al. [4])
young subjects have an $E > A$ pattern (normal). The higher $E$ represents rapid decrease of LV pressure in the early diastole due to preserved LV myocardial relaxation. In this case, most of the filling from LA to LV is completed by $E$ wave and there is not much remaining blood in the LA, thus generating a small $A$ wave.

Patients with an $E < A$ pattern have abnormal myocardial relaxation (grade 1) usually associated with normal LA pressures. The abnormality in diastole initially occurs in impairment of relaxation. When relaxation is slowed and incomplete, early LV diastolic pressures rise, early diastolic suction falls, and these decrease the $E$ velocity. Thus, LV filling becomes increasingly dependent on an increase in LA contraction to push blood into the LV during late diastole if LA function is not impaired. Subsequently, the transmitral flow velocity pattern shows $E/A < 0.8$. The majority of subjects aged $\geq 60$ years without histories of cardiovascular disease have $E < A$ pattern and DT $> 200$ ms and can be considered normal for age. The mean LA pressure is usually not elevated in patients with grade 1 diastolic dysfunction, except for some patients with severely impaired myocardial relaxation, as in chronic hypertensive heart disease or hypertrophic cardiomyopathy. In these diseases, the grade 1 filling pattern can be altered to a grade 2 filling pattern using a diastology exercise stress test or by preload augmentation (Fig. 10) [15, 16].

The pseudonormal LV filling pattern ($E/A$ ratio is 0.8–1.5, grade 2) is associated with an increase in mean LA pressure as well as abnormal relaxation. When the myocardium becomes stiff and the distensibility is reduced, LV pressure rises rapidly through the diastole and the end-diastolic pressure is significantly elevated. The increased LV stiffness causes an increase in the crossing pressure of LA and LV resulting in an increased pressure gradient and an increased $E$ velocity. Because the elevated LV end-diastolic pressure causes an increased afterload for LA contraction, there is a small $A$ wave.

The RFP ($E/A$ ratio $> 2$) may improve to a pseudonormal LV filling pattern with a reduction in preload (reversible restrictive grade 3) or may stay irreversible (grade 4). The RFP may occasionally revert to impaired relaxation with successful therapy in the reversible restrictive patients, whereas in others, the LV filling remains restrictive (grade 4) patients. The presence of an irreversible RFP represents the most advanced abnormality in diastolic function and conveys the worst prognosis.

Pulmonary venous flow velocities

The pulmonary venous flow velocities used to be recorded by transesophageal echocardiography. However, progress

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Fig. 7 Grades of diastolic function. The Doppler echocardiography measures associated with each diastolic filling pattern are shown. Impaired relaxation (asterisk) (grade 1) can be associated with normal (grade 1a) or elevated (grade 1b) left ventricular (LV) filling pressures. The arrows indicate the dynamic nature of the diastic filling patterns in response to alterations in loading conditions. A atrial systolic transmitral flow wave, $a'$ atrial systolic mitral annular velocity, $Adur$ the $A$ wave duration, $AR$ pulmonary venous atrial reversal, $ARdur$ atrial reversal duration, $D$ pulmonary venous diastolic filling wave, $e'$ early diastolic mitral annular velocity, $S$ pulmonary venous systolic filling wave, $s'$ systolic mitral annular velocity, $V_p$ propagation velocity. Adapted from Garcia et al. [13].
Fig. 8 Schematic representation of left ventricular (LV) and left atrial (LA) pressures (upper) and transmitral flow velocity patterns (lower) in normal patients and in different types of diastolic dysfunction. This schema divides patients into four filling patterns: normal pattern of relaxation and filling; impaired relaxation or grade 1 mild diastolic dysfunction; pseudonormal relaxation, or grade 2 moderate diastolic dysfunction; and restrictive filling pattern, or grade 3 severe diastolic dysfunction. Adapted from Zile and Brutsaert [1].

Fig. 9 Simultaneous recording of transmitral flow velocity pattern (upper) and mitral annular velocity pattern (lower) in normal and each diastolic dysfunction grades. E early diastolic transmitral flow velocity, A atrial systolic transmitral flow velocity, e' early diastolic mitral annular velocity, a' atrial systolic mitral annular velocity.

Fig. 10 Diastology stress test. Simultaneous Doppler recordings of transmitral flow (upper panel) and left ventricular out flow tract flow (lower panel) velocities at baseline and during leg positive pressure. Transmitral flow velocity pattern changed from relaxation abnormality pattern to pseudonormal pattern with the reduction of left ventricular output by leg positive pressure (90 mmHg).
of technology enables clinicians to record these velocities clearly by transthoracic echocardiography and the velocity pattern sometimes offers useful information for estimating filling pressure; i.e., differentiating pseudonormal mitral patterns from normal patterns [17].

The pulmonary venous flow velocity pattern usually consists of (1) first systolic (PVS1) and second systolic (PVS2) waves; (2) a diastolic wave (PVD); and (3) an atrial reversal wave (AR). The PVS1 wave reflects active atrial relaxation and disappears in atrial fibrillation [18]. The PVS2 and PVD waves are represented by the X and Y descents of the LA pressure tracing, respectively. The PVS2 wave is generated by passive LA filling and descent of mitral annulus, which could be influenced by LV contraction [19], mitral regurgitation [20], and LA reservoir function [21]. The PVD wave represents conduit function of LA and usually acts similar to the mitral E velocity. The AR wave reflects atrial contraction (booster pump function) and increases in the situation of elevated LVEDP. There is also a distinct reversed wave during early systole (pulmonary venous flow at mitral valve closure: PVC) that is frequently observed in the presence of an elevated LA pressure, such as in the setting of mitral stenosis [22] or LA myxoma [23]. The PVC develops in the presence of elevated LA pressure during closure of the mitral valve resulting in regurgitant flow from the LA into the pulmonary veins where resistance is lower.

In patients with impaired relaxation, the PVS2 and PVS2/PVD ratio increase and the deceleration time of the PVD wave prolongs, which compensates for the impairment of early diastolic LV filling. In patients with pseudonormal pattern, the PVS2 wave is decreased ("blunted") and the PVD wave increases resulting in a decrease in PVS2/PVD ratio, which occurs with a large AR wave (>35 cm/s). In patients with a restrictive mitral inflow pattern (a deceleration time <150 ms), the pulmonary venous flow shows a lower PVS2 and higher PVD velocities (severely blunted systolic flow) and increased atrial reversals (unless atrial systolic failure), suggesting decreased LV operating compliance.

The AR wave is believed to be due to reflux flow into the pulmonary veins during LA contraction. The AR wave also disappears because of a lack of active LA contraction in patients with atrial fibrillation. Increased AR velocity (>35 cm/s) suggests elevated LV filling pressures. However, patients with diastolic dysfunction may also have concomitant LA contraction dysfunction and the AR velocity may decrease in these patients, especially those with restrictive pattern. A difference between the transmitral A wave and pulmonary venous AR wave duration greater than 30 ms also indicates elevated LV end-diastolic filling pressures [24].

Mitral annular velocities

The mitral annular velocities obtained by the pulsed tissue Doppler recording are now an important component in interpreting the diastolic filling pattern, estimation LV filling pressures, and differentiating constrictive pericarditis from restrictive cardiomyopathies [25]. For the assessment of diastolic function, measurements are made at the septal and lateral mitral valve leaflet insertion points into the mitral annulus in the apical 4-chamber view. In a normal subject, the diastolic motion velocity of the mitral annulus consists of two components—the early diastolic wave (e') and the atrial systolic wave (a') [26, 27]. These velocities change in parallel with the early diastolic (E) and atrial systolic (A) transmitral flow velocities, respectively, in normal subjects and most patients. However, the transmitral and tissue Doppler variables show a difference in waveforms depending on loading conditions, particularly changes in preload [27, 28]. The tissue Doppler annular e' velocity falls as myocardial relaxation worsens (prolongation of τ) with progressive diastolic dysfunction. In contrast, the transmitral E wave velocity is preload dependent, related to myocardial relaxation and LA pressures. The E wave velocity falls initially in grade 1 diastolic dysfunction as myocardial relaxation worsens but increases again as LA pressures rise in grade 2 and 3 diastolic dysfunction. Because the lateral e' is typically greater than the septal e' [29], a different cutoff value should be used for evaluating e' as an index for ventricular relaxation. The American Society of Echocardiography (ASE) guideline for the assessment of diastolic function recommends that septal e' ≥8 and lateral e' ≥10 are normal cutoff points. Patients with septal e' <8 or lateral e' <10 are classified to have diastolic dysfunction (Fig. 11) [30].

Time interval between E and e'

The time interval (TE-e') between the onset of the early diastolic transmitral flow velocity, as measured by conventional Doppler echocardiography, and that of the early diastolic mitral annular velocity, as measured by tissue Doppler imaging, has been reported to be related to the time constant of the LV pressure decay (τ) in an animal and human study [31, 32]. In a normal young heart, the e' wave occurs at the same time as, or earlier than, the E wave, suggesting that the elastic recoil of the myocardium promotes LV filling [31]. However, in patients with elevated LV filling pressure, the E wave precedes the e'. This finding suggests that a marked increase in LA pressure causes the mitral valve to open earlier in the process of a delay in the elastic recoil of the LV wall, and that the blood pushed into LV from LA by elevated LA pressure expands the LV wall, which generates the onset of e'. It was
reported that the ratio of the isovolumic relaxation time to TE-\(e\) can be used to estimate the mean pulmonary capillary wedge pressure, even in patients with mitral valve disease [33]. In the new ASE guidelines, an isovolumic relaxation time/TE-\(e\) \(\leq 2\) is associated with elevated LV filling pressures [30].

**Color M-mode flow propagation velocity**

The slope of the flow propagation velocity (\(V_p\)) during early diastolic filling using color M-mode Doppler expresses the pressure gradient between the mitral orifice and apex. \(V_p\) \(>50\) cm/s is considered normal and \(V_p\) \(<50\) cm/s is consistent with diastolic dysfunction [34, 35]. In patients with dilated cardiomyopathies, an \(E/V_p\) ratio \(>2.5\) can predict elevated pulmonary capillary wedge pressures; however, \(V_p\) can be increased in patients with normal LV volumes and EF despite impaired relaxation. Consequently, the \(V_p\) is most reliable as an index of LV relaxation in patients with depressed EF and dilated LV.

**Left atrial size**

While the mitral valve opens during ventricular diastole, the chamber is directly exposed to LV pressure for a long period of time. The LA also is an important transporting chamber, which transmits blood from the pulmonary veins to the LV during diastolic atrial filling and systolic atrial emptying. Therefore, the LA size may be an important index reflecting “disease history” in patients with LV dysfunction, especially diastolic dysfunction [36]. Measuring LA size is similar to measuring hemoglobin \(A_1C\) in diabetes—a long-term biomarker of average metabolic state. The LA size is considered a long-term biomarker of average LV diastolic pressure and diastolic dysfunction. Normal LA size can be seen in grade 1; however, patients with pseudonormal or restrictive filling certainly have a dilated LA [37]. LA volume, measured by 2- or 3-dimensional echocardiography, is more accurate than the LA diameter determined using M-mode echocardiography. The measurement of LA volume is highly feasible and reliable in 2-dimensional echocardiographic studies, with the most accurate measurements obtained using the apical 4-chamber and 2-chamber views, and calculated by Simpson’s method or area-length method. The LA volume is indexed to body surface area and is considered to be abnormal when it is \(>34\) ml/m\(^2\) [38].

**Strain and strain rate, twist, and more**

Myocardial strain and strain rate are excellent parameters for the quantification of regional contractility and may also provide important information in the evaluation of diastolic function. Furthermore, LV twist and the peak untwisting rate are proposed to evaluate LV diastolic function (Fig. 12) [39]. These myocardial deformation and torsion measurements can be derived from tissue Doppler or from speckle tracking techniques [40–44]. Wang et al. [45] showed that in patients with systolic HF, the longitudinal, circumferential, and radial strain, and LV twist measurements are all impaired. In contrast, in patients with diastolic HF, LV longitudinal and radial strains are reduced, but circumferential strain and LV twist are preserved. These measurements are only available with expensive high-end ultrasound machines and research analytical software. The analysis of strain and torsion remain
investigational at present and are still not included in a routine echocardiographic examination. Other limitations of myocardial deformation and torsion measurements include the Doppler angle dependency in the tissue Doppler method and the requirement for high-quality 2D images in speckle tracking—both need significant post processing time. Evaluation of these new indices in patients with diastolic HF revealed that most of the patients exhibit some abnormality of regional systolic function, but it has not been shown that such abnormalities are responsible for the clinical syndrome. Additional investigation is required with these new echocardiographic techniques.

Estimation of filling pressure

Patients with depressed EF

The mitral inflow pattern can be used to estimate filling pressures with reasonable accuracy in patients with depressed EF. Furthermore, the changes in the mitral flow pattern can be used to track filling pressures in response to medical therapy. In patients with impaired relaxation patterns and peak $E$ velocities $<50$ cm/s, LV filling pressures are usually normal. Patients with restrictive filling ($E/A \geq 2$) have an increased mean LA pressure (Fig. 13).

The use of additional Doppler parameters is recommended in patients with $E/A$ ratios $\geq 1$ to $<2$.

The $E/e'$ ratio uses the tissue Doppler annular $e'$ velocity to adjust for the myocardial relaxation contribution to mitral $E$ velocity, thereby allowing an estimate of LV filling pressures $[28, 46]$. The septal, lateral, or an average of these velocities can be used to calculate the $E/e'$ ratio. Therefore, one should use different cutoff values for estimating elevated filling pressures. When septal $e'$ is used, an $E/e'$ ratio $\leq 8$ is associated with normal pulmonary capillary wedge pressure and an $E/e'$ ratio $\geq 15$ suggests an elevated capillary wedge pressure $[46]$. There is a relatively wide gray zone used in patients when the $E/e'$ falls between 9 and 14 and other Doppler parameters are necessary to assess the LV filling pressures.

Using pulmonary venous flow velocity, PVS$_2$/PVD $<1$, AR velocity $>35$ cm/s, and AR–A duration $\geq 30$ ms indicates elevated LV filling pressures $[24]$. However, recording of the AR wave is often challenging by transthoracic approach.

The Valsalva maneuver is the most commonly used method to alter loading conditions, reducing LV preload with forceful expiration against a closed nose and mouth. In normal subjects, there is a decrease in the mitral $E$ and $A$ velocities but no change in $E/A$ ratio. In patients with a pseudonormal filling pattern, increased LA pressures are
suppressed with the reduction in preload. The mitral 
$E$ velocity decreases, the DT prolongs, and the $A$ velocity 
remains unchanged or increases, unmasking an impaired 
relaxation pattern. A reduction in the $E$ velocity by 50% 
and a reversal in the $E/A$ ratio to $< 1$ have been used as 
diagnostic criteria for elevated LV filling pressure.

Patients with normal (preserved) EF

The estimation of LV filling pressures in patients with 
normal EF is more challenging than in patients with 
depressed EF. However, the most commonly used and 
easiest-to-interpret parameter to estimate filling pressure 
is the $E/e'$ ratio in this patient group. An average $E/e'$ 
ratio $\leq 8$ indicates patients with normal LV filling pres-

tures, whereas the ratio $\geq 13$ indicates an increase in LV 
filling pressures [47]. Other measurements are required 
when the $E/e'$ ratio is between 9 and 13 (Fig. 14). 
Maximal LA volume $\geq 34$ ml/m$^2$, AR–A duration 
$\geq 30$ ms, a change in $E/A$ ratio with the Valsalva 
maneuver of $\geq 0.5$, systolic pulmonary artery pressure 
$> 35$ mmHg (in the absence of pulmonary disease), and 

isovolumic relaxation time/TE-$e'$ $< 2$ indicate elevated 
LV filling pressure.
Therapy of diastolic dysfunction

The treatment goals of diastolic heart dysfunction are similar to those of systolic heart dysfunction. Not only do we seek to improve survival in our patients but we also aim to improve our patients’ quality of life by reducing symptoms, increasing exercise tolerance, and decreasing hospitalizations.

The first target in treating diastolic dysfunction is decreasing the filling pressure (pulmonary venous pressure). We can reduce LV volume using diuretics and vasodilators. Maintaining atrial contraction is important because atrial fibrillation worsens the situation. Reducing heart rate and increasing diastolic duration by any means are effective in most cases.

The second goal is to prevent and/or treat pathologic causes of diastolic dysfunction. Myocardial ischemia or infarction is one of the major contributors to diastolic dysfunction. Although there are no data demonstrating that coronary revascularization leads to an improvement in diastolic HF outcomes, revascularization and prevention of ischemia may be effective to improve diastolic function. In patients with LV hypertrophy, the prevention and reduction of hypertrophy is essential. Lowering the blood pressure allows the ventricle to relax more adequately thereby increasing early diastolic filling and this may lead to regression of the LV hypertrophy.

There have not been many large trials for the treatment of diastolic HF. The CHARM-Preserved trial of patients with HF and preserved EF indicated only a marginal benefit of candesartan [48]. A recent trial using irbesartan also failed to demonstrate the effect of angiotensin receptor blockers to improve the survival of patients with diastolic HF with preserved EF [49]. It would be important to have large-scale clinical trials to guide the therapy of diastolic HF; however, these trials will need standard definitions as well as require a large sample size and a long follow-up period to provide beneficial results [50].

Conclusions

Diastolic HF is becoming common and it is lethal. Diagnosis and staging of diastolic dysfunction provide a framework for the approach to management of individuals with diastolic HF. Echocardiography is a powerful tool enabling the clinician to noninvasively assess diastolic function [51]. This not only allows the clinician to diagnose diastolic dysfunction but also provides information regarding the underlying cardiac disease, filling pressures, and prognosis. To date, no single Doppler echocardiographic index of diastolic dysfunction has yielded a robust criterion for elevated LV filling pressure and multiple indices are required to increase the sensitivity of the diagnosis. Clinicians who take care of HF patients should continue to make critical use of current Doppler echocardiographic evaluations and utilize this information to improve survival and the quality of life in these patients.

References

51. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. Circulation. 2009;120:802–9.