

# Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

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Echocardiographic assessment of left ventricular (LV) diastolic function is an integral part of the routine evaluation of patients presenting with symptoms of dyspnea or heart failure. The 2009 American Society of Echocardiography (ASE) and European Association of Echocardiography (now European Association of Cardiovascular Imaging [EACVI]) guidelines for diastolic function assessment were comprehensive, including several two-dimensional (2D) and Doppler parameters to grade diastolic dysfunction and to estimate LV filling pressures.<sup>1</sup> Notwithstanding, the inclusion of many parameters in the guidelines was perceived to render diastolic function assessment too complex, because several readers have interpreted the guidelines as mandating all the listed parameters in the document to fall within specified values before assigning a specific grade. The primary goal of this update is to simplify the approach and thus increase the utility of the guidelines in daily clinical practice.

LV diastolic dysfunction is usually the result of impaired LV relaxation with or without reduced restoring forces (and early diastolic suction), and increased LV chamber stiffness, which increase cardiac filling pressures. Thus, when performing an echocardiographic study in patients with potential diastolic dysfunction, one should search for signs of impaired LV relaxation, reduced restoring forces and increased diastolic stiffness. More important, LV filling pressure should be estimated because elevated LV diastolic pressure in the absence of increased LV end-diastolic volume is strong evidence in favor of well-developed diastolic dysfunction. In the majority of clinical studies, LV filling pressures and diastolic function grade can be determined reliably by a few simple echocardiographic parameters with a high feasibility. In addition, technical developments have emerged that provide new indices that appear promising for studying LV diastolic function. This update places more emphasis on applying the most useful, reproducible, and feasible 2D and Doppler measurements from the 2009 guidelines.

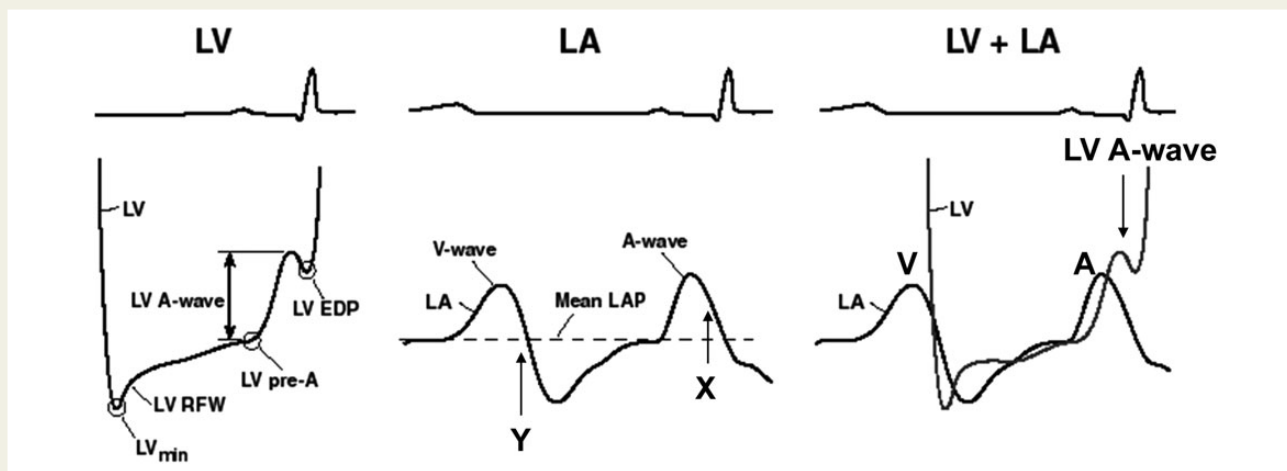
Before applying the guidelines, it is essential to consider what the term *LV filling pressures* refers to. The term *LV filling pressures* can refer to mean pulmonary capillary wedge pressure (PCWP) (which is an indirect estimate of LV diastolic pressures), mean left atrial (LA) pressure (LAP), LV pre-A pressure, mean LV diastolic pressure, and LV end-diastolic pressure (LVEDP). The different LV and LA

diastolic pressures mentioned above (*Figure 1*) have different correlates with Doppler signals. For example, in the early stages of diastolic dysfunction, LVEDP is the only abnormally elevated pressure because of a large atrial pressure wave, while mean PCWP and LAP remain normal. With tachycardia and/or increased LV afterload, mean PCWP and LAP increase which provides the basis for the diastolic stress test. Thus, it is important that one is clear on which pressure is being estimated as there are different Doppler variables that correlate with an increase in LVEDP only versus those that reflect an increase in both LAP and LVEDP. Although the current recommendations are focused on echocardiographic techniques, it should be noted that both nuclear scans and cardiac magnetic resonance can be used to evaluate LV filling rates and volumes. Notably, measurements derived by both techniques are affected by LV relaxation and LV filling pressures and are quite similar to measurements and derivatives obtained from mitral inflow velocities.

*Tables 1 and 2* summarize the technical aspects, hemodynamic determinants, and clinical applications including limitations of each of the Doppler and 2D parameters.<sup>2–50</sup> Doppler signals that occur at end-diastole correlate best with LVEDP. These include mitral peak A velocity at tips level, A-wave duration at the annulus, A velocity deceleration time (DT), pulmonary vein peak Ar velocity, Ar velocity duration, Ar-A duration, and tissue Doppler–derived mitral annular a' velocity. Mitral peak E-wave velocity, E/A ratio, E velocity DT, E/e' ratio, pulmonary vein systolic-to-diastolic velocity ratio, and peak velocity of tricuspid regurgitation (TR) by continuous-wave (CW) Doppler relate best with earlier occurring LV diastolic pressures (mean PCWP, pre-A pressure, and mean LV diastolic pressure).

# 1. General Principles for Echocardiographic Assessment of LV Diastolic Function

The application of the guidelines starts with taking note of the clinical data, heart rate, blood pressure, 2D and Doppler findings with respect to LV volumes/wall thickness, ejection fraction (EF), LA volume, presence and severity of mitral valve disease as well as the underlying rhythm. The guidelines are not necessarily applicable to children or in the perioperative setting. This is an important first step because there may be recommendations that are specific to the underlying pathology. Second, the quality of the Doppler signal as well as the limitations for each parameter should be carefully examined. If a Doppler signal is suboptimal, that signal should not be used in formulating conclusions about LV diastolic function (*Figures 2 and 3*). Third, the presence of a single measurement that falls within the normal range for a given age group does not necessarily indicate normal diastolic function (see below). Given the several hemodynamic factors that affect each signal, some measurements may fall in the normal range despite the presence of diastolic dysfunction, and none of the indices should be used in isolation. Therefore, consistency between two or more of the indices should be relied upon in an individual patient. The echocardiographic indices of diastolic function should always be interpreted in a wider context that includes clinical status and the other 2D and other Doppler



**Figure 1** (Left) LV diastolic pressures recording. Arrows point to LV minimal pressure (min), LV rapid filling wave (RFW), LV pre-A pressure (pre-A), A wave rise with atrial contraction and end-diastolic pressure (EDP). (Middle) LAP recording showing “V” and “A” waves marked along with Y and X descent (Right) Simultaneous LV and LAP recording showing early and late transmitral pressure gradients. Notice that LA “A wave” pressure precedes the late diastolic rise (LV A wave) in LV pressure.

parameters. Although often overlooked in reporting, the underlying pathology shown by 2D and color Doppler is critical to reaching the correct conclusions about LV diastolic function. For example, the algorithm for estimation of LV filling pressures is less likely to be helpful in a patient with normal vital signs and normal 2D and Doppler findings.

With respect to the grading of LV diastolic dysfunction, it is the recommendation of the writing group to determine the grade of diastolic function based on the presence or absence of elevated LV filling pressures as a first step. While useful in some cases, the lower feasibility and reproducibility of flow propagation velocity ( $V_p$ ) and time intervals ( $T_{E-e'}$ ) led the writing group to place less emphasis on their routine acquisition and analysis. The writing group strived to recommend algorithms that are applicable to most patients with cardiac disease. Notwithstanding this effort, the algorithms are not 100% accurate. For the most successful application of the guidelines, it is incumbent on the echocardiographer to have a solid understanding of the physiologic rationale behind each variable, the situations that make any given variable less reliable, and the technical aspects and acquisition and analysis of Doppler and 2D signals.

The following sections are applicable to the general population of patients seen in an echocardiography laboratory but not in the presence of specific diseases or rhythm disorders, which are discussed separately later on in the document.

## 2. Diagnosis of Diastolic Dysfunction in the Presence of Normal LVEF

Differentiation between normal and abnormal diastolic function is complicated by overlap between Doppler indices values in healthy individuals and those with diastolic dysfunction. Furthermore, normal aging is associated with a number of changes in the heart and

vascular system, especially slowing of LV relaxation which may lead to diastolic dysfunction. Therefore, filling patterns in the elderly resemble those observed in mild diastolic dysfunction in younger patients (40–60 years), and age should be taken into account when evaluating diastolic function variables.<sup>51–65</sup>

The mechanisms of diastolic dysfunction in healthy sedentary elderly appear to be due in part to increased LV stiffness compared with younger individuals.<sup>63</sup> Presumably there is also slowing of myocardial relaxation in the elderly, which can account for the decrease in mitral E/A ratio and in  $e'$  velocity (Figure 4), but the data on aging and relaxation are not entirely consistent across the studies.<sup>64</sup> Furthermore, apparently healthy older individuals may have undetected coronary artery disease or other subclinical disorders that could lead to the wide normal ranges. Some indices, however, are less age dependent, and this includes E/ $e'$  ratio, which is very rarely  $>14$  in normal individuals,<sup>52</sup> changes in mitral inflow velocities with Valsalva maneuver, and the difference in duration between pulmonary vein Ar velocity and mitral A velocity. The Valsalva maneuver can help distinguish normal LV filling from pseudonormal filling (and whether restrictive LV filling is reversible or not) because a decrease in E/A ratio of  $\geq 50\%$ , not caused by E and A velocities fusion, is highly specific for increased LV filling pressures and supports the presence of diastolic dysfunction (Figures 5 and 6). The procedure should be standardized by continuously recording mitral inflow using pulsed-wave Doppler for 10 sec during the straining phase of the maneuver.<sup>1,14</sup> Likewise, an increase in pulmonary vein Ar velocity duration versus mitral A duration (Ar-A) is consistent with increased LVEDP and diastolic dysfunction. Pulmonary artery systolic pressure (PASP), provided pulmonary vascular disease is excluded, can identify patients with increased LV filling pressures as resting values for estimated PASP are relatively age independent (Table 3). In many patients, LV and LA structural changes may help differentiate between normal and abnormal diastolic function.<sup>1</sup> Similar to LA enlargement in the absence of chronic atrial arrhythmia, which is often

**Table 1** Two-dimensional and Doppler methods for assessment of LV diastolic function

Variable	Acquisition	Analysis
Peak E-wave velocity (cm/sec)	<ol style="list-style-type: none"> <li>(1) Apical four-chamber with color flow imaging for optimal alignment of PW Doppler with blood flow.</li> <li>(2) PW Doppler sample volume (1–3 mm axial size) between mitral leaflet tips.</li> <li>(3) Use low wall filter setting (100–200 MHz) and low signal gain.</li> <li>(4) Optimal spectral waveforms should not display spikes or feathering.</li> </ol>	Peak modal velocity in early diastole (after ECG T wave) at the leading edge of spectral waveform
Peak A-wave velocity (cm/sec)	<ol style="list-style-type: none"> <li>(1) Apical four-chamber with color flow imaging for optimal alignment of PW Doppler with blood flow</li> <li>(2) PW Doppler sample volume (1–3 mm axial size) between mitral leaflet tips.</li> <li>(3) Use low wall filter setting (100–200 MHz) and low signal gain.</li> <li>(4) Optimal spectral waveforms should not display spikes or feathering.</li> </ol>	Peak modal velocity in late diastole (after ECG P wave) at the leading edge of spectral waveform
MV A duration (msec)	<ol style="list-style-type: none"> <li>(1) Apical four-chamber with color flow imaging for optimal alignment of PW Doppler with blood flow.</li> <li>(2) PW Doppler sample volume (1–3 mm axial size) at level of mitral annulus (limited data on how duration compares between annulus and leaflet tips)</li> <li>(3) Use low wall filter setting (100–200 MHz) and low signal gain.</li> <li>(4) Optimal spectral waveforms should not display spikes or feathering.</li> </ol>	Time interval from A-wave onset to end of A wave at zero baseline. If E and A are fused (E velocity > 20 cm/sec when A velocity starts), A-wave duration will often be longer because of increased atrial filling stroke volume.
MV E/A ratio	See above for proper technique of acquisition of E and A velocities.	MV E velocity divided by A-wave velocity
MV DT (msec)	Apical four-chamber: pulsed Doppler sample volume between mitral leaflet tips	Time interval from peak E-wave along the slope of LV filling extrapolated to the zero-velocity baseline.
Pulsed-wave TDI e' velocity (cm/sec)	<ol style="list-style-type: none"> <li>(1) Apical four-chamber view: PW Doppler sample volume (usually 5–10 mm axial size) at lateral and septal basal regions so average e' velocity can be computed.</li> <li>(2) Use ultrasound system presets for wall filter and lowest signal gain.</li> <li>(3) Optimal spectral waveforms should be sharp and not display signal spikes, feathering or ghosting.</li> </ol>	Peak modal velocity in early diastole at the leading edge of spectral waveform
Mitral E/e'	See above for acquisition of E and e' velocities	MV E velocity divided by mitral annular e' velocity
LA maximum volume index (mL/BSA)	<ol style="list-style-type: none"> <li>(1) Apical four- and two-chamber: acquire freeze frames 1–2 frames before MV opening.</li> <li>(2) LA volume should be measured in dedicated views in which LA length and transverse diameters are maximized.</li> </ol>	Method of disks or area-length method and correct for BSA. Do not include LA appendage or pulmonary veins in LA tracings from apical four- and apical two-chamber views.
PV S wave (cm/sec)	<ol style="list-style-type: none"> <li>(1) Apical four-chamber with color flow imaging to help position pulsed Doppler sample volume (1–3 mm axial size).</li> <li>(2) Sample volume placed at 1–2 cm depth into right (or left) upper PV.</li> <li>(3) Use low wall filter setting (100–200 MHz) and low signal gain.</li> <li>(4) Optimized spectral waveforms should not display signal spikes or feathering.</li> </ol>	Peak modal velocity in early systole at the leading edge of spectral waveform
PV D wave (cm/sec)	Same as for PV S wave.	Peak modal velocity in early diastole after MV opening at leading edge of spectral waveform
PV AR duration (msec)	Apical four-chamber: sample volume placed at 1–2 cm depth into right (or left) upper PV with attention to presence of LA wall motion artifacts	Time interval from AR-wave onset to end of AR at zero baseline
PV S/D ratio	See above for acquisition of pulmonary vein S and D velocities.	PV S wave divided by D-wave velocity or PV S wave time-velocity integral/PV D wave time-velocity integral.

Continued

**Table I Continued**

Variable	Acquisition	Analysis
CW Doppler: TR systolic jet velocity (m/sec)	(1) Parasternal and apical four-chamber view with color flow imaging to obtain highest Doppler velocity aligned with CW. (2) Adjust gain and contrast to display complete spectral envelope without signal spikes or feathering	Peak modal velocity during systole at leading edge of spectral waveform
Valsalva maneuver	Recording obtained continuously through peak inspiration and as patient performs forced expiration for 10 sec with mouth and nose closed.	Change in MV E velocity and E/A ratio during peak strain and following release
Secondary measures		
Color M-mode Vp (cm/sec)	Apical four-chamber with color flow imaging for M-mode cursor position, shift color baseline in direction of mitral valve inflow to lower velocity scale for red/yellow inflow velocity profile	Slope of inflow from MV plane into LV chamber during early diastole at 4-cm distance
IVRT	Apical long-axis or five-chamber view, using CW Doppler and placing sample volume in LV outflow tract to simultaneously display end of aortic ejection and onset of mitral inflow.	Time between aortic valve closure and MV opening. For IVRT, sweep speed should be 100 mm/sec.
TE-e'	Apical four-chamber view with proper alignment to acquire mitral inflow at mitral valve tips and using tissue Doppler to acquire septal and lateral mitral annular velocities.	Time interval between peak of R wave in QRS complex and onset of mitral E velocity is subtracted from time interval between QRS complex and onset of e' velocity. RR intervals should be matched and gain and filter settings should be optimized to avoid high gain and filter settings. For time intervals, sweep speed should be 100 mm/sec.

A, atrial filling; AR, Atrial reversal; BSA, body surface area; CW, continuous wave; D, diastole; e', early diastolic; E, early filling; ECG, electrocardiographic; IVRT, isovolumic relaxation time; LA, left atrium; MV, mitral valve; PV, pulmonary vein; PW, pulsed-wave; S, systole; TDI, tissue Doppler imaging; TR, tricuspid regurgitation. All Doppler and M-mode recordings are preferably acquired at a sweep speed of 100 mm/sec.

a marker of long-term or chronic elevation of LAP, pathologic LV hypertrophy is usually associated with increased LV stiffness and diastolic dysfunction.<sup>1</sup> Furthermore, in patients with heart failure with preserved EF (HFpEF), LV global longitudinal function is often impaired and thus may be used to differentiate between normal and abnormal myocardial function.<sup>66</sup> Although not an index of LV diastolic function, abnormal LV longitudinal systolic function can be detected by measurements of the mitral annular plane systolic excursion using M-mode, tissue Doppler–derived mitral annulus systolic velocity, and LV global longitudinal strain (GLS) by speckle-tracking. This approach has not been widely tested, but in patients with normal EFs and inconclusive data after evaluating diastolic filling, the finding of impaired GLS and reduced s' velocity can be used as an indication of myocardial dysfunction. The reduced longitudinal strain in patients with HFpEF is consistent with several studies that have demonstrated reduced systolic mitral annular velocity in this patient population. It is also consistent with the fact that LV systolic and diastolic functions are tightly coupled.

In summary, the following four variables should be evaluated when determining whether LV diastolic function is normal (Figure 7) or abnormal. The presence of several abnormal findings as well as cutoff values with high specificity for myocardial disease is recommended to decrease false positive diagnoses of diastolic dysfunction. The four recommended variables and their abnormal cutoff values are annular e' velocity (septal e' < 7 cm/sec, lateral e' < 10 cm/sec), average E/e' ratio > 14, LA maximum volume index >

34 mL/m<sup>2</sup>, and peak TR velocity > 2.8 m/sec. On the basis of the writing group's collective expert opinion, average E/e' ratio is recommended for simplification. Although E/e' ratio may be obtained at septal or lateral annulus, and different values exist because of the normally higher lateral annular velocities, an average E/e' ratio > 14 is used throughout this document and is consistent with recent studies in normal subjects.<sup>52</sup> It is recognized that at times only the lateral e' or septal e' velocity is available and clinically valid and in these circumstances a lateral E/e' ratio > 13 or a septal E/e' > 15 is considered abnormal. The latter sentence applies to laboratories that acquire only septal or lateral velocities. The above are general guidelines for annular velocities and ratios. Age appropriate cutoff values, when available, should be considered when evaluating older individuals. LA maximum volume index is recommended and not LA anteroposterior diameter by M-mode, as LA enlargement can occur in the medial-lateral and superior-inferior directions only, resulting in an increased LA volume while the chamber anteroposterior diameter is still within the normal range.

LV diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function. LV diastolic dysfunction is present if more than half of the available parameters meet these cutoff values. The study is inconclusive if half of the parameters do not meet the cutoff values (Figure 8A). For example, a 60-year-old patient with a septal e' velocity of 6 cm/sec, septal E/e' ratio of 10, LA maximum volume index of 30 mL/m<sup>2</sup>, but no recorded TR signal has normal diastolic function.

**Table 2** Utility, advantages and limitations of variables used to assess LV diastolic function

Variable	Utility and physiologic background	Advantages	Limitations
Mitral E velocity	E-wave velocity reflects the LA-LV pressure gradient during early diastole and is affected by alterations in the rate of LV relaxation and LAP.	<ol style="list-style-type: none"> <li>(1) Feasible and reproducible.</li> <li>(2) In patients with dilated cardiomyopathy and reduced LVEF, mitral velocities correlate better with LV filling pressures, functional class, and prognosis than LVEF.</li> </ol>	<ol style="list-style-type: none"> <li>(1) In patients with coronary artery disease and patients with HCM in whom LVEF is <math>&gt;50\%</math>, mitral velocities correlate poorly with LV filling pressures</li> <li>(2) More challenging to apply in patients with arrhythmias.</li> <li>(3) Directly affected by alterations in LV volumes and elastic recoil.</li> <li>(4) Age dependent (decreasing with age).</li> </ol>
Mitral A velocity	A-wave velocity reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function.	Feasible and reproducible.	<ol style="list-style-type: none"> <li>(1) Sinus tachycardia, first-degree AV block and paced rhythm can result in fusion of the E and A waves. If mitral flow velocity at the start of atrial contraction is <math>&gt;20</math> cm/sec, A velocity may be increased.</li> <li>(2) Not applicable in AF/atrial flutter patients.</li> <li>(3) Age dependent (increases with aging).</li> </ol>
Mitral E/A ratio	Mitral inflow E/A ratio and DT are used to identify the filling patterns: normal, impaired relaxation, PN, and restrictive filling.	<ol style="list-style-type: none"> <li>(1) Feasible and reproducible.</li> <li>(2) Provides diagnostic and prognostic information.</li> <li>(3) In patients with dilated cardiomyopathy, filling patterns correlate better with filling pressures, functional class, and prognosis than LVEF.</li> <li>(4) A restrictive filling pattern in combination with LA dilation in patients with normal EFs is associated with a poor prognosis similar to a restrictive pattern in dilated cardiomyopathy.</li> </ol>	<ol style="list-style-type: none"> <li>(1) The U-shaped relation with LV diastolic function makes it difficult to differentiate normal from PN filling, particularly with normal LVEF, without additional variables.</li> <li>(2) If mitral flow velocity at the start of atrial contraction is <math>&gt;20</math> cm/sec, E/A ratio will be reduced due to fusion.</li> <li>(3) Not applicable in AF/atrial flutter patients.</li> <li>(4) Age dependent (decreases with aging).</li> </ol>
Mitral E-velocity DT	DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV stiffness.	<ol style="list-style-type: none"> <li>(1) Feasible and reproducible.</li> <li>(2) A short DT in patients with reduced LVEFs indicates increased LVEDP with high accuracy both in sinus rhythm and in AF.</li> </ol>	<ol style="list-style-type: none"> <li>(1) DT does not relate to LVEDP in normal LVEF</li> <li>(2) Should not be measured with E and A fusion due to potential inaccuracy.</li> <li>(3) Age dependent (increases with aging).</li> <li>(4) Not applied in atrial flutter.</li> </ol>
Changes in mitral inflow with Valsalva maneuver	Helps distinguishing normal from PN filling patterns. A decrease of E/A ratio of $\geq 50\%$ or an increase in A-wave velocity during the maneuver, not caused by E and A fusion, are highly specific for increased LV filling pressures.	When performed adequately under standardized conditions (keeping 40 mm Hg intrathoracic pressure constant for 10 sec) accuracy in diagnosing increased LV filling pressures is good.	<ol style="list-style-type: none"> <li>(1) Not every patient can perform this maneuver adequately. The patient must generate and sustain a sufficient increase in intrathoracic pressure, and the examiner needs to maintain the correct sample volume location between the mitral leaflet tips during the maneuver.</li> <li>(2) It is difficult to assess if it is not standardized.</li> </ol>

Continued



**Table 2 Continued**

Variable	Utility and physiologic background	Advantages	Limitations
Mitral "L" velocity	Markedly delayed LV relaxation in the setting of elevated LV filling pressures allows for ongoing LV filling in mid diastole and thus L velocity. Patients usually have bradycardia.	When present in patients with known cardiac disease (e.g., LVH, HCM), it is specific for elevated LV filling pressures. However, its sensitivity is overall low.	Rarely seen in normal LV diastolic function when the subject has bradycardia but it is then usually <20 cm/sec.
IVRT	IVRT is $\leq 70$ msec in normal subjects and is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT shortens and its duration is inversely related to LV filling pressures in patients with cardiac disease.	<ol style="list-style-type: none"> <li>(1) Overall feasible and reproducible.</li> <li>(2) IVRT can be combined with other mitral inflow parameters as E/A ratio to estimate LV filling pressures in patients with HFrEF.</li> <li>(3) It can be combined with LV end-systolic pressure to estimate the time constant of LV relaxation (<math>\tau</math>).</li> <li>(4) It can be applied in patients with mitral stenosis in whom the same relation with LV filling pressures described above holds.</li> <li>(5) In patients with MR and in those after MV replacement or repair, it can be combined with <math>T_{E-e'}</math> to estimate LV filling pressures.</li> </ol>	<ol style="list-style-type: none"> <li>(1) IVRT duration is in part affected by heart rate and arterial pressure.</li> <li>(2) More challenging to measure and interpret with tachycardia.</li> <li>(3) Results differ on the basis of using CW or PW Doppler for acquisition.</li> </ol>
Pulsed-wave TDI-derived mitral annular early diastolic velocity: $e'$	A significant association is present between $e'$ and the time constant of LV relaxation ( $\tau$ ) shown in both animals and humans. The hemodynamic determinants of $e'$ velocity include LV relaxation, restoring forces and filling pressure.	<ol style="list-style-type: none"> <li>(1) Feasible and reproducible.</li> <li>(2) LV filling pressures have a minimal effect on <math>e'</math> in the presence of impaired LV relaxation.</li> <li>(3) Less load dependent than conventional blood-pool Doppler parameters.</li> </ol>	<ol style="list-style-type: none"> <li>(1) Limited accuracy in patients with CAD and regional dysfunction in the sampled segments, significant MAC, surgical rings or prosthetic mitral valves and pericardial disease.</li> <li>(2) Need to sample at least two sites with precise location and adequate size of sample volume.</li> <li>(3) Different cutoff values depending on the sampling site for measurement.</li> <li>(4) Age dependent (decreases with aging).</li> </ol>
Mitral E/ $e'$ ratio	$e'$ velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/ $e'$ ratio can be used to predict LV filling pressures.	<ol style="list-style-type: none"> <li>(1) Feasible and reproducible.</li> <li>(2) Values for average E/<math>e'</math> ratio &lt; 8 usually indicate normal LV filling pressures, values &gt; 14 have high specificity for increased LV filling pressures.</li> </ol>	<ol style="list-style-type: none"> <li>(1) E/<math>e'</math> ratio is not accurate in normal subjects, patients with heavy annular calcification, mitral valve and pericardial disease.</li> <li>(2) "Gray zone" of values in which LV filling pressures are indeterminate.</li> <li>(3) Accuracy is reduced in patients with CAD and regional dysfunction at the sampled segments.</li> <li>(4) Different cutoff values depending on the site used for measurement.</li> </ol>
$T_{E-e'}$ time interval	Can identify patients with diastolic dysfunction due to delayed onset of $e'$ velocity compared with onset of mitral E velocity.	<ol style="list-style-type: none"> <li>(1) Ratio of IVRT to <math>T_{E-e'}</math> can be used to estimate LV filling pressures in normal subjects and patients with mitral valve disease.</li> <li>(2) <math>T_{E-e'}</math> can be used to differentiate patients with restrictive cardiomyopathy who have a prolonged time interval from those with pericardial constriction in whom it is not usually prolonged.</li> </ol>	More challenging to acquire satisfactory signals with close attention needed to location, gain, filter settings as well as matching RR intervals.

Continued

**Table 2 Continued**

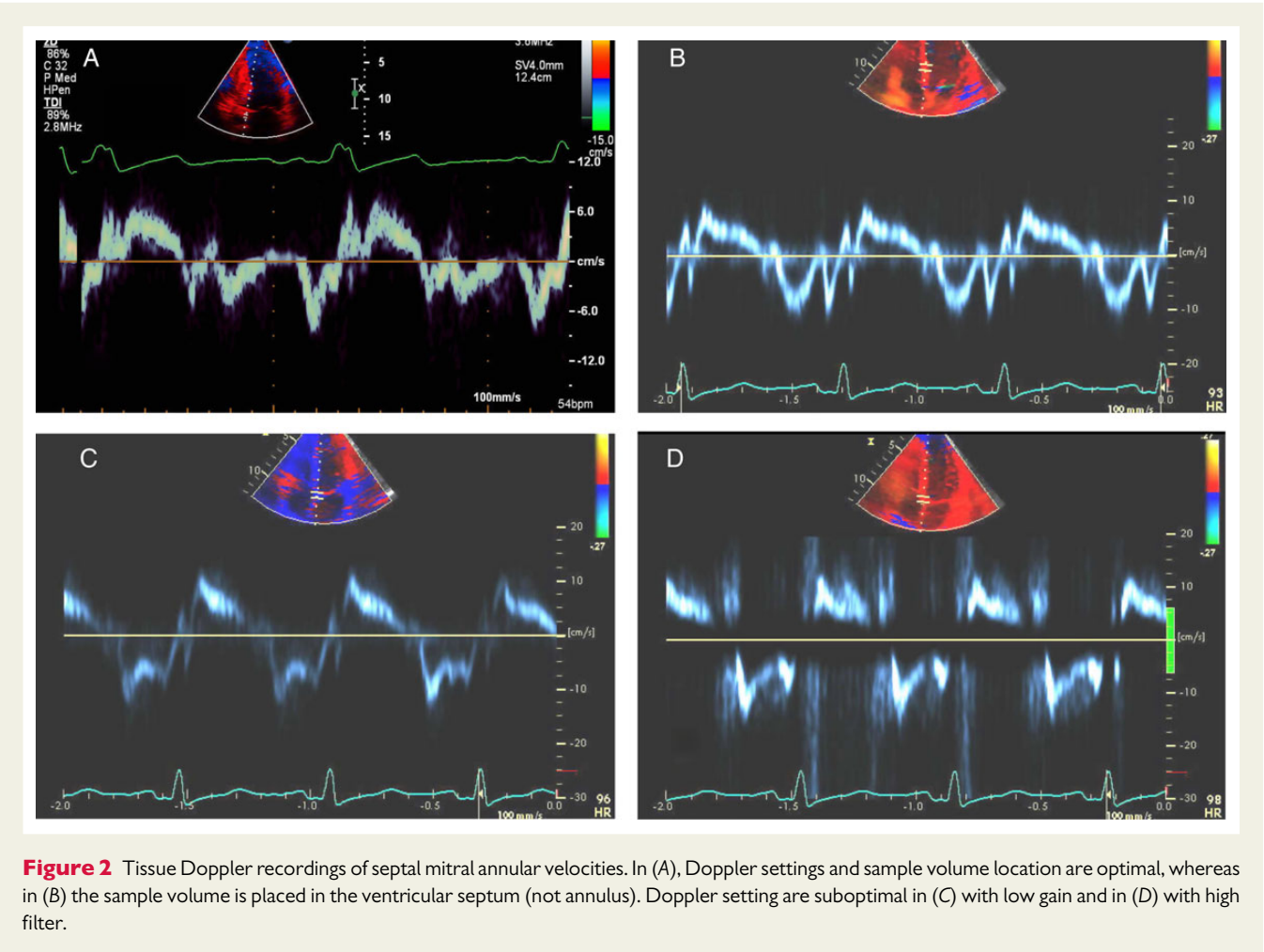
Variable	Utility and physiologic background	Advantages	Limitations
LA maximum volume index	LA volume reflects the cumulative effects of increased LV filling pressures over time. Increased LA volume is an independent predictor of death, heart failure, AF, and ischemic stroke.	(1) Feasible and reproducible. (2) Provides diagnostic and prognostic information about LV diastolic dysfunction and chronicity of disease. (3) Apical four-chamber view provides visual estimate of LA and RA size which confirms LA is enlarged.	(1) LA dilation is seen in bradycardia, high-output states, heart transplants with biatrial technique, atrial flutter/fibrillation, significant mitral valve disease, despite normal LV diastolic function. (2) LA dilatation occurs in well-trained athletes who have bradycardia and are well hydrated. (3) Suboptimal image quality, including LA foreshortening, in technically challenging studies precludes accurate tracings. (4) It can be difficult to measure LA volumes in patients with ascending and descending aortic aneurysms as well as in patients with large interatrial septal aneurysms.
Pulmonary veins: systolic (S) velocity, diastolic (D) velocity, and S/D ratio	S-wave velocity (sum of S1 and S2) is influenced by changes in LAP, LA contractility, and LV and RV contractility. D-wave velocity is mainly influenced by early diastolic LV filling and compliance and it changes in parallel with mitral E velocity. Decrease in LA compliance and increase in LAP is associated with decrease in S velocity and increase in D velocity.	(1) Reduced S velocity, S/D ratio < 1, and systolic filling fraction (systolic VTI/total forward flow VTI) < 40% indicate increased mean LAP in patients with reduced LVEFs. (2) In patients with AF, DT of diastolic velocity (D) in pulmonary vein flow can be used to estimate mean PCWP.	(1) Feasibility of recording PV inflow can be suboptimal, particularly in ICU patients. (2) The relationship between PV systolic filling fraction and LAP has limited accuracy in patients with normal LVEF, AF, mitral valve disease and HCM.
Ar-A duration	The time difference between duration of PV flow and mitral inflow during atrial contraction is associated with LV pressure rise because of atrial contraction and LVEDP. The longer the time difference, the higher LVEDP.	(1) PV Ar duration > mitral A duration by 30 msec indicates an increased LVEDP. (2) Independent of age and LVEF. (3) Accurate in patients with MR and patients with HCM.	(1) Adequate recordings of Ar duration may not be feasible by TTE in several patients. (2) Not applicable in AF patients. (3) Difficult to interpret in patients with sinus tachycardia or first-degree AV block with E and A fusion.
CW Doppler TR systolic jet velocity	A significant correlation exists between systolic PA pressure and noninvasively derived LAP. In the absence of pulmonary disease, increased systolic PA pressure suggests elevated LAP.	Systolic PA pressure can be used as an adjunctive parameter of mean LAP. Evidence of pulmonary hypertension has prognostic implications.	(1) Indirect estimate of LAP. (2) Adequate recording of a full envelope is not always possible, though intravenous agitated saline or contrast increases yield. (3) With severe TR and low systolic RV-RA pressure gradient, accuracy of calculation is dependent on reliable estimation of RA systolic pressure.
CW Doppler PR end-diastolic velocity	A significant correlation exists between diastolic PA pressure and invasively as well as noninvasively derived LAP. In the absence of pulmonary disease, increased diastolic PA pressure is consistent with elevated LAP.	Diastolic PA pressure can be used as an adjunctive parameter of mean LAP. Evidence of pulmonary hypertension has prognostic implications.	(1) Adequate recording of a full PR jet envelope is not always possible though intravenous contrast increases yield. (2) Accuracy of calculation is dependent on the reliable estimation of mean RAP. (3) If mean PA pressure is >40 mm Hg or PVR >200 dynes·s·cm <sup>-5</sup> , PA diastolic pressure is higher by >5 mm Hg over mean PCWP.

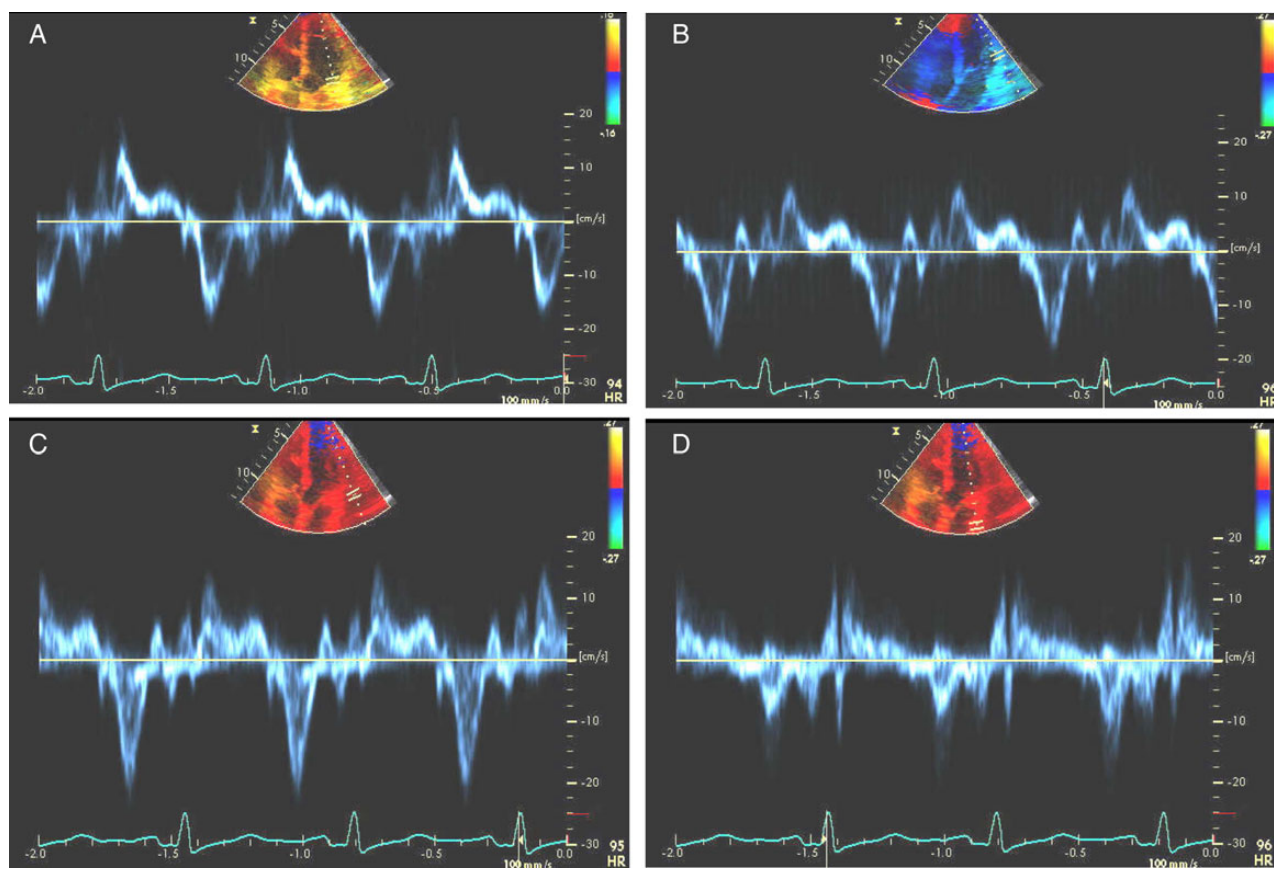
Continued



Variable	Utility and physiologic background	Advantages	Limitations
Color M-mode Vp: Vp, and E/Vp ratio	Vp correlates with the time constant of LV relaxation ( $\tau$ ) and can be used as a parameter of LV relaxation. E/Vp ratio correlates with LAP.	(1) Vp is reliable as an index of LV relaxation in patients with depressed LVEFs and dilated left ventricle but not in patients with normal EFs. (2) $E/Vp \geq 2.5$ predicts PCWP > 15 mm Hg with reasonable accuracy in patients with depressed EFs.	(1) There are different methods for measuring mitral-to-apical flow propagation. (2) In patients with normal LV volumes and LVEF but elevated LV filling pressures, Vp can be misleadingly normal. (3) Lower feasibility and reproducibility. (4) Angulation between M-mode cursor and flow results in erroneous measurements.

AR, Atrial reversal velocity in pulmonary veins; PA, pulmonary artery; PN, pseudonormal; PR, pulmonary regurgitation; PV, pulmonary vein; PVR, pulmonary vascular resistance; RA, right atrial; TDI, tissue Doppler imaging.





**Figure 3** Tissue Doppler recordings of lateral mitral annular velocities. In (A), Doppler sample volume is located in part in LV cavity. In (B) the sample volume is in basal segment of lateral wall, in (C) the location is partly outside the heart altogether, and in (D) it is located in the left atrium above the mitral annulus.

#### Key Points

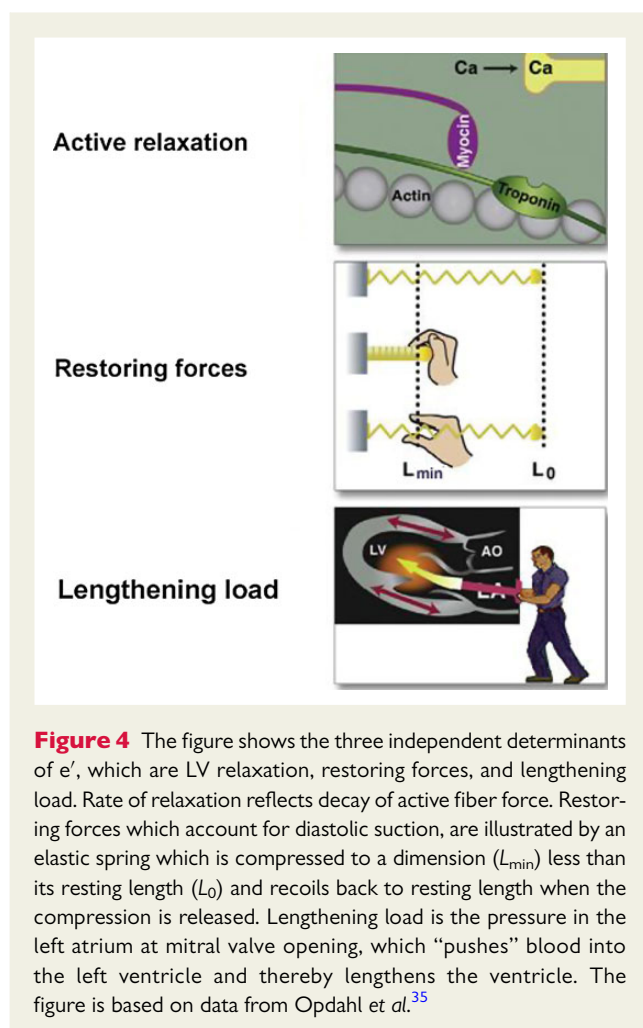
- (1) The four recommended variables for identifying diastolic dysfunction and their abnormal cutoff values are annular  $e'$  velocity: septal  $e' < 7$  cm/sec, lateral  $e' < 10$  cm/sec, average  $E/e'$  ratio  $> 14$ , LA volume index  $> 34$  mL/m<sup>2</sup>, and peak TR velocity  $> 2.8$  m/sec.
- (2) LV diastolic function is normal if more than half of the available variables do not meet the cutoff values for identifying abnormal function. LV diastolic dysfunction is present if more than half of the available parameters meet these cutoff values. The study is inconclusive if half of the parameters do not meet the cutoff values.

### 3. Echocardiographic Assessment of LV Filling Pressures and Diastolic Dysfunction Grade

The key variables recommended for assessment of LV diastolic function grade include mitral flow velocities, mitral annular  $e'$  velocity,  $E/e'$  ratio, peak velocity of TR jet, and LA maximum volume index (Figure 8B). Supplementary methods are pulmonary vein velocities and as a means to identify mild reduction in systolic function, LV

GLS by speckle-tracking echocardiography (STE). Because patients with reduced LVEFs also have impaired diastolic function (examples shown in Figures 9–11 for heart failure with reduced EF [HFrEF]), the evaluation has a different focus than in patients with normal LVEF ( $\geq 50\%$ ) (examples shown in Figures 12–15 for HFpEF). The main reason for evaluating diastolic function in patients with reduced EFs is to estimate LV filling pressure. As in several other patient groups, it is important to look for consistency between the different parameters. When using such an integrated approach, a reliable estimate of LV filling pressure can be achieved in most patients.<sup>67,68</sup> Given the presence of situations in which LAP and LVEDP are different and because LAP is the pressure that relates better with mean PCWP and thus pulmonary congestion symptoms at the time of the echocardiographic examination, the algorithm is presented with the premise of estimating mean LAP. The approach starts with mitral inflow velocities and is applied in the absence of atrial fibrillation (AF), significant mitral valve disease (at least moderate mitral annular calcification [MAC], any mitral stenosis or mitral regurgitation [MR] of more than moderate severity, mitral valve repair or prosthetic mitral valve), LV assist devices, left bundle branch block, and ventricular paced rhythm.

The proposed algorithm is based on expert consensus and has not been validated. Because diastolic dysfunction is a result of underlying



myocardial disease in patients with reduced or preserved LVEF, a rather similar approach can be considered in these populations. When the mitral inflow pattern shows an E/A ratio  $\leq 0.8$  along with a peak E velocity of  $\leq 50$  cm/sec, then mean LAP is either normal or low. The corresponding grade of diastolic dysfunction is grade I. When the mitral inflow pattern shows an E/A ratio  $\geq 2$ , LA mean pressure is elevated and grade III diastolic dysfunction is present. DT is usually short in these patients ( $< 160$  msec) but in some patients it can exceed 160 msec in the presence of an E velocity  $> 120$  cm/sec as it takes a longer time for a higher E velocity to decelerate. In this situation, the writing group recommends using only the E/A ratio in the classification scheme. On the other hand, mitral DT should be used for assessment of LV diastolic function in patients with recent cardioversion to sinus rhythm who can have a markedly reduced mitral A velocity because of LA stunning at the time of the echocardiographic examination, thus leading to an E/A ratio  $\geq 2$  despite the absence of elevated LV filling pressures (Figure 16). Of note, in young individuals ( $< 40$  years of age), E/A ratios  $> 2$  may be a normal finding,<sup>51</sup> and therefore in this age group other signs of diastolic dysfunction should be sought. Importantly, normal subjects have normal annular  $e'$  velocity which can be used to verify the presence of normal diastolic function.

When mitral inflow shows an E/A  $\leq 0.8$  and the peak E velocity is  $> 50$  cm/sec, or if the E/A ratio is  $> 0.8$  but  $< 2$ , other signals are

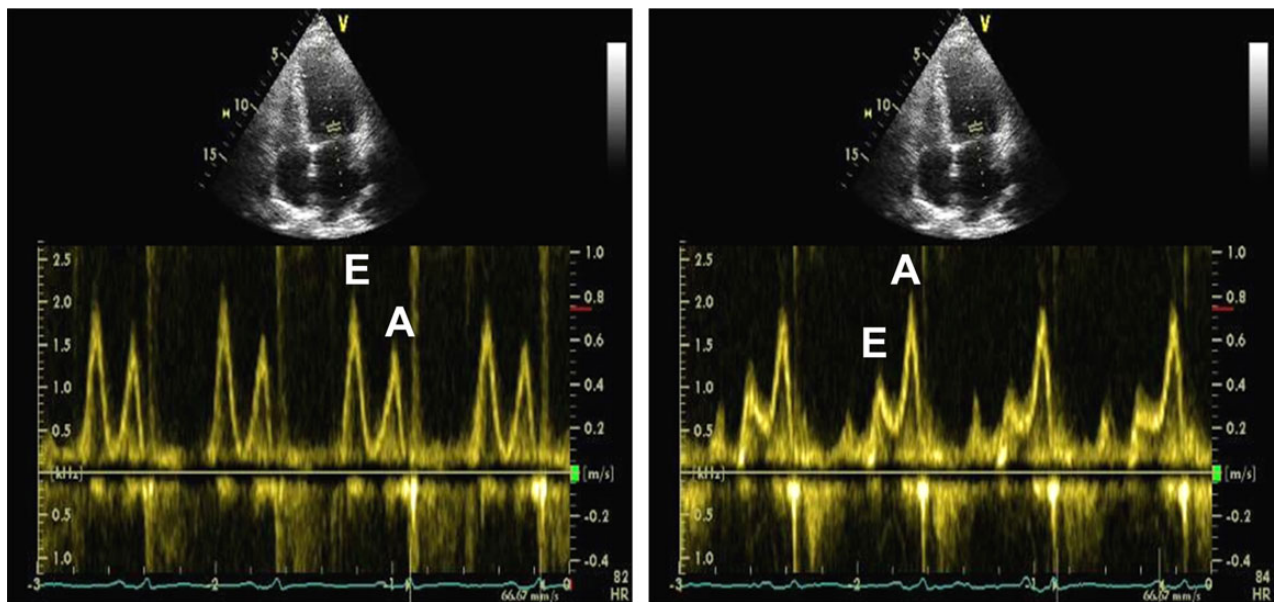
necessary for accurate evaluation. We recommend the following parameters: peak velocity of TR jet by CW Doppler obtained from multiple views, E/ $e'$  ratio and LA maximum volume index. A TR jet peak velocity  $> 2.8$  m/sec supports the presence of elevated LV filling pressures, and the same conclusion can be reached when E/ $e'$  ratio is elevated. In patients in whom one of the three main criteria is not available, the ratio of pulmonary vein peak systolic to peak diastolic velocity or systolic time-velocity integral to diastolic time-velocity integral  $< 1$  supports the presence of elevated LV filling pressures. In healthy young people ( $< 40$  years of age), pulmonary venous S/D ratio can be  $< 1$ , but the normality of findings including mitral annular  $e'$  velocity and LA maximum volume index should rarely cause confusion. Importantly, among the above mentioned parameters, the peak velocity of TR jet by CW Doppler provides a direct estimate of PASP when combined with right atrial pressure. Because it is uncommon to have primary pulmonary arterial disease coexisting with HFrEF, an elevated PASP supports the presence of elevated LAP.

If all three parameters are available for interpretation and only one of three meets the cutoff value, then LAP is normal and there is grade I diastolic dysfunction. If two of three or all three available parameters meet the corresponding cutoff values then LAP is elevated and there is grade II diastolic dysfunction. If only one parameter is available, LAP and grade of diastolic dysfunction should not be reported and likewise if there is discrepancy between the only two available parameters. The assessment of LV filling pressures is important in patients with HFrEF as it can successfully guide medical treatment.<sup>69</sup>

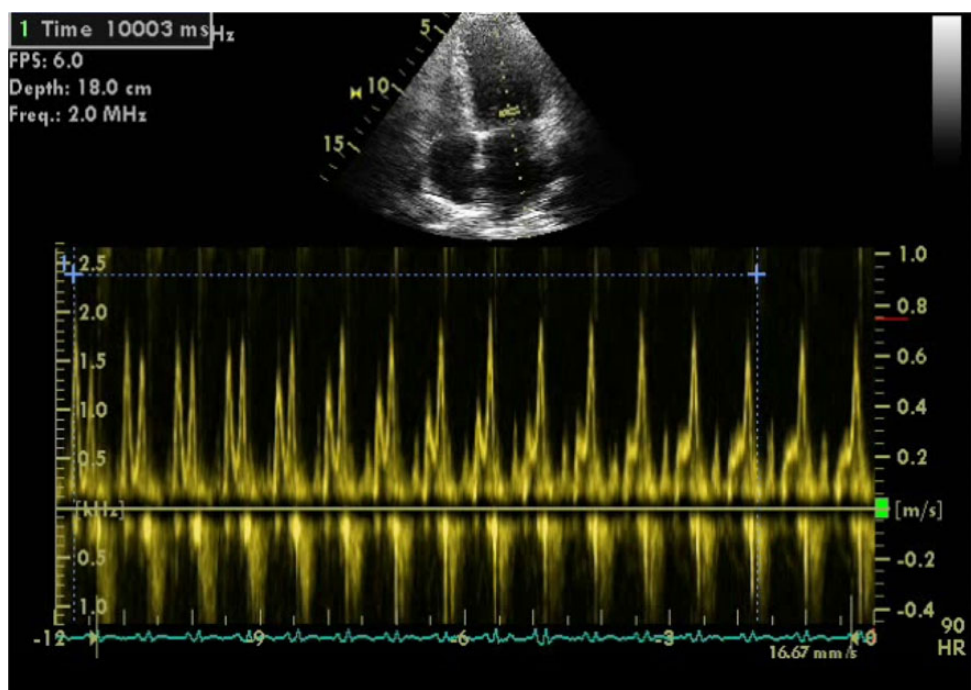
In patients with preserved EFs, the same initial evaluation of clinical presentation and 2D and color Doppler echocardiographic findings such as LVEF, regional wall motion abnormalities, LV hypertrophy, LA maximum volume index and significant mitral valve disease is performed to aid the assessment of LV diastolic function. Cardiac structural as well as functional information should be used when assessing diastolic function in patients with preserved EFs. In particular an enlarged LA that is clearly larger than the right atrium in the optimally aligned apical four-chamber view is strongly suggestive of chronically elevated LV filling pressure, provided conditions such as anemia, atrial arrhythmias and mitral valve disease can be excluded. Athletes may also have enlarged atria without increased LV filling pressures. However, a normal LA volume index does not exclude the presence of diastolic dysfunction when other findings are consistent with its presence. In particular, a normal LA volume is often noted in patients in the earliest stage of diastolic dysfunction and in situations with an acute increase in LV filling pressures. For LV hypertrophy (most reliably confirmed by LV mass that exceeds gender-specific normal range<sup>53</sup>), the finding of pathologic LV hypertrophy is consistent with diastolic dysfunction. Elevated PASP calculated from the TR jet (Figure 17) is strongly suggestive of elevated LV filling pressure unless pulmonary parenchymal or vascular disease is known to be present.

Similar to patients with depressed EFs, LAP is likely normal in the presence of an E/A ratio  $\leq 0.8$  along with a peak E velocity of  $\leq 50$  cm/sec in patients with structural heart disease and normal EF. The corresponding grade of diastolic dysfunction is grade I. In patients with an E/A  $\leq 0.8$  along with a peak E velocity of  $> 50$  cm/sec, or an E/A ratio  $> 0.8$  but  $< 2$ , additional parameters should be





**Figure 5** Valsalva maneuver in a patient with grade II diastolic dysfunction. At baseline, E/A ratio is 1.3 (left) and decreases to 0.6 (impaired relaxation pattern) with Valsalva.



**Figure 6** Continuous recording of mitral inflow during standardized Valsalva maneuver for 10 sec showing the decrease in E/A ratio with straining, which is consistent with elevated LV filling pressures.

examined. As in patients with depressed LVEFs, these include LA maximum volume index, peak velocity of TR jet and average  $E/e'$  ratio. Importantly, all three indices have been shown to be of value in identifying patients with HFrEF.<sup>45,70,71</sup> Cutoff values for elevated LAP

are average  $E/e' > 14$ , LA maximum volume index  $> 34 \text{ mL/m}^2$  and TR jet  $> 2.8 \text{ m/sec}$ . Because the pulmonary venous S/D ratio often is  $< 1$  in healthy young individuals, this index is of little value in patients with normal LVEF.

**Table 3** Proportion of normal subjects with abnormal LA volume index and Doppler velocities

Parameter	20–40 y			40–60 y			≥ 60 y			Global cohort		
	Total (N = 172) n/N (%)	Male (N = 79) n/N (%)	Female (N = 93) n/N (%)	Total (N = 194) n/N (%)	Male (N = 80) n/N (%)	Female (N = 114) n/N (%)	Total (N = 83) n/N (%)	Male (N = 39) n/N (%)	Female (N = 44) n/N (%)	Total (N = 449) n/N (%)	Male (N = 198) n/N (%)	Female (N = 251) n/N (%)
Septal $e' < 8$ cm/sec	2/170 (1.2)	2/79 (2.5)	0/91 (0)	38/193 (19.7)	13/80 (16.3)	25/113 (22.1)	46/83 (55.4)	22/39 (56.4)	24/44 (54.5)	86/446 (19.3)	37/198 (18.7)	49/248 (19.8)
Lateral $e' < 8$ cm/sec	2/167 (1.2)	1/76 (1.3)	1/91 (1.1)	11/192 (5.7)	4/80 (5.0)	7/112 (6.3)	15/79 (19.0)	5/36 (13.9)	10/43 (23.3)	28/438 (6.4)	10/192 (5.2)	18/246 (7.3)
Lateral $e' < 10$ cm/sec	3/167 (1.8)	2/76 (2.6)	1/91 (1.1)	30/192 (15.6)	9/80 (11.3)	21/112 (18.8)	41/79 (51.9)	17/36 (47.2)	24/43 (55.8)	74/438 (16.9)	28/192 (14.6)	46/246 (18.7)
Average (septal-lateral) $E/e' > 14$	0/158 (0)	0/75 (0)	0/83 (0)	3/184 (1.6)	1/76 (1.3)	2/108 (1.9)	1/78 (1.3)	1/36 (2.8)	0/42 (0)	4/420 (1.0)	2/187 (1.1)	2/233 (0.9)
Septal $E/e' > 15$	0/162 (0)	0/78 (0)	0/84 (0)	2/185 (1.1)	1/76 (1.3)	1/109 (0.9)	3/81 (3.7)	2/38 (5.3)	1/43 (2.3)	5/428 (1.2)	3/192 (1.6)	2/236 (0.8)
Lateral $E/e' > 13$	0/159 (0)	0/75 (0)	0/84 (0)	3/184 (1.6)	1/76 (1.3)	2/108 (1.9)	0/78 (0)	0/36 (0)	0/42 (0)	3/421 (0.7)	1/187 (0.5)	2/234 (0.9)
LA volume index $> 34$ mL/m <sup>2</sup> (*)	10/117 (8.5)	4/53 (7.5)	6/64 (9.4)	18/127 (14.2)	7/51 (13.7)	11/76 (14.5)	3/50 (6.0)	2/24 (8.3)	1/26 (3.8)	31/294 (10.5)	13/128 (10.2)	18/166 (10.8)
SPAP $> 36$ mm Hg	1/106 (0.9)	1/48 (2.1)	0/58 (0.0)	0/131 (0.0)	0/57 (0.0)	0/74 (0.0)	0/57 (0.0)	0/24 (0.0)	0/33 (0.0)	1/294 (0.3)	1/129 (0.8)	0/165 (0.0)
SPAP $> 45$ mm Hg	0/106 (0.0)	0/48 (0.0)	0/58 (0.0)	0/131 (0.0)	0/57 (0.0)	0/74 (0.0)	0/57 (0.0)	0/24 (0.0)	0/33 (0.0)	0/294 (0.0)	0/129 (0.0)	0/165 (0.0)

SPAP, Systolic pulmonary artery pressure.

\*LA volume index  $> 34$  mL/m<sup>2</sup> by biplane Simpson method (adapted from Caballero et al.<sup>53</sup>).

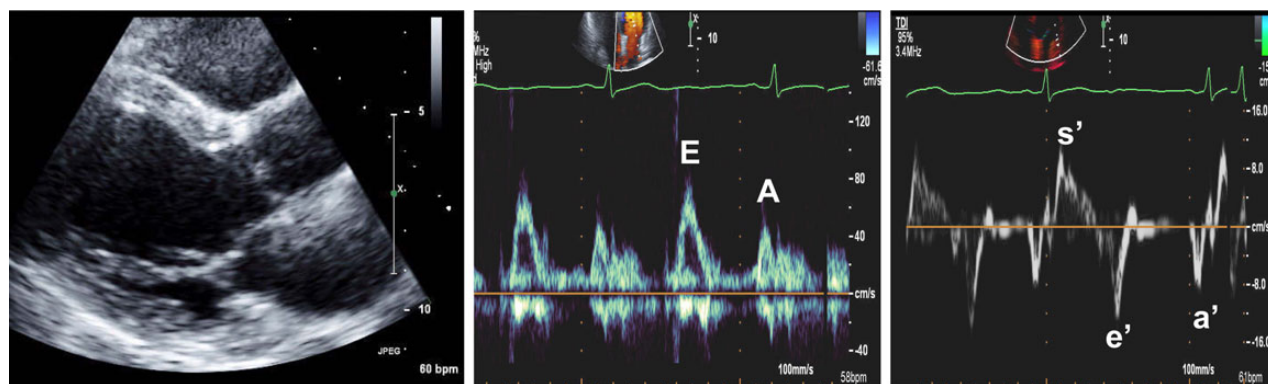
When two of three or all three variables meet the cutoff threshold, mean LAP is elevated and there is grade II diastolic dysfunction. Conversely, if two of three or all three variables do not meet the cutoff threshold, then LAP is normal and grade I diastolic dysfunction is present. If one of two available parameters gives opposite information to the other signal, or if there is only one parameter with satisfactory quality for analysis, neither LAP nor diastolic grade should be reported. In the presence of an E/A ratio  $\geq 2$ , grade III diastolic dysfunction is present. Table 4 presents a summary of the expected findings for the different grades of diastolic dysfunction.

### Key Points

- (1) In patients with reduced LVEFs, transmitral inflow pattern is usually sufficient to identify patients with increased LAP and DT of mitral E velocity is an important predictor of outcome.
- (2) In patients with preserved LVEFs, several parameters, including 2D variables, are often needed to estimate LAP.
- (3) In patients with depressed EFs and in patients with normal EFs and myocardial disease, if E/A ratio is  $\leq 0.8$  along with a peak E velocity of  $\leq 50$  cm/sec, then mean LAP is either normal or low and patient has grade I diastolic dysfunction.
- (4) In patients with depressed EFs and in patients with normal EFs and myocardial disease, if E/A ratio is  $\geq 2$ , LA mean pressure is elevated and grade III diastolic dysfunction is present. DT is usually short in patients with HFrEF and restrictive filling pattern ( $< 160$  msec). However, in patients with HFpEF, DT can be normal despite elevated LV filling pressures.
- (5) In patients with depressed EFs and in patients with normal EFs and myocardial disease, E/A ratio  $\leq 0.8$  along with a peak E velocity of  $> 50$  cm/sec, or an E/A ratio  $> 0.8$  but  $< 2$ , additional parameters are needed. These include peak TR velocity,  $E/e'$  ratio and LA maximum volume index. Their cutoff values to conclude elevated LAP are peak velocity of TR jet  $> 2.8$  m/sec, average  $E/e'$  ratio  $> 14$ , and LA maximum volume index  $> 34$  mL/m<sup>2</sup>. If more than half or all of the variables meet the cutoff values, then LAP is elevated and grade II diastolic dysfunction is present. If only one of three available variables meets the cutoff value, then LAP is normal and grade I diastolic dysfunction is present. In case of 50% discordance or with only one available variable, findings are inconclusive to estimate LAP.
- (6) In patients with depressed LVEFs, pulmonary vein S/D ratio may be used if one of the three main parameters is not available. A ratio  $< 1$  is consistent with increased LAP.

## 4. Conclusions on Diastolic Function in the Clinical Report

Although several invasive parameters of LV diastolic function such as the time constant of LV relaxation ( $\tau$ ) or LV chamber stiffness may be inferred or derived from Doppler echocardiographic findings, the association between invasive and noninvasive parameters is not perfect. Furthermore to date, there is no specific targeted treatment for these abnormalities that has proved useful in clinical trials. In comparison, specific comments on the status of LV filling pressures are more helpful to the referring physician in terms of narrowing a differential diagnosis. The conclusion could be one of three options: normal, elevated or cannot be determined (Table 5 shows examples from several laboratories on reporting findings about LV diastolic function). The writing group believes it is important to



**Figure 7** Example of normal findings from a young subject. Left shows normal LV size in parasternal long-axis view, with a normal mitral inflow pattern and E/A ratio  $> 1$  in middle panel. Lateral  $e'$  velocity is normal at 12 cm/sec (left).

include this conclusion when feasible, particularly in patients referred with symptoms of dyspnea or diagnosis of “heart failure.” In addition, the grade of LV diastolic dysfunction should be included in the reports along with the estimated LV filling pressures. The rationale for this recommendation comes from several single center and epidemiologic studies showing the independent and incremental prognostic information provided by LV diastolic dysfunction grade in several settings including HFrEF, HFpEF and acute myocardial infarction.<sup>72–87</sup> Finally, when feasible, comparison with previous studies and comments about changes in diastolic dysfunction grade or lack thereof, should be added as this can inform treatment decisions and predict future events of admissions for heart failure and total mortality.<sup>88–93</sup> Consideration may be given to diastolic stress testing in borderline cases (see section on diastolic stress test). Furthermore, right heart catheterization may be needed in difficult cases to determine if PCWP is elevated or if there is a discrepancy between right ventricular (RV) and LV filling pressures indicating the presence of pulmonary vascular disease.

#### Key Points

- (1) Conclusions on LV diastolic function should be included routinely in reports when feasible, particularly in patients referred with symptoms of dyspnea or diagnosis of heart failure.
- (2) The report should comment on LV filling pressures and the grade of LV diastolic dysfunction. If available, comparison with previous studies is encouraged to detect and comment on changes in diastolic function grade over time.

## 5. Estimation of LV Filling Pressures in Specific Cardiovascular Diseases

The following sections discuss the pathophysiology of disorders with abnormal cardiac structure, valve disease and atrial arrhythmias,

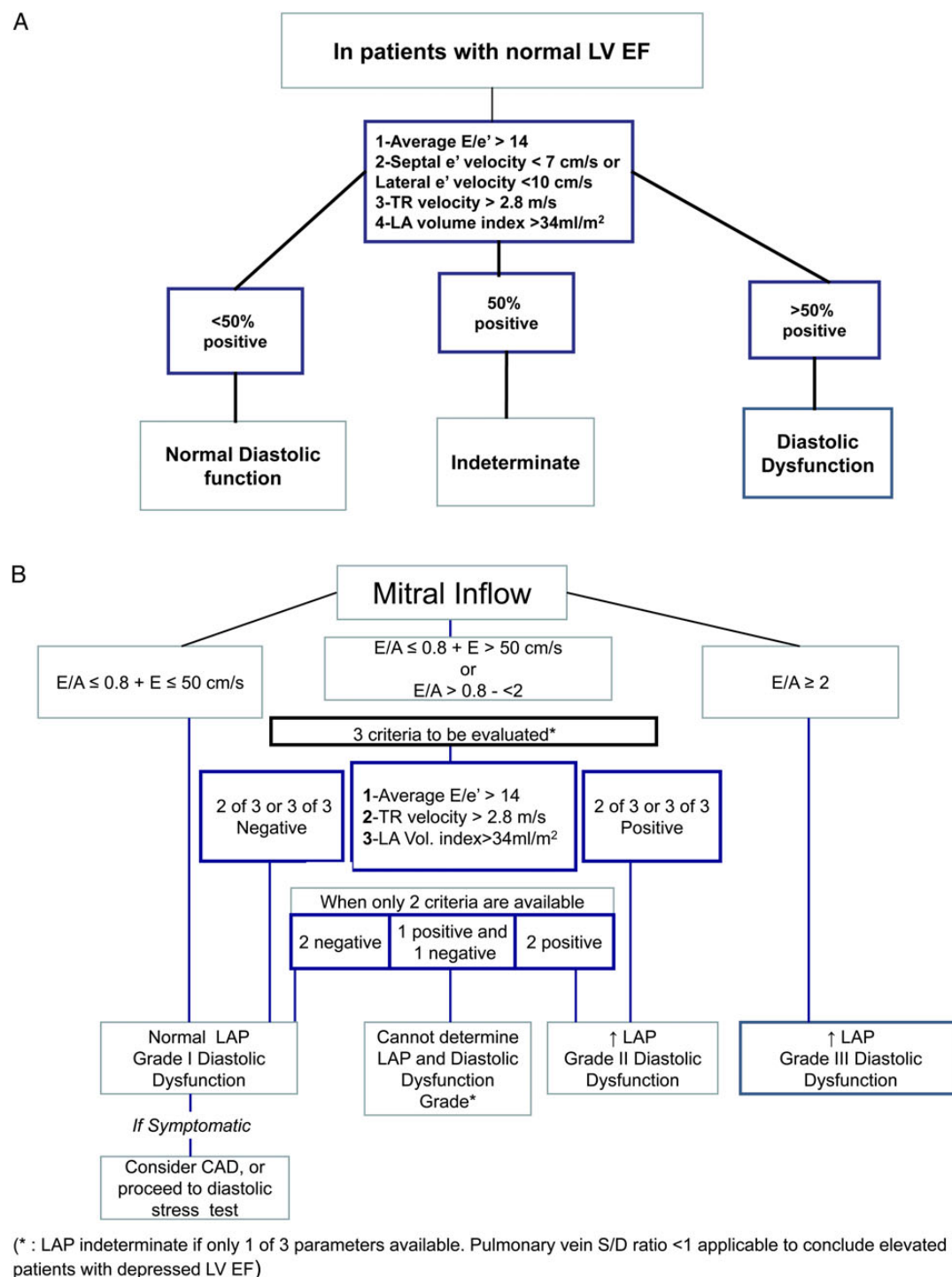
which modify the relationship between indices of diastolic function and LV filling pressure (Table 6). In some of the disorders the algorithm outlined above has significant limitations. PASP estimated from the TR jet, however, is a valid index of LAP in all conditions mentioned, provided there is no evidence of pulmonary vascular or parenchymal disease. In the absence of AF or atrial flutter, mitral valve disease or heart transplantation, an increased LA volume with a normal appearing right atrial size is a robust indicator of elevated LAP. One significant limitation to this marker is if heart failure therapy has resulted in normalization of pressures with persistent LA dilatation. In this setting, the presence of increased TR velocity  $> 2.8$  m/sec is suggestive of elevated LAP.

### 5.1. Hypertrophic Cardiomyopathy

A comprehensive approach is recommended for assessment of LV diastolic function and filling pressures in patients with hypertrophic cardiomyopathy (HCM) (example shown in Figure 18). This includes  $E/e'$  ratio, LA volume index, pulmonary vein atrial reversal velocity, and peak velocity of TR jet by CW Doppler.<sup>100–106,113,114</sup> In general, individual variables when used alone, have modest correlations with LV filling pressures in patients with HCM, likely related to variability in phenotype, muscle mass, amount of myocardial fiber disarray, and obstructive versus nonobstructive physiology. This leads to different combinations of altered relaxation and compliance and resultant variations of mitral inflow patterns. Aside from assessment of LV filling, 2D and Doppler indices of LV diastolic function provide incremental prognostic information in this population. In children with HCM, septal  $E/e'$  ratio predicted adverse outcomes including death, cardiac arrest and ventricular tachycardia.<sup>102</sup> There are similar results in adults with HCM, showing worse outcomes in patients with an enlarged left atrium, abnormal diastolic function detected by  $E/e'$  ratio, or restrictive LV filling.<sup>104–106,113,114</sup>

More recently, studies using STE have reported the association between LV systolic and diastolic strain, LA strain and LV diastolic function. Furthermore, they have provided mechanistic insights

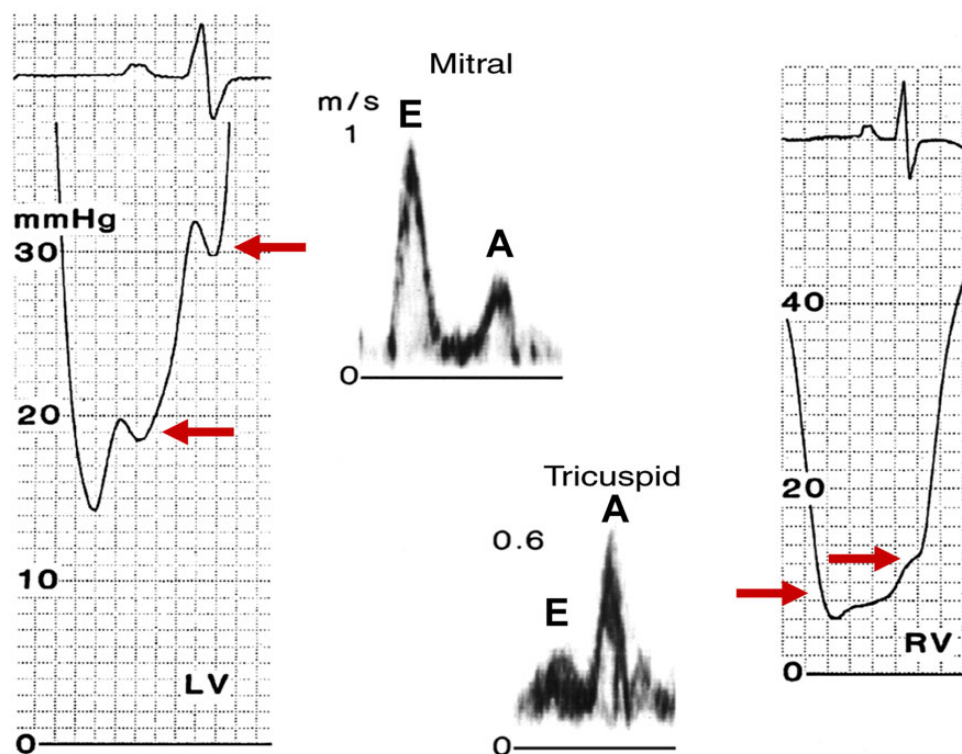




**Figure 8** (A) Algorithm for diagnosis of LV diastolic dysfunction in subjects with normal LVEF. (B) Algorithm for estimation of LV filling pressures and grading LV diastolic function in patients with depressed LVEFs and patients with myocardial disease and normal LVEF after consideration of clinical and other 2D data.

linking LV function, including torsion and untwisting, to exercise tolerance.<sup>115–120</sup> There is growing interest in studying the relation between early diastolic vortices and LV filling in HCM.<sup>121</sup> While

promising, additional studies and technical developments are needed before they can be endorsed as routine measurements in patients with HCM.



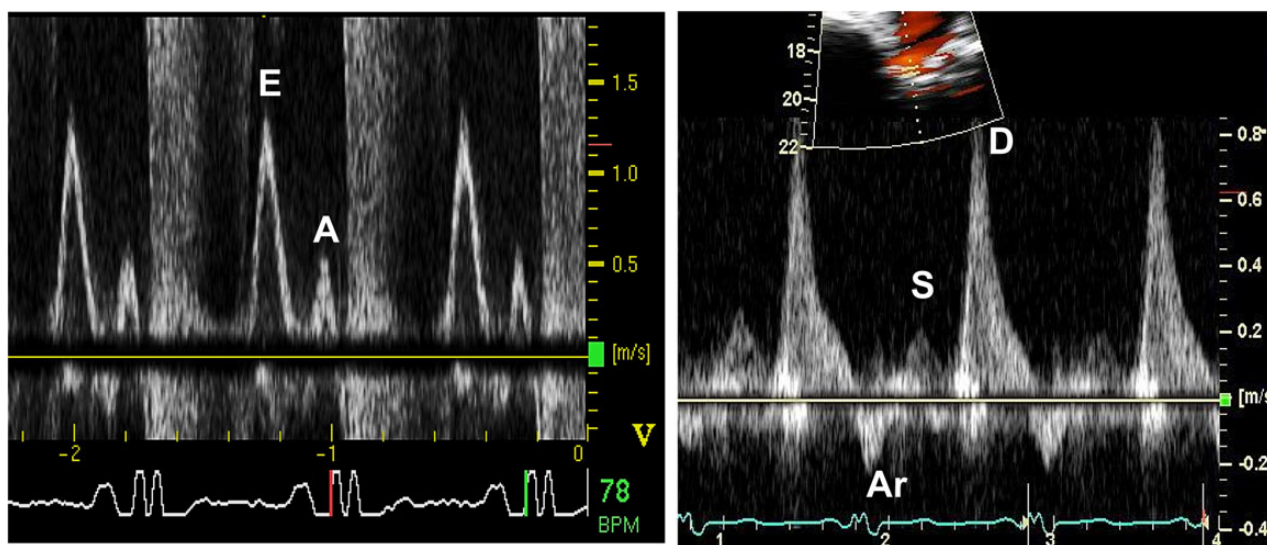
**Figure 9** LV and RV pressure recordings along with mitral inflow and tricuspid inflow obtained from a patient with dilated cardiomyopathy. LV pressure recordings are shown to the left with red arrows denoting LV pre-A pressure and LVEDP. Both are increased with LV pre-A pressure at 19 mm Hg and LVEDP at 30 mm Hg. Mitral inflow (top) shows restrictive filling pattern. In comparison, RV pressure recordings (right) show RV pre-A pressure at 8 mm Hg and RV end-diastolic pressure (RVEDP) at 12 mm Hg. The corresponding tricuspid inflow pattern (bottom) shows an impaired relaxation pattern. In the presence of normal LV and RV filling pressures and myocardial dysfunction, both tricuspid inflow and mitral inflow reveal an impaired relaxation pattern. Thus, the presence in this case of an impaired relaxation pattern for tricuspid inflow and a restrictive filling pattern for mitral inflow supports the conclusion that LV filling pressures are elevated. Abbreviations as in other figures.

### Key Points

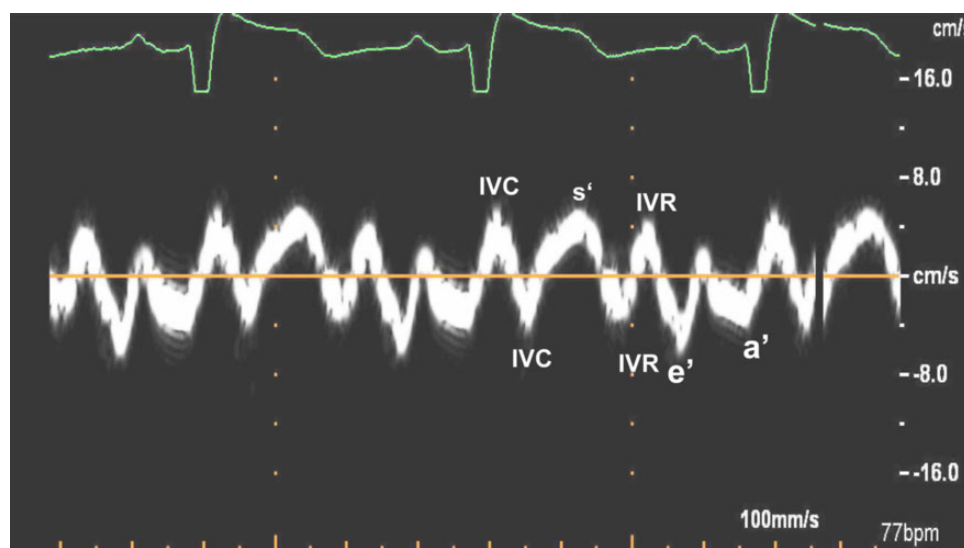
- (1) Variables recommended for evaluation of diastolic function in patients with HCM are average  $E/e'$  ratio ( $> 14$ ), LA volume index ( $> 34$  mL/m<sup>2</sup>), pulmonary vein atrial reversal velocity (Ar-A duration  $\geq 30$  msec), and peak velocity of TR jet by CW Doppler ( $> 2.8$  m/sec). The parameters can be applied irrespective of the presence or absence of dynamic obstruction and MR, except for patients with more than moderate MR, in whom only Ar-A duration and peak velocity of TR jet are still valid.
- (2) If more than half of the variables (total available variables three or four) meet the cutoff values, then LAP is elevated and grade II diastolic dysfunction is present. If  $< 50\%$  of the variables (total available variables three or four) meet the cutoff values, then LAP is normal and grade I diastolic dysfunction is present. In case of 50% discordance with two or four available variables, findings are inconclusive to estimate LAP. Estimation of LAP is not recommended if there is only parameter with a satisfactory signal.
- (3) Grade III diastolic dysfunction is present in the presence of a restrictive filling pattern and abnormally reduced mitral annular  $e'$  velocity (septal  $< 7$  cm/sec, lateral  $< 10$  cm/sec).

## 5.2. Restrictive Cardiomyopathy

Restrictive cardiomyopathies are composed of a heterogeneous group of heart muscle diseases including idiopathic restrictive cardiomyopathy, cardiac amyloidosis, and sarcoidosis.<sup>122</sup> In the earlier stages of cardiac amyloidosis, diastolic function can vary from grade 1 diastolic dysfunction with impaired relaxation and normal LV filling pressures to grade 2 (pseudonormalization). In later stages, grade 3 diastolic dysfunction occurs when LV relaxation is impaired along with markedly elevated LV filling pressures.<sup>107</sup> There has been a gradual evolution of the diastolic function techniques applied in studying these patients, initially using mitral inflow and pulmonary vein flow, to tissue Doppler and now STE, which can be used to measure strain and strain rate. The advanced stages of restrictive cardiomyopathy, are characterized by typical restrictive physiology with a dip and plateau pattern for early diastolic LV pressure changes with time, mitral inflow  $E/A$  ratio  $> 2.5$ , DT of E velocity  $< 150$  msec, isovolumic relaxation time (IVRT)  $< 50$  msec,<sup>108,123</sup> decreased septal and lateral  $e'$  velocities (3–4 cm/sec),<sup>124,125</sup> but with a higher lateral  $e'$  compared with septal  $e'$  velocity (unlike



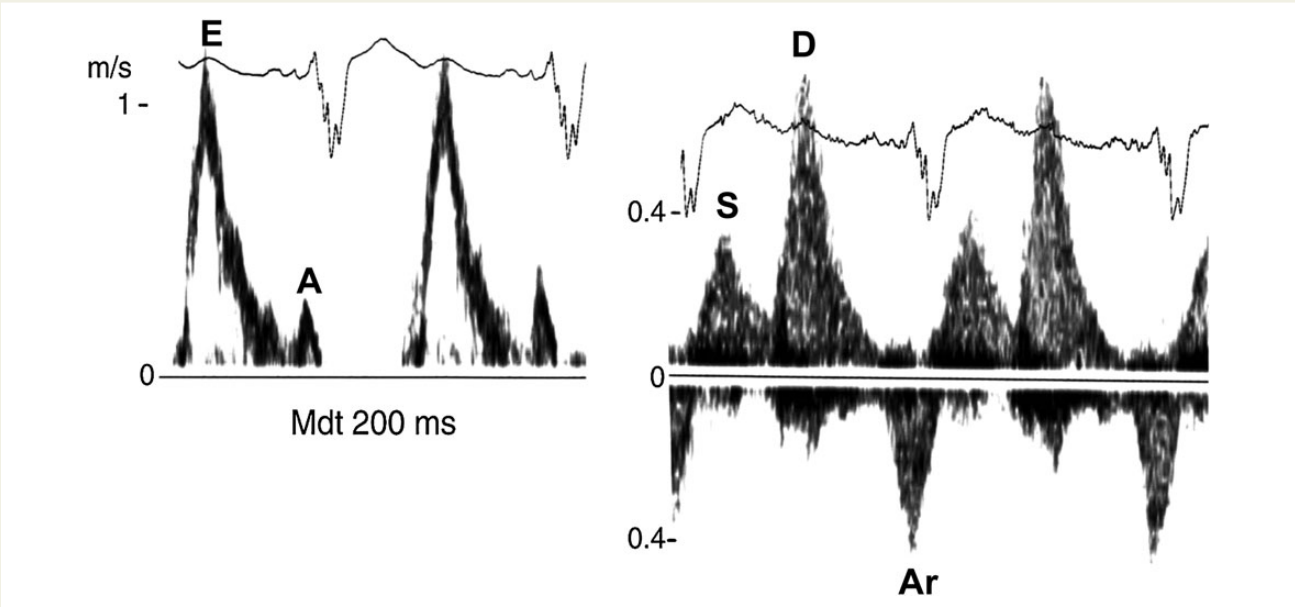
**Figure 10** Mitral inflow (left) and pulmonary venous flow (right) from a patient with HFrEF. Notice the increased E/A ratio  $>2$  and reduced S/D ratio in pulmonary venous flow. Both findings are consistent with increased LAP in this patient population.



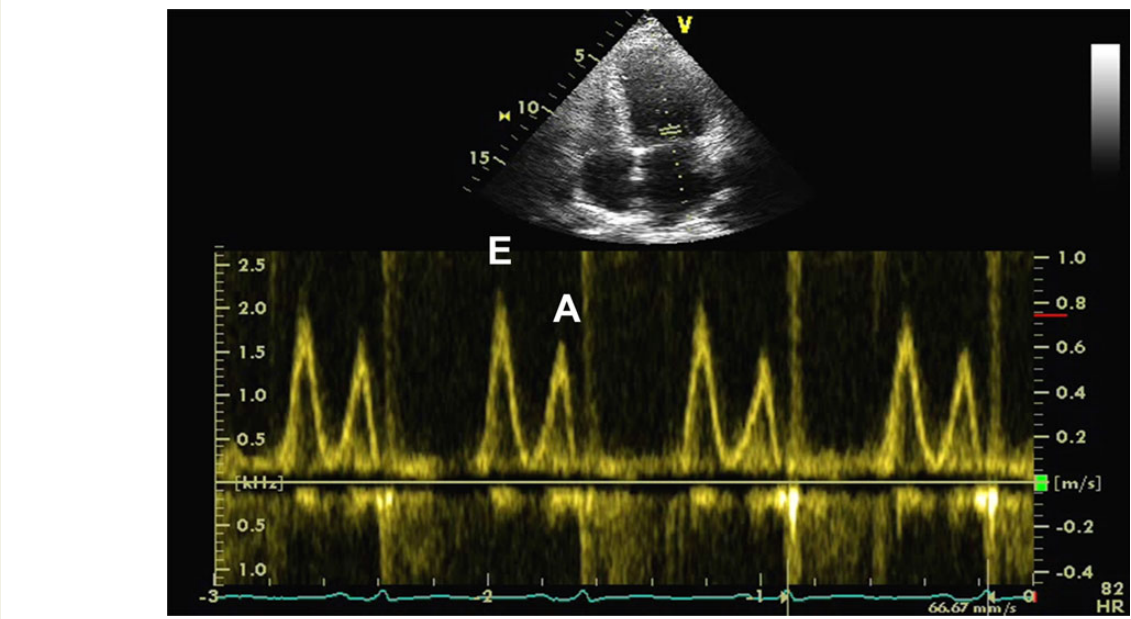
**Figure 11** Septal tissue Doppler velocities from a patient with HFrEF and ventricular dyssynchrony. Mitral annular  $e'$  (early diastolic annular velocity) should be distinguished from the biphasic velocity during isovolumic relaxation (IVR) period. Mitral annular late diastolic velocity ( $a'$ ) follows the "P" wave. Isovolumic contraction velocity (IVC) is biphasic. Systolic ejection velocity ( $s'$ ) follows IVC velocity and precedes IVR velocity.

constrictive pericarditis, in which septal  $e'$  is often higher, or annulus reversus),<sup>126</sup>  $E/e'$  ratio  $> 14$ , as well as a markedly increased LA volume index ( $>50 \text{ mL/m}^2$ )<sup>127,128</sup>. Figure 19 shows a validated algorithm from the Mayo Clinic comparing constrictive pericarditis with restrictive cardiomyopathy. The presence of a normal annular  $e'$  velocity in a patient referred with heart failure diagnosis should raise suspicion of pericardial constriction.

Grade 3 diastolic dysfunction is associated with a poor outcome in patients with restrictive cardiomyopathy.<sup>109</sup> It is important to make the distinction between restrictive LV filling, which can occur with other diseases such as coronary artery disease, dilated cardiomyopathy and HCM, and restrictive cardiomyopathy. STE of LV myocardium in patients with cardiac amyloidosis has shown a distinctive phenotype of apical sparing (Figure 20) using a polar plot



**Figure 12** (Left) Mitral inflow from a patient with HFpEF. Mitral inflow pattern is consistent with elevated LV filling pressures. Notice the abbreviated mitral A velocity with short duration. DT of mitral E velocity (Mdt) measured at 200 msec. This is seen in patients with markedly delayed LV relaxation such that LV diastolic pressure continues to decline after mitral valve opening. (Right) Pulmonary venous flow from the same patient. Notice the decreased S/D ratio and the increased amplitude and velocity of Ar signal consistent with increased LVEDP. Abbreviations as in other figures.

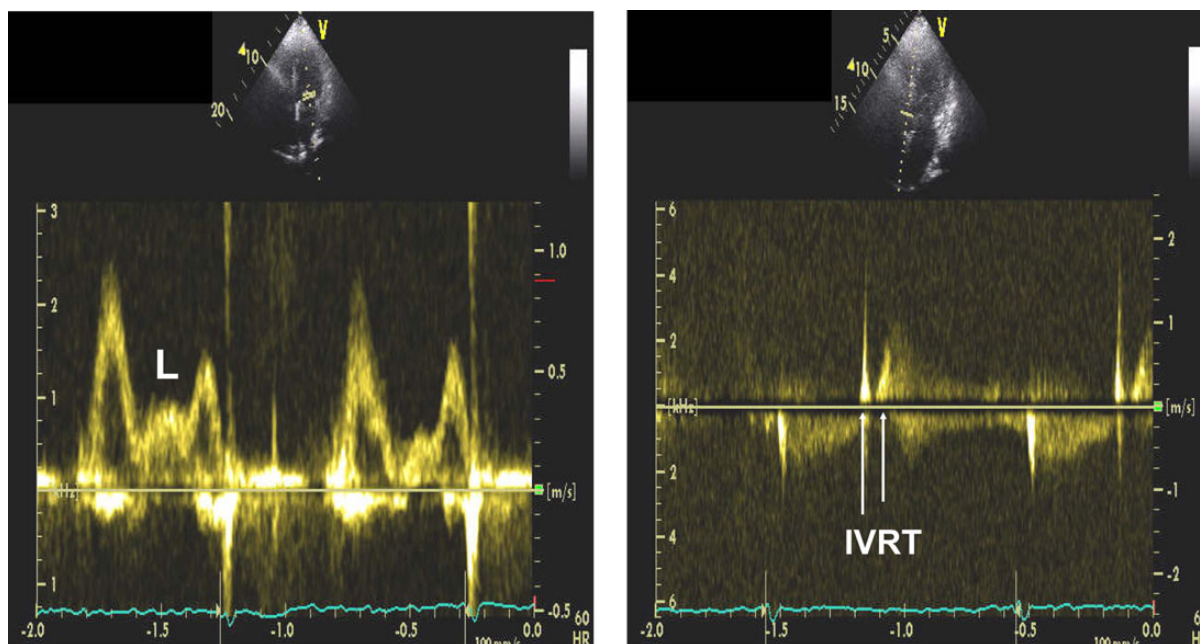


**Figure 13** Mitral inflow from a patient with hypertensive heart disease with normal EF. Patient has LV hypertrophy and a moderately enlarged left atrium. Mitral inflow shows pseudonormal LV filling pattern consistent with elevated LV filling pressures and grade II diastolic dysfunction.

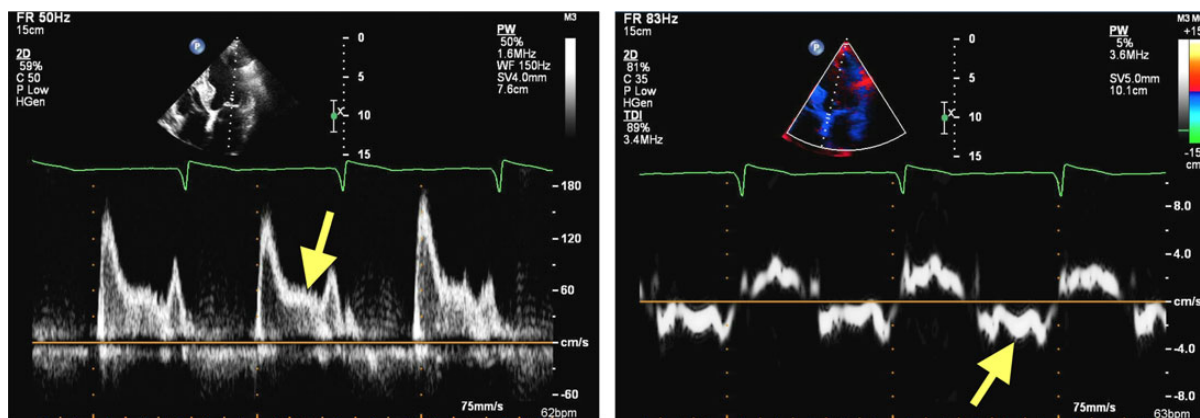
of LV longitudinal strain compared with hypertensive heart disease, HCM, and aortic stenosis.<sup>129</sup> Similar to tissue Doppler imaging, the ratio of LV free wall strain to LV septal strain by STE is about 1 in

patients with restrictive cardiomyopathy, whereas it is usually <1 in patients with constriction because of less deformation of the LV anterolateral wall compared with the LV septum.<sup>130</sup>





**Figure 14** Mitral inflow (left) and IVRT (right) from another patient with HFpEF and heart rate 60 beats/min. E velocity was 96 cm/sec with A velocity of 65 cm/sec. Mid-diastolic flow (L velocity) is present because of the slow and impaired LV relaxation and the increased LAP. The arrows in the right panel point to IVRT between aortic valve closure and mitral valve opening. IVRT was short at 48 msec consistent with increased LAP.



**Figure 15** L velocity from a patient in sinus rhythm and increased LAP. Notice the presence of L velocity in mitral inflow and septal tissue Doppler signals (arrows).

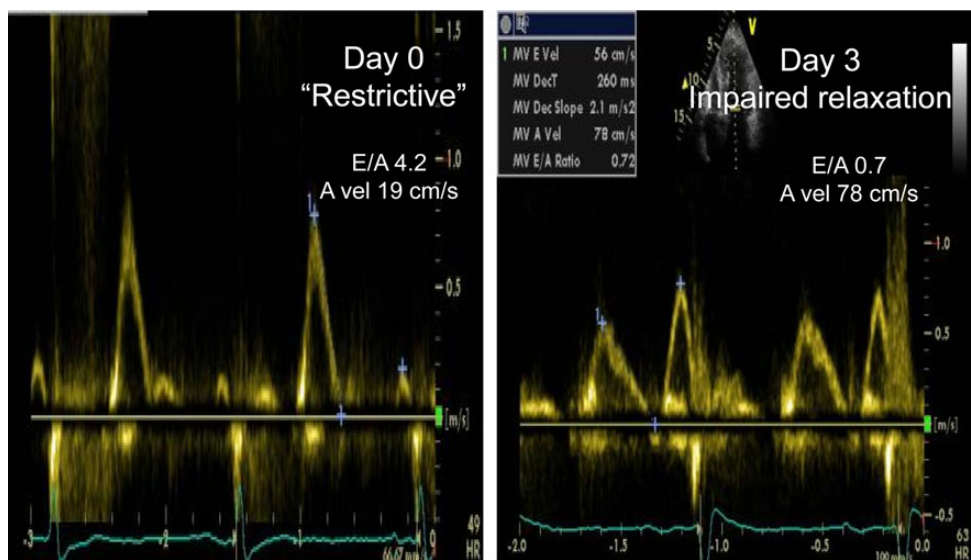
### Key Points

- (1) Patients with early disease usually have grade I diastolic dysfunction that progresses to grade II as the severity of the disease advances.
- (2) In patients with advanced disease, grade III diastolic dysfunction is present and is characterized by mitral inflow E/A ratio  $> 2.5$ , DT of E velocity  $< 150$  msec, IVRT  $< 50$  msec, and decreased septal and lateral  $e'$  velocities (3–4 cm/sec).
- (3) Patients with constrictive pericarditis usually have septal  $e'$  velocity higher than lateral  $e'$  velocity, or annulus reversus, and E/ $e'$  ratio should not be used to estimate LV filling pressures in patients with constrictive pericarditis.

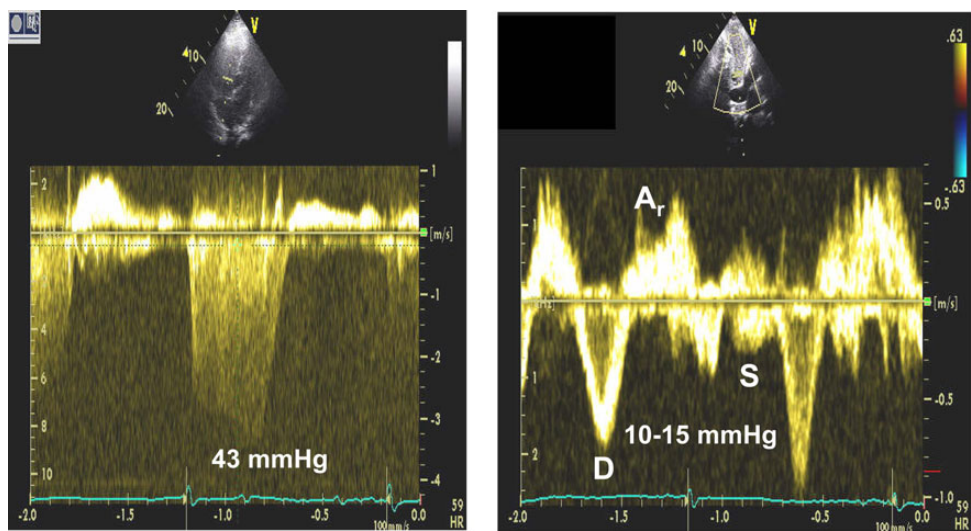
## 5.3. Valvular Heart Disease

### 5.3.1 Mitral Stenosis

In this condition, transmitral blood flow velocities and mitral annular dynamics are largely determined by the degree of valvular disease and therefore of limited value as indicators of LV disease. Typically, patients with mitral stenosis have normal or reduced LV diastolic pressures, except for the rare occurrence of coexisting myocardial disease. The same hemodynamic findings are present in patients with other etiologies of LV inflow obstruction, such as prosthetic mitral valve, large LA tumor, cor triatriatum sinistrum, and congenital mitral valve stenosis. Nevertheless, a semiquantitative estimation



**Figure 16** LA stunning after cardioversion. On the day of the cardioversion, LA stunning leads to markedly reduced mitral A velocity of 19 cm/sec and an apparent “restrictive LV filling” on the basis of mitral E/A ratio. Three days later, LA function improves with increased A velocity and a decreased E/A ratio consistent with impaired LV relaxation but normal LV filling pressures.



**Figure 17** TR velocity (3.3 m/sec) by CW Doppler (left) and hepatic venous flow (right) from a patient with HFpEF. RV-to-right atrial pressure gradient was 43 mm Hg and hepatic venous flow showed predominant forward flow during diastole (D), consistent with elevated right atrial pressure (10–15 mm Hg). Thus, PASP was estimated at 53 to 58 mm Hg. In normal elderly subjects without cardiac disease, predominant forward flow in hepatic veins occurs during systole. As right atrial mean pressure increases, flow pattern shifts so most flow occurs during diastole. Furthermore, the atrial reversal signal (Ar) that occurs because of right atrial contraction generating a positive pressure gradient between the right atrium and the hepatic veins increases in amplitude and duration with increasing RA pressure as seen in this recording. (Nagueh SF, Kopelen HA, Zoghbi WA. Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. *Circulation* 1996;93:1160–9; Rudski LG, Lai WVV, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713).

of instantaneous LAP can be provided in early and late diastole by Doppler variables. The shorter the IVRT (corresponds to time interval between second heart sound and mitral valve opening snap) and the higher the peak E-wave velocity, the higher the early diastolic LAP. LAP is significantly elevated at end-diastole if the mitral A velocity remains >1.5 m/sec at this point.



**Table 4** LV relaxation, filling pressures and 2D and Doppler findings according to LV diastolic function

	Normal	Grade I	Grade II	Grade III
LV relaxation	Normal	Impaired	Impaired	Impaired
LAP	Normal	Low or normal	Elevated	Elevated
Mitral E/A ratio	$\geq 0.8$	$\leq 0.8$	$> 0.8$ to $< 2$	$> 2$
Average E/e' ratio	$< 10$	$< 10$	10–14	$> 14$
Peak TR velocity (m/sec)	$< 2.8$	$< 2.8$	$> 2.8$	$> 2.8$
LA volume index	Normal	Normal or increased	Increased	Increased

**Table 5** Examples of conclusions on LV diastolic function from clinical laboratories

Example 1 (conclusion would contain an item from each of 1, 2, and 3)	(1) LV relaxation impaired or normal (2) LV filling pressures normal, elevated or borderline elevated (3) Grade I diastolic dysfunction or grade II diastolic dysfunction or grade III diastolic dysfunction
Example 2 (conclusion would contain one of the six options shown to the right)	(a) Normal diastolic function (b) Impaired LV relaxation, normal LAP (c) Impaired LV relaxation, mildly elevated LAP (d) Impaired LV relaxation, elevated LAP (e) Restrictive LV filling pattern, indicating markedly elevated LAP (f) Indeterminate
Example 3 (conclusion would contain one of the six options shown to the right)	(a) Normal diastolic function (b) Impaired LV relaxation, normal LAP (c) Impaired LV relaxation, increased LVEDP (d) Impaired LV relaxation, elevated LAP (e) Restrictive LV filling pattern, indicating markedly elevated LAP (f) Indeterminate
Example 4 (conclusion would contain one of the five options shown to the right)	(1) Normal diastolic function and filling pressure (2) Grade 1 (impaired relaxation with low to normal filling pressure) (3) Grade 2 (moderate increase in filling pressure) (4) Grade 3 (marked elevation in filling pressure)
Example 5 (conclusion would contain one of the three options shown to the right)	(1) Increased filling pressure (2) Normal filling pressure (3) Constrictive pericarditis
Example 6 (conclusion would contain one of the three options shown to the right)	(1) Findings consistent with diastolic dysfunction (2) Findings suggestive of probable diastolic dysfunction (3) Findings raise the possibility of diastolic dysfunction.

The time interval between onset of mitral E velocity and annular e' velocity can be applied to estimate LV filling pressures in patients with mitral valve disease. In the presence of impaired LV relaxation, the e' velocity is not only reduced but also delayed such that it occurs at the LA-LV pressure crossover point. In comparison, mitral E velocity occurs earlier with elevated LAP. Thus the time interval between the onset of mitral E velocity and annular e' velocity is prolonged and can correct for the effect of LV relaxation on IVRT. IVRT/T<sub>E-e'</sub> ratio correlates well with mean PCWP and LAP in patients with mitral stenosis (Figure 21). However, the E/e' ratio is not useful.<sup>110</sup>

### 5.3.2 MR

Primary MR leads to LA and LV enlargement and an increase in the compliance of both chambers, which attenuates the increase in

LAP. If LA compensation is incomplete, mean LAP and right-sided pressures increase, which is related to the additional regurgitant volume, not to LV dysfunction. With LV diastolic dysfunction, a myocardial component of increased filling pressures is added over time. The sequence is opposite to that seen in primary myocardial disease such as dilated cardiomyopathy, which leads to increased filling pressures earlier on and later to functional MR. Therefore, in patients with secondary MR, echocardiographic correlates of increased filling pressures reflect the combination of both myocardial and valvular disorders. Moderate and severe MR usually lead to an elevation of peak E velocity and a decrease in pulmonary venous systolic velocity and thus the S/D ratio in pulmonary venous flow. In severe MR, pulmonary venous flow reversal can be seen in late systole. Thus, MR per se can induce changes in transmitral and pulmonary venous flow patterns resembling advanced LV

**Table 6** Assessment of LV filling pressures in special populations

Disease	Echocardiographic measurements and cutoff values
AF <sup>43,94–99</sup>	Peak acceleration rate of mitral E velocity ( $\geq 1,900$ cm/sec <sup>2</sup> ) IVRT ( $\leq 65$ msec) DT of pulmonary venous diastolic velocity ( $\leq 220$ msec) E/Vp ratio ( $\geq 1.4$ ) Septal E/e' ratio ( $\geq 11$ )
Sinus tachycardia <sup>41,44</sup>	Mitral inflow pattern with predominant early LV filling in patients with EFs $< 50\%$ IVRT $\leq 70$ msec is specific (79%) Pulmonary vein systolic filling fraction $\leq 40\%$ is specific (88%) Average E/e' $> 14$ (this cutoff has highest specificity but low sensitivity) When E and A velocities are partially or completely fused, the presence of a compensatory period after premature beats often leads to separation of E and A velocities which can be used for assessment of diastolic function
HCM <sup>100–106</sup>	Average E/e' ( $> 14$ ) Ar-A ( $\geq 30$ msec) TR peak velocity ( $> 2.8$ m/sec) LA volume ( $> 34$ mL/m <sup>2</sup> ).
Restrictive cardiomyopathy <sup>13,107–109</sup>	DT ( $< 140$ msec) Mitral E/A ( $> 2.5$ ) IVRT ( $< 50$ msec has high specificity) Average E/e' ( $> 14$ )
Noncardiac pulmonary hypertension <sup>32</sup>	Lateral E/e' can be applied to determine whether a cardiac etiology is the underlying reason for the increased pulmonary artery pressures When cardiac etiology is present, lateral E/e' is $> 13$ , whereas in patients with pulmonary hypertension due to a noncardiac etiology, lateral E/e' is $< 8$
Mitral stenosis <sup>110</sup>	IVRT ( $< 60$ msec has high specificity) IVRT/T <sub>E-e'</sub> ( $< 4.2$ ) Mitral A velocity ( $> 1.5$ m/sec)
MR <sup>110–112</sup>	Ar-A ( $\geq 30$ msec) IVRT ( $< 60$ msec has high specificity) IVRT/T <sub>E-e'</sub> ( $< 5.6$ ) may be applied for the prediction of LV filling pressures in patients with MR and normal EFs Average E/e' ( $> 14$ ) may be considered only in patients with depressed EFs

A comprehensive approach is recommended in all of the above settings, which includes estimation of PASP using peak velocity of TR jet ( $> 2.8$  m/sec) and LA maximum volume index ( $> 34$  mL/m<sup>2</sup>). Conclusions should not be based on single measurements. Specificity comments refer to predicting filling pressures  $> 15$  mm Hg. Note that the role of LA maximum volume index to draw inferences on LAP is limited in athletes, patients with AF, and/or those with mitral valve disease.

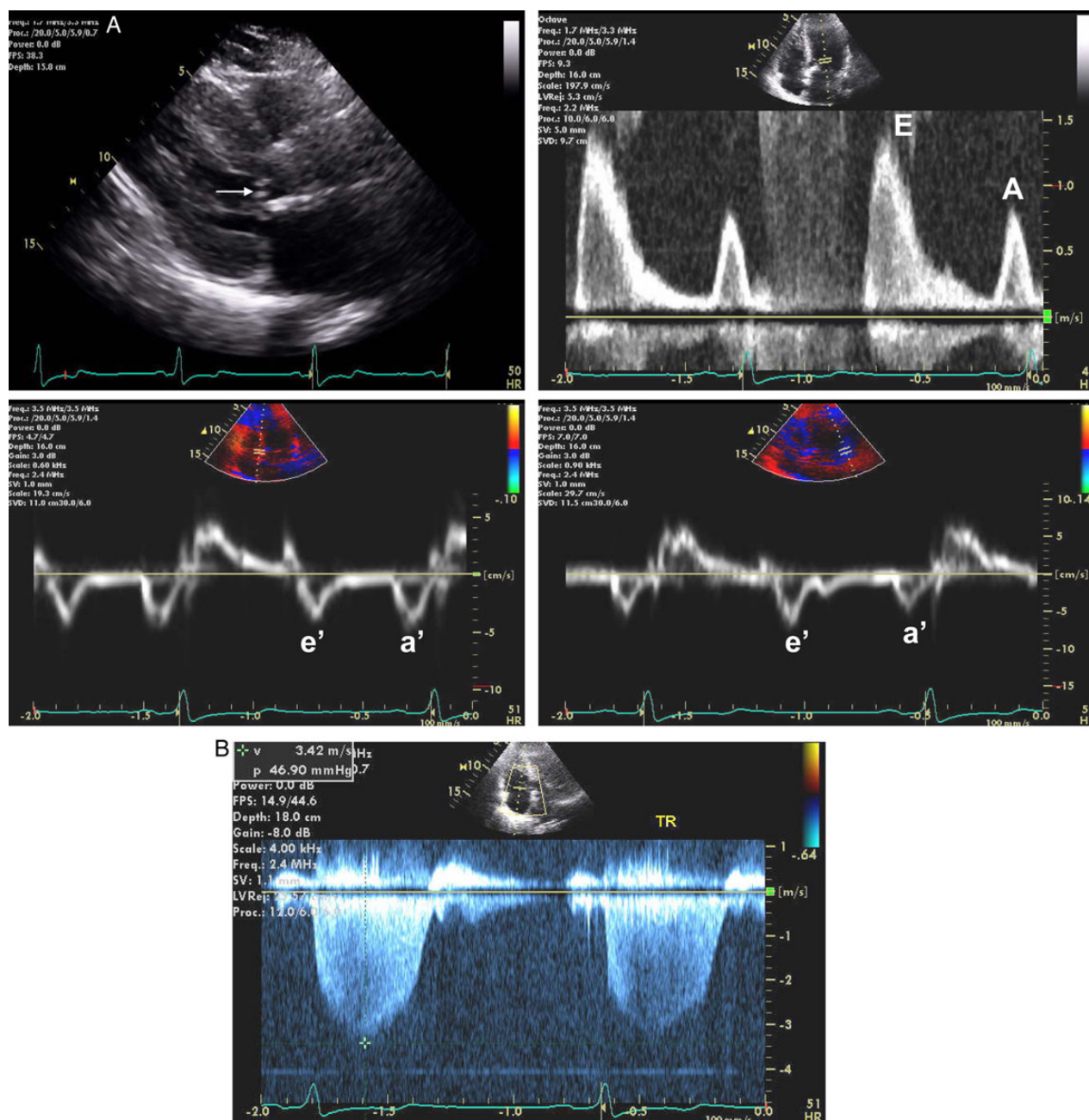
dysfunction, with the possible exception of the difference in duration between Ar and mitral A velocity.<sup>111</sup> MR velocity recording by CW Doppler can provide a highly specific, though not sensitive, sign of increased LAP with early peaking and usually a reduced LV pressure–LAP gradient. The utility of E/e' in predicting LV filling pressures in the setting of moderate or severe MR is more complex.<sup>112,131,132</sup> In patients with depressed EFs, an increased E/e' ratio has a direct significant relation with LAP and predicts hospitalizations and mortality.<sup>112,132</sup> E/e' does not appear to be useful in patients with primary MR and normal EFs, though some investigators have noted a good correlation between E/e' ratio and mean wedge pressure as well as PASP in this population.<sup>133</sup> IVRT and the ratio of IVRT to T<sub>E-e'</sub> correlate reasonably well with mean PCWP, regardless of EF.<sup>110</sup> An IVRT/T<sub>E-e'</sub> ratio  $< 3$  readily predicts PCWP  $> 15$  mm Hg in this patient subgroup. In patients with AF and MR, use of matched intervals (necessitating acquisition of a large number of cycles) or use of “index beats” is necessary.<sup>134</sup> It is challenging to assess LV relaxation and LV filling pressures after mitral valve surgery-repair or replacement, although time intervals and PA pressures could be of value.

### 5.3.3 MAC

MAC frequently accompanies hypertensive heart disease, aortic sclerosis, coronary artery disease and chronic kidney disease and is prevalent in elderly patients. In patients with moderate to severe MAC, mitral orifice area is decreased, leading to increased diastolic transmitral velocities, while lateral or posterior e' may be decreased due to restriction of the posterior mitral leaflet excursion.<sup>135</sup> Thus, an increase in E/e' ratio occurs due to the mechanical effect of mitral calcification. Since underlying conditions such as hypertension may also cause diastolic dysfunction, separation of the effect of mitral calcification from that of LV diastolic dysfunction on E/e' ratio may not be possible in the individual patient. It is not known if septal e' velocity or myocardial velocities distal to annular calcification can be of value in these patients.

### 5.3.4 Aortic Stenosis and Regurgitation

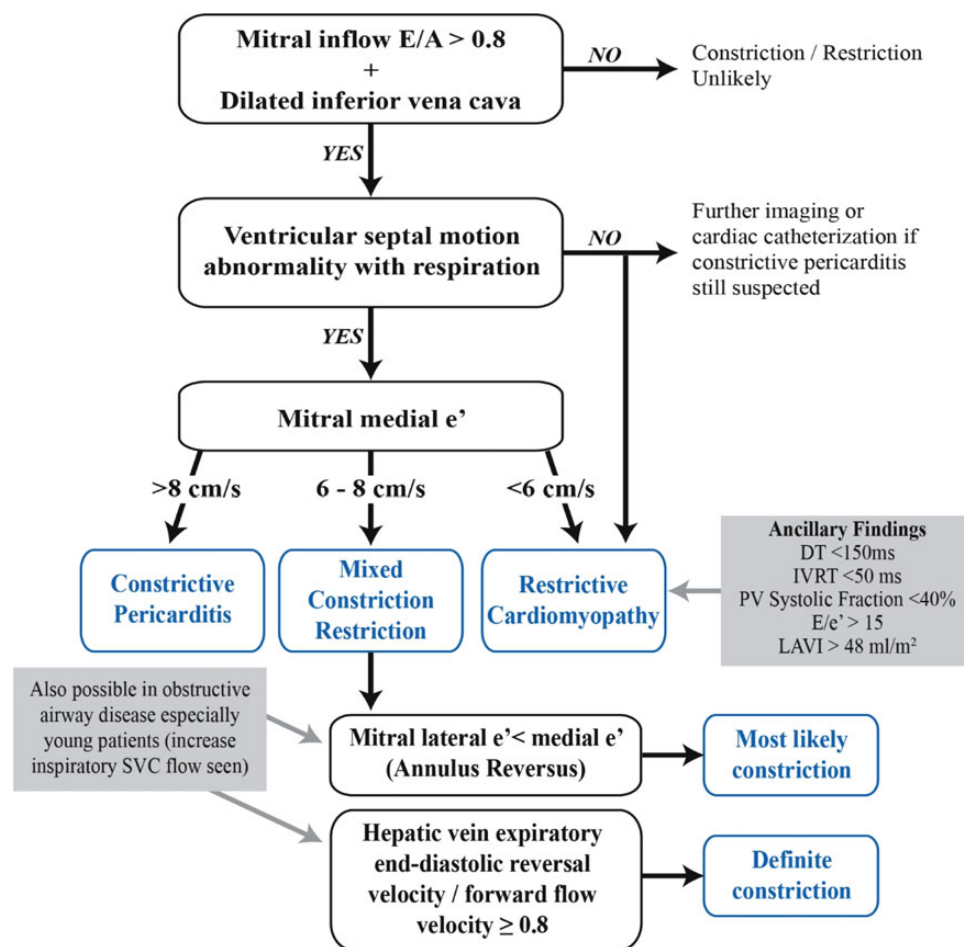
There are usually no major challenges to the application of the guidelines in patients with aortic stenosis, except for the coexistence of moderate to severe MAC, for which the limitations noted in the previous section apply. For patients with severe aortic



**Figure 18** (A) Two-dimensional imaging of a patient with HCM (left top) in the parasternal long-axis view showing systolic anterior motion of the mitral valve (arrow). Mitral inflow shows an E/A ratio  $> 1$  (right top). Septal (bottom left) and lateral (bottom right) tissue Doppler early (e') and late (a') diastolic velocities are markedly reduced consistent with severely impaired LV relaxation. Average E/e' ratio is  $> 14$ , consistent with elevated mean LAP. Abbreviations as in other figures. (B) Peak TR velocity (3.42 m/sec) by CW Doppler from the same patient in (A). Peak RV-to-right atrial systolic pressure gradient is 47 mm Hg. Thus, PASP is  $\geq 47$  mm Hg.

regurgitation (AR), the AR jet can interfere with the recording of mitral inflow velocities and careful positioning of the sample volume is needed to avoid contamination with the AR jet. In severe acute AR, the presence of abbreviated LV diastolic filling period, premature closure of the mitral valve, and diastolic MR indicate the presence of elevated LV filling pressures. In chronic severe AR, the mitral

inflow pattern often shows predominant early diastolic filling with short DT of mitral E velocity. There are limited data on the accuracy of estimation of LV filling pressures in patients with chronic severe AR. In patients with AR, the presence of LA enlargement, average E/e' ratio  $> 14$ , and TR peak velocity  $> 2.8$  m/sec support the presence of increased LV filling pressures.



**Figure 19** Algorithm comparing constrictive pericarditis and restrictive cardiomyopathy. Note restriction is associated with elevated E/A ratio, short DT and decreased mitral annular velocity ( $<6$  cm/sec). The figure is based on data from Welch TD, Ling LH, Espinosa RE, et al. Echocardiographic diagnosis of constrictive pericarditis: Mayo Clinic criteria. *Circ Cardiovasc Imaging* 2014;7:526–34.

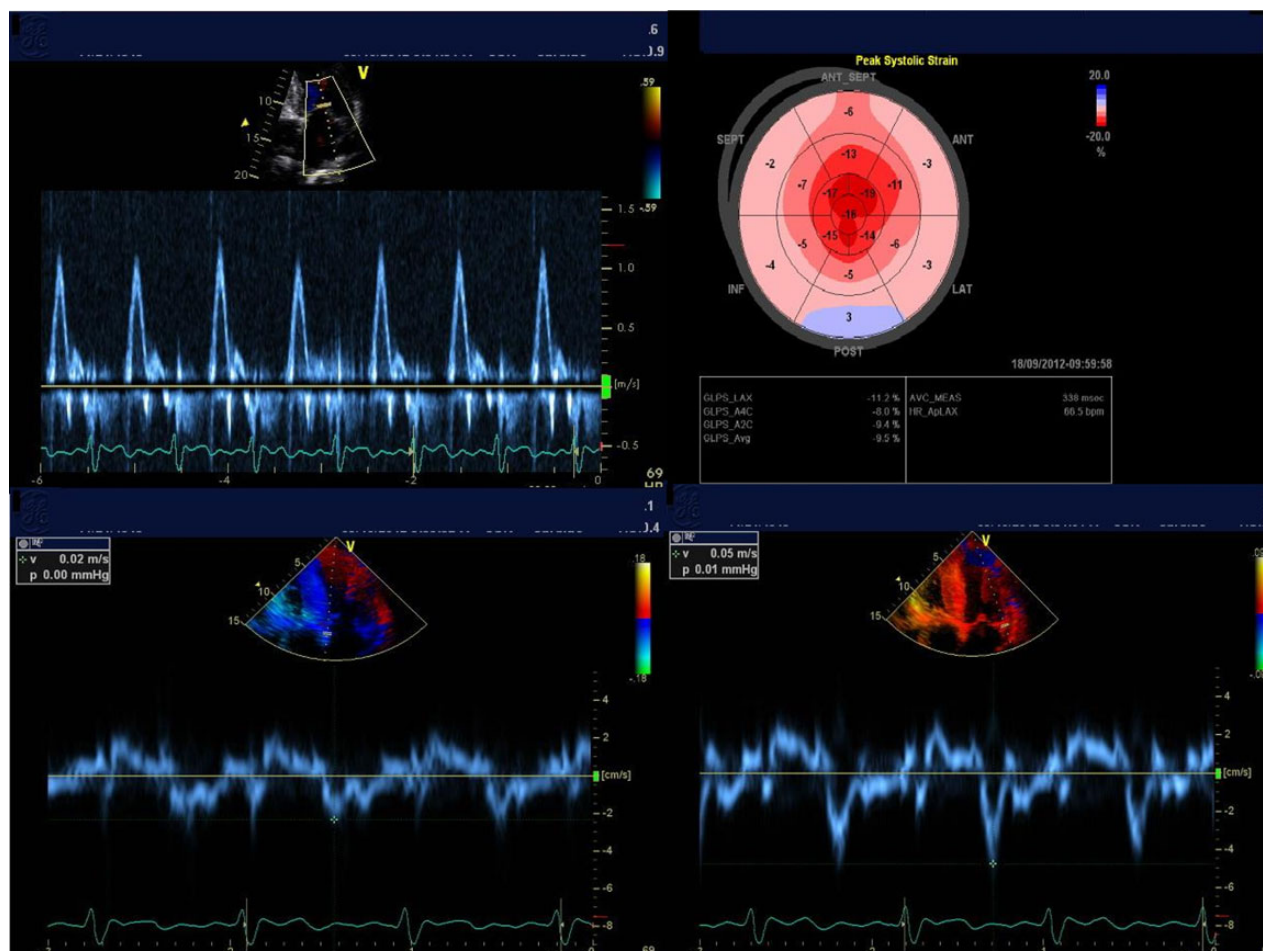
### Key Points

- (1) Mitral stenosis renders assessment of LV diastolic function more challenging, but IVRT,  $T_{E-e'}$ , and mitral inflow peak velocity at early and late diastole can be of value in the semiquantitative prediction of mean LAP.
- (2) The time interval Ar-A and IVRT/ $T_{E-e'}$  ratio may be applied for estimation for prediction of LV filling pressures in patients with MR and normal LVEF, whereas  $E/e'$  ratio may be considered only in patients with MR and depressed EF.
- (3) The guidelines in patients without valvular heart disease can be applied to patients with aortic stenosis, irrespective of severity of valvular stenosis. This excludes patients with heavy MAC.
- (4) In patients with severe AR be it acute or chronic, premature closure of mitral valve, diastolic MR, LA enlargement, average  $E/e'$  ratio  $> 14$ , and TR peak velocity  $> 2.8$  m/sec are consistent with elevated LV filling pressures.

## 5.4. Heart Transplantation

The transplanted heart is affected by many factors that influence LV diastolic function making the interpretation of diastolic function more difficult. First, the donor heart is denervated, leading to sinus tachycardia with reduced heart rate variability.<sup>136</sup> In turn, sinus tachycardia results in fusion of mitral E and A velocities. The biatrial surgery technique usually results in two intact SA nodes beating at different rates (donor and remaining right atrial tissue from recipient heart) which can each affect mitral inflow causing beat to beat variability in mitral E and A velocities. Furthermore, atrial function can be impaired because of the midatrial anastomoses between the donor and the recipient hearts. In comparison, the bicaval surgery technique may not impede atrial function.<sup>137</sup> Pulmonary venous flow is usually not helpful in assessing LV diastolic function and filling pressures. The contraction of the remnant recipient atrial tissue interacts with the systolic pulmonary forward flow component when





**Figure 20** Restrictive physiology in advanced cardiac amyloidosis showing (left upper) elevated E/A ratio and short DT, decreased mitral annular septal velocities (left lower) and lateral velocities (right lower) and apical sparing on deformation imaging (right upper).

it occurs during systole and can lead to lower S velocity, whereas pulmonary vein Ar velocity can be markedly increased if recipient atrial contraction occurs at end-diastole.

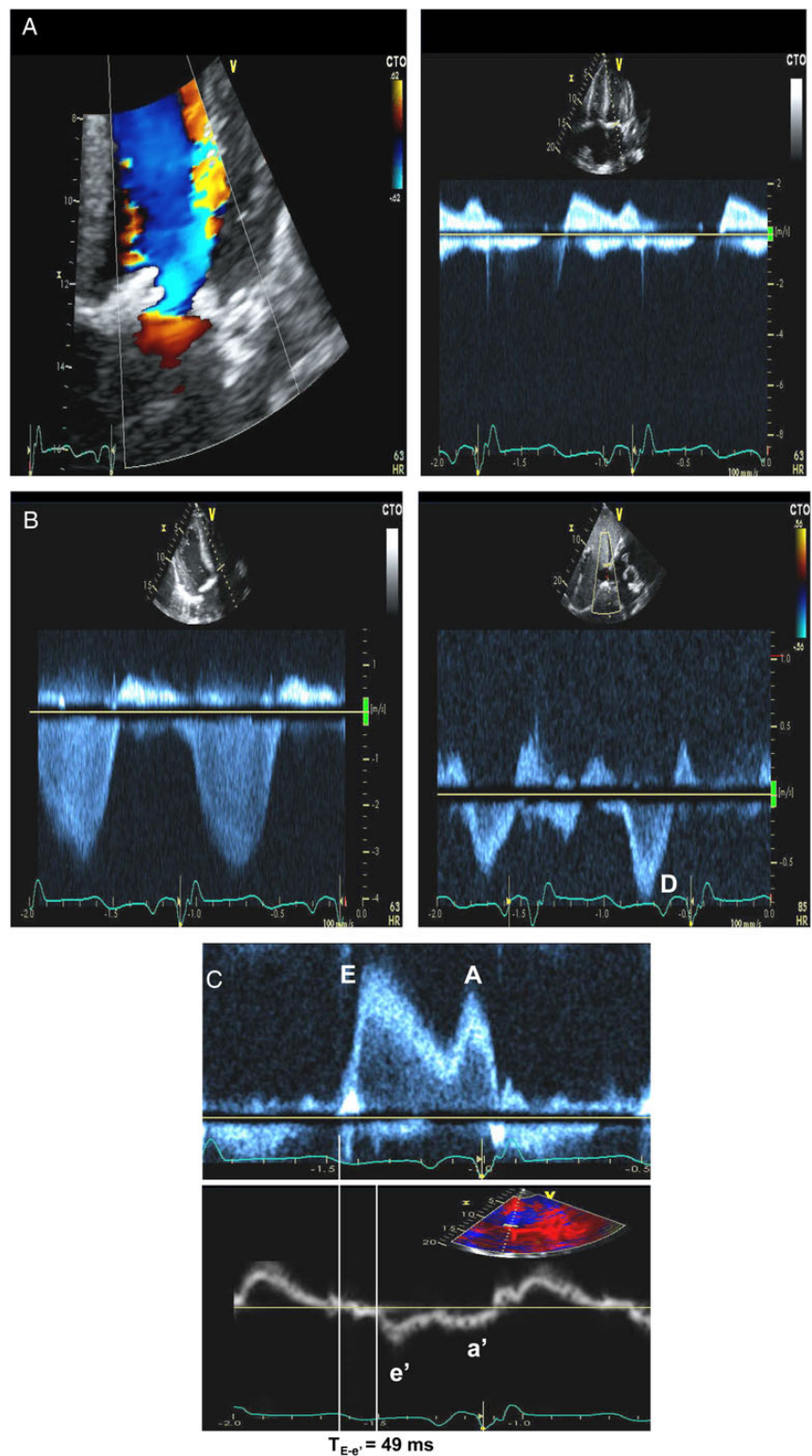
A restrictive appearing filling pattern in patients with preserved EFs is a common finding after heart transplantation and is observed in patients with normal LV diastolic function as donor hearts are usually obtained from healthy young individuals.<sup>138</sup> It is most pronounced in the early weeks after surgery and can change at follow-up.<sup>139,140</sup> While LV diastolic pressures can be normal at rest, a large increase in LVEDP has been noted during exercise.<sup>141</sup>

Similar considerations as described above also exist for  $e'$  velocity as it is influenced by translational motion of the heart. Of note, myocardial tissue velocities are lowest early after surgery and tend to increase during the following weeks and months, though some studies noted that they were reduced 1 year after transplantation compared with a normal population.<sup>142–146</sup> LV diastolic dysfunction has often been described as a sensitive sign of early graft rejection as myocardial edema causes increased diastolic stiffness and filling pressures in the presence of a normal EF

(Figure 22). Later on, myocardial fibrosis seen with chronic graft rejection can lead to a restrictive LV filling pattern and markedly reduced annular velocities (Figure 23). However, no single diastolic parameter appears reliable enough to predict graft rejection.<sup>146</sup> As in other diseases, PASP estimation using the TR jet can be helpful as a surrogate measurement of mean LAP in the absence of pulmonary disease.

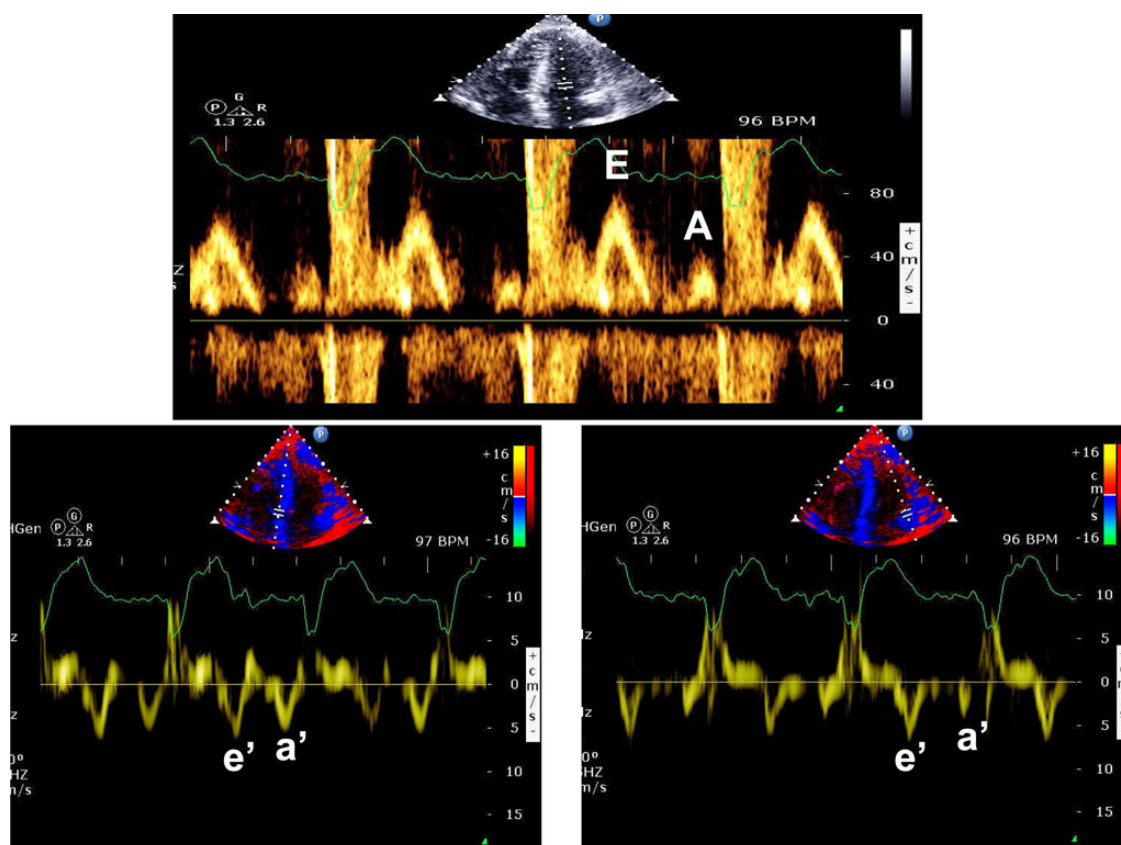
#### Key Points

- (1) A restrictive appearing filling pattern in patients with preserved EFs is a common finding after heart transplantation and is observed in patients with normal LV diastolic function as donor hearts are usually obtained from healthy young individuals.
- (2) No single diastolic parameter appears reliable enough to predict graft rejection. PASP estimation using the TR jet can be helpful as a surrogate measurement of mean LAP in the absence of pulmonary disease.



**Figure 21** Patient with mitral stenosis and LV diastolic dysfunction. (A) Color Doppler flow across stenotic mitral valve showing flow acceleration zone (left) and CW Doppler (right) of forward diastolic mitral inflow showing increased peak velocity (1.5 m/sec) and gradient (peak gradient = 8 mm Hg and mean gradient = 3.4 mm Hg) across the stenotic mitral valve. (B) TR jet by CW Doppler (left) showing RV-to-right atrial pressure gradient of 49 mm Hg. Hepatic venous flow (right) shows forward flow only in diastole (D) consistent with increased right atrial pressure. Together, there is evidence of pulmonary hypertension. (C) Mitral inflow (top) and septal mitral annulus tissue Doppler velocities (bottom). Notice the delayed  $e'$  velocity such that mitral E begins before annular  $e'$  velocity ( $T_{E-e'} = 49 \text{ msec}$ ). Abbreviations as in other figures.





**Figure 22** Mitral inflow (top) and septal (bottom left) and lateral (bottom right) mitral annular velocities by tissue Doppler from a patient with heart transplantation and LV diastolic dysfunction. Notice the reduced septal and lateral  $e'$  velocities (5–6 cm/sec). Abbreviations as in other figures.

## 5.5. Atrial Fibrillation

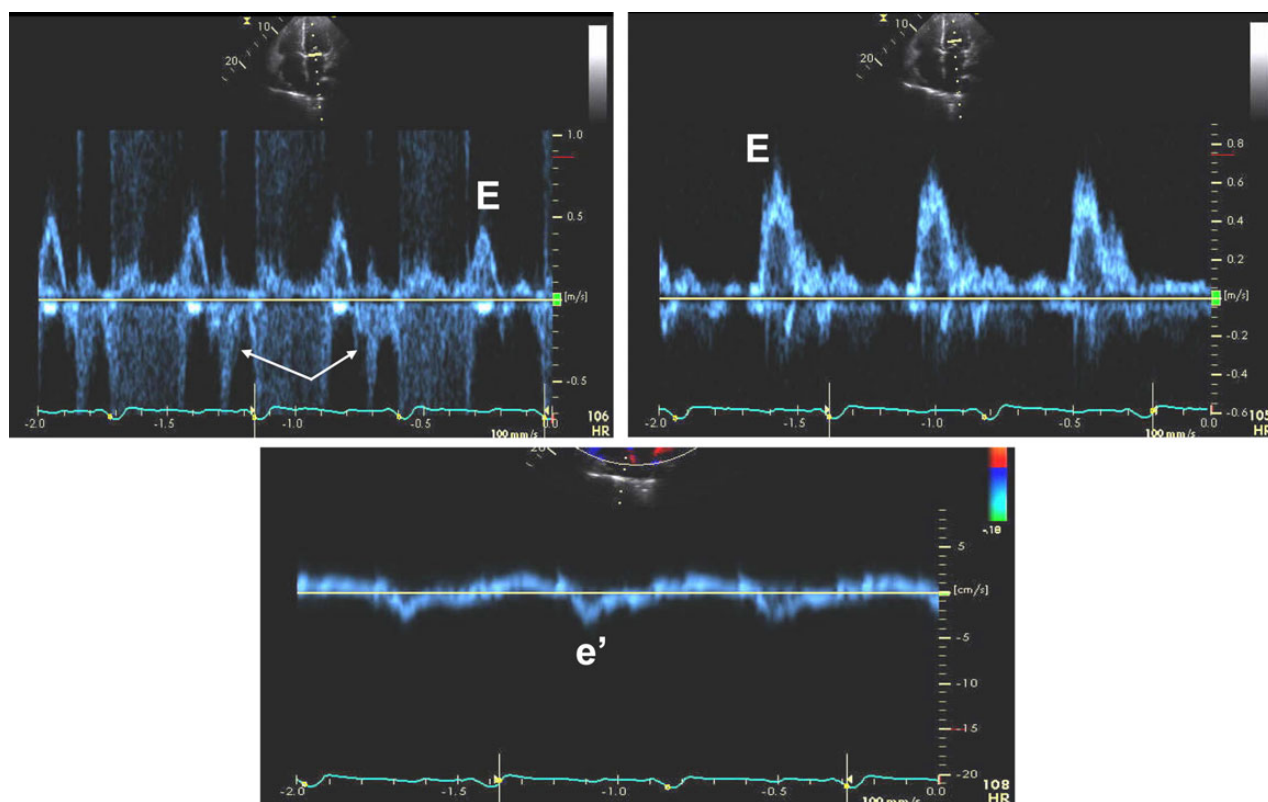
LV diastolic dysfunction causes LA dilatation, which can lead to AF,<sup>147–149</sup> and the presence of AF is not uncommon in patients with heart failure. In patients with AF, Doppler assessment of LV diastolic function is limited by the variability in cycle length, the absence of organized atrial activity, and the frequent occurrence of LA enlargement regardless of filling pressures. In general, when LVEF is depressed in patients with AF, mitral DT ( $\leq 160$  msec) has reasonable accuracy for the prediction of increased LV diastolic pressures and adverse clinical outcomes.<sup>94,95</sup> Other Doppler measurements that can be applied include peak acceleration rate of mitral E velocity ( $\geq 1,900$  cm/sec<sup>2</sup>), IVRT ( $\leq 65$  msec), DT of pulmonary venous diastolic velocity ( $\leq 220$  msec), E/mitral Vp (E/Vp;  $\geq 1.4$ ), and E/ $e'$  ratio ( $\geq 11$ ).<sup>43,94–96</sup> Similar to sinus rhythm, the time interval between onset of mitral E and annular  $e'$  velocity could be measured. The delay in annular  $e'$  velocity occurs in the setting of impaired LV relaxation and when combined with “IVRT-IVRT/ $T_{E-e'}$ ” ratio can be used to predict LV filling pressures.<sup>150,151</sup>

It is critical to average several cardiac cycles and to use matched RR intervals for both E and  $e'$  velocities. This often poses important limitations to the routine application of these measurements in clinical practice. Recently the simultaneous recording of E and  $e'$  velocities using a dual Doppler probe has made it possible to analyze both the peak velocity as well as the timing of mitral E and

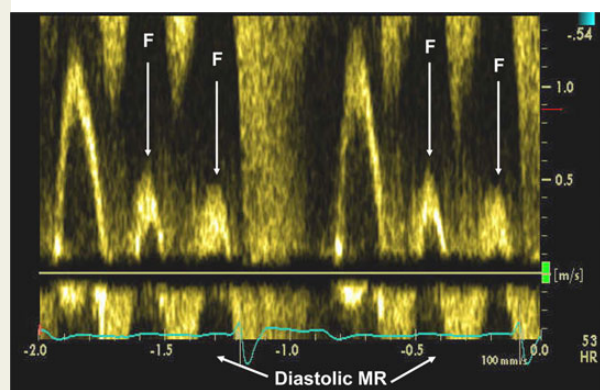
annular  $e'$  velocities from the same cardiac cycle, which led to improved accuracy in the estimation of LV filling pressure in this patient population.<sup>97–99</sup> In the absence of this system, one can use velocity measurements from 10 consecutive cycles, though velocities and time intervals averaged from three nonconsecutive beats with cycle lengths within 10% to 20% of the average heart rate are still useful.<sup>94</sup> In addition, the variability of mitral inflow velocity with the RR cycle length should be examined, as patients with increased filling pressures have less beat to beat variation.<sup>94</sup> Examples are shown in Figures 24–27.

### Key Points

- (1) Peak TR velocity  $> 2.8$  m/sec is suggestive of elevated LAP.
- (2) In patients with depressed LVEFs, mitral DT ( $\leq 160$  msec) has reasonable accuracy for the prediction of increased LV diastolic pressures and adverse clinical outcomes.
- (3) In patients with incomplete TR jet other Doppler measurements can be applied, including peak acceleration rate of mitral E velocity  $\geq 1,900$  cm/sec<sup>2</sup>, IVRT  $\leq 65$  msec, DT of pulmonary venous diastolic velocity  $\leq 220$  msec, E/Vp ratio  $\geq 1.4$ , and E/ $e'$  ratio  $\geq 11$ .
- (4) The variability of mitral inflow velocity with the RR cycle length is of value in patients with AF, as patients with increased filling pressures have less beat to beat variation.



**Figure 23** Mitral inflow (top left: pulsed-wave Doppler of mitral inflow at level of mitral annulus; top right: pulsed-wave Doppler of mitral inflow at level of mitral valve tips) from another heart transplantation patient in a ventricular paced rhythm and with severely depressed LV systolic function and diastolic dysfunction (bottom: markedly reduced septal  $e'$  velocity at 2–3 cm/sec). Notice the presence of short DT of mitral E velocity (<150 msec), abbreviated diastolic flow duration with premature termination of forward flow. There is also diastolic MR (arrows). All of the above findings are consistent with markedly elevated LV filling pressures, which includes LVEDP. Abbreviations as in other figures.

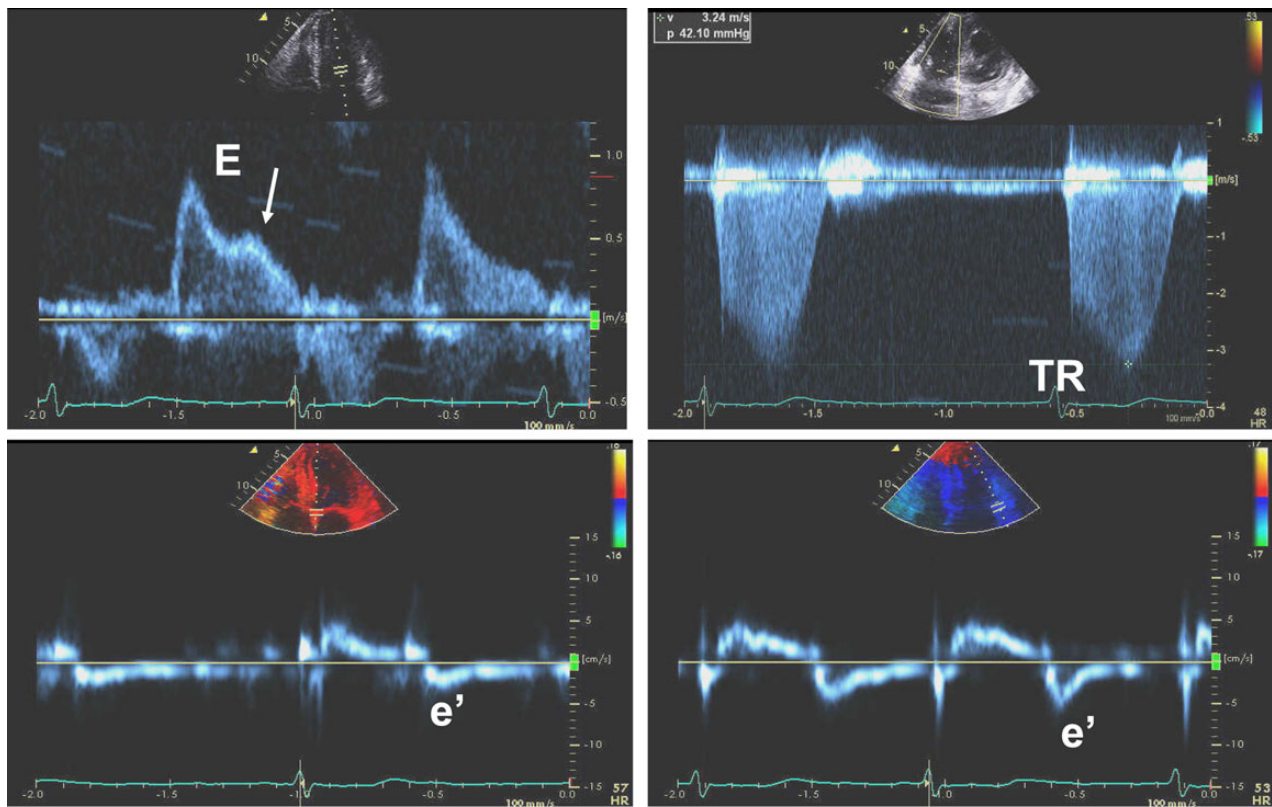


**Figure 24** Doppler recording from a patient with atrial flutter. Notice the presence of flutter waves (F) and diastolic MR (arrows).

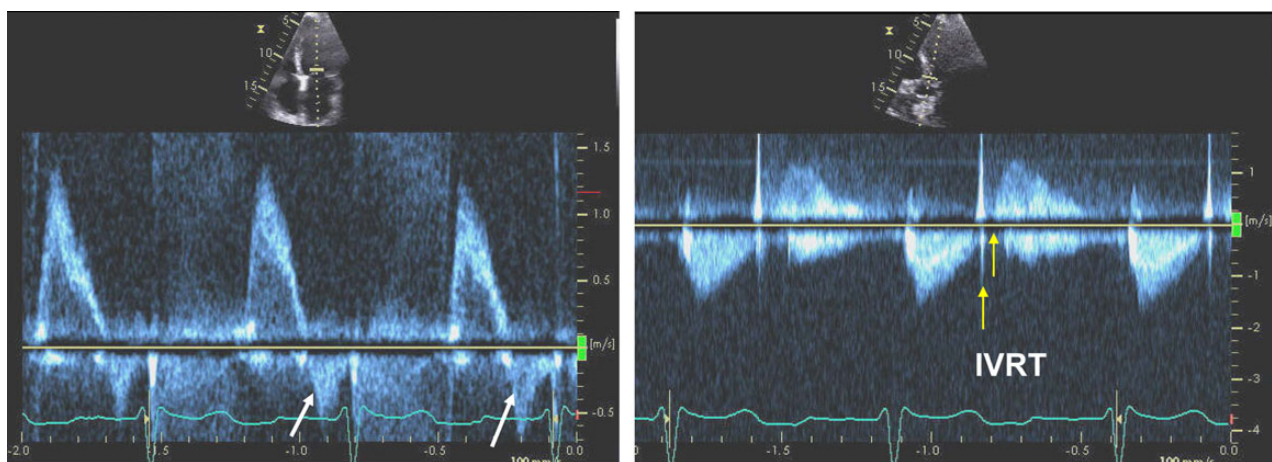
## 5.6. Atrioventricular Block and Pacing

In the normal heart, sinus node depolarization spreads through the right and LA myocytes, arriving at the atrioventricular (AV) node within 200 msec. A properly timed atrial contraction can increase cardiac output by 25% to 30%. Electrical activation then travels

roughly twice as fast through the specialized cardiac conduction system, proceeding down the His-Purkinje system and right and left bundles, which activate both ventricles simultaneously starting at the endocardium and spreading to the epicardium; with electrical repolarization taking place from epicardium to endocardium. Normal subjects have near simultaneous contraction and relaxation of all ventricular segments, which is demonstrated as a synchronous systolic inward and outward diastolic movement of both ventricles. Abnormalities of the cardiac conduction system due to disease, aging, drugs, or pacing can adversely affect AV synchrony and synchronous LV contraction and relaxation, which may reduce functional aerobic capacity by altering LV systolic and diastolic function, and thus the diastolic variables used to assess diastolic function. If the PR interval is too short, atrial filling is terminated early by ventricular contraction thus reducing mitral A duration, LV end-diastolic volume, and cardiac output. A first-degree AV block of 200 to 280 msec is usually well tolerated if the LVEF and heart rate are normal. However, in patients with shortened diastolic filling periods due to markedly impaired LV relaxation, faster heart rates, bundle branch block or ventricular pacing, a first-degree AV block of >280 msec usually results in “fusion” of E and A velocities (Figure 27). If atrial contraction occurs before early diastolic mitral flow velocity has decreased to  $\leq 20$  cm/sec, the E/A velocity ratio is reduced because of a higher A-wave velocity.<sup>152</sup> This “fusion” of early and late diastolic filling



**Figure 25** Doppler recordings from a patient with AF and elevated LV filling pressures. Mitral inflow (top left) shows increased peak diastolic velocity (E) at 90 to 100 cm/sec and increased acceleration rate. L velocity is seen in the mitral inflow signal (arrow). TR peak velocity (top right) is  $\cong 3.2$  m/sec, corresponding to RV-to-right atrial pressure gradient of 42 mm Hg and thus increased PASP. Septal (bottom left) and lateral (bottom right) annular diastolic velocities are markedly reduced with an average E/e' ratio  $\cong 30$ . Collectively, the above findings are consistent with increased LV filling pressures.

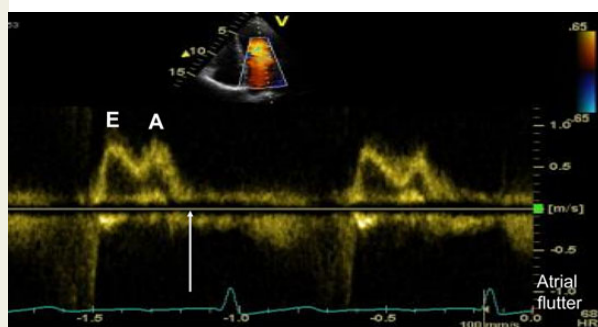


**Figure 26** Doppler recordings from a patient with increased LV filling pressures. Notice the increased peak velocity and acceleration rate of the diastolic forward flow signal (left). IVRT is short at 50 ms (right). Arrows point to diastolic MR which is consistent with increased LVEDP.

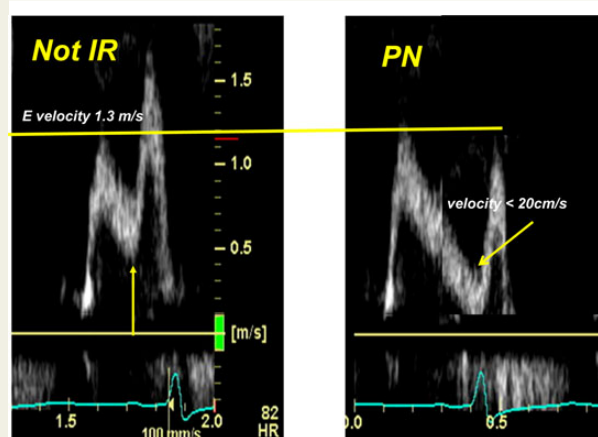
with an E/A velocity ratio of  $<1$  can be misinterpreted as impaired relaxation filling pattern (Figure 28). In addition with mitral E and A fusion, the larger atrial stroke volume increases the mitral A-wave duration and pulmonary venous peak systolic velocity and

time-velocity integral. Diastolic fusion of filling waves can also limit exercise capacity because LV end-diastolic volume is reduced, lowering maximal cardiac output. At PR values  $> 320$  msec, AV synchrony becomes “unphysiologic” because of marked E- and A-wave fusion, or





**Figure 27** Mitral inflow in a patient with a first-degree AV block. Notice merging of mitral E and A velocities and the shortened diastolic filling period. Mitral A velocity ends before end-diastole (arrow) and leads to an abbreviated diastolic filling period.



**Figure 28** Effect of heart rate on merging of E and A velocities and need to consider mitral velocity at onset of A. Left panel recording was obtained at heart rate of 82/min with mitral velocity at onset of A exceeding 20 cm/sec (arrow), which if not considered (subtracted from peak A velocity) results in the erroneous conclusion of impaired relaxation pattern. Right panel was obtained from the same patient at heart rate of 65 beats/min in whom mitral velocity at onset of A is < 20 cm/sec. The right panel shows that the patient indeed has pseudonormal LV filling.

filling only with atrial contraction (uniphasic A wave), and diastolic MR is seen.<sup>153</sup> In these patients maximal exercise capacity is almost always limited because of the inability to increase LV filling with increasing heart rate. If only the mitral A wave is present, only TR velocity can be used as a possible indicator of LV filling pressures.

A right bundle branch block results in delayed activation of the RV myocardium as electrical depolarization must spread through myocytes instead of the specialized conduction system. Although minor changes in LV and RV synchrony are observed no studies have convincingly shown that this leads to clinically meaningful changes in LV diastolic variables or exercise capacity. This is also true of left anterior or right posterior hemiblock. In contrast, left bundle branch block is frequently associated with organic heart disease and

impaired LV diastolic function. As with other disease states with impaired relaxation, the effect on mitral filling variables is heavily influenced by LV stiffness and loading conditions. With normal LAP, an impaired LV relaxation filling pattern is seen, while pseudonormal and restrictive patterns occur with progressive increases in LV stiffness and LAP. As long as no fusion of mitral E and A velocities occurs, the variables used to evaluate diastolic function and filling pressures likely remain valid.

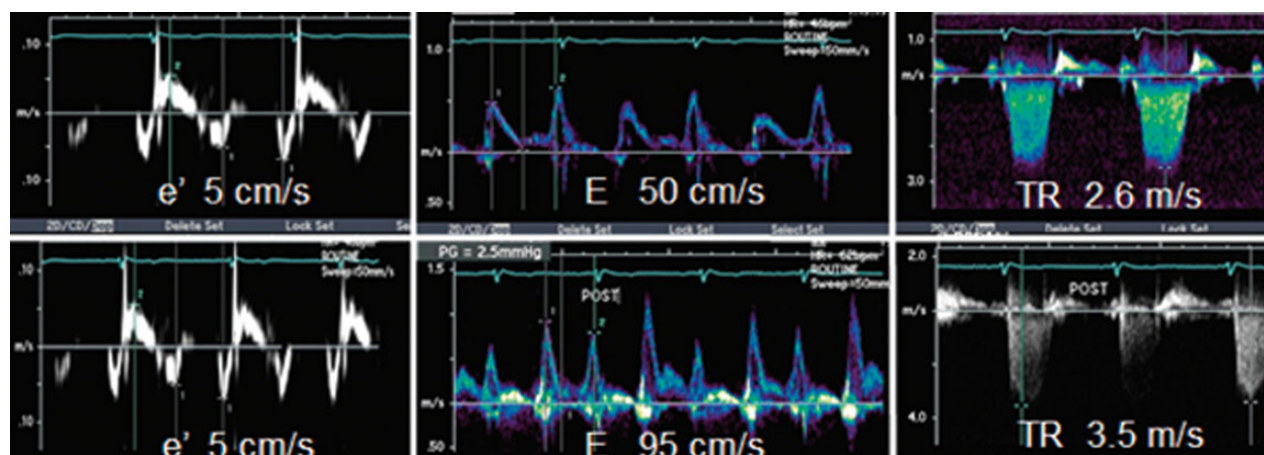
The effect of cardiac pacing on LV systolic and diastolic function varies by patient group. Chronic RV pacing is known to be deleterious by inducing LV dyssynchrony, leading to a reduction in LV ejection fraction, stroke volume, impaired LV filling and an increased incidence of heart failure and AF.<sup>154</sup> Patients who mostly need atrial pacing with rare RV pacing are believed to have no alterations in systolic and diastolic function. In patients with AV delay, pacemaker settings are often set with a long AV delay to encourage fusion or native QRS beats to minimize RV pacing. When this requires an excessively long PR interval, E and A velocities fuse and diastolic MR may be seen. As discussed previously, the alteration in E and A velocities and pulmonary venous flow variables limits their clinical application for diastolic function assessment in this setting. There are few studies that have looked at the utility of mitral annular velocities in this setting and it appears that their accuracy is less in the presence of left bundle branch block, RV pacing, and in patients who have received cardiac resynchronization therapy.<sup>67,155</sup>

### Key Points

- (1) In patients with first degree AV block, the variables used to evaluate diastolic function and filling pressures likely remain valid as long as there is no fusion of mitral E and A velocities.
- (2) The accuracy of mitral annular velocities and E/e' ratio is less in the presence of left bundle branch block, RV pacing, and in patients who have received cardiac resynchronization therapy.
- (3) If only mitral A velocity is present, only TR peak velocity (> 2.8 m/sec) can be used as an indicator of LV filling pressures.

## 6. Diastolic Stress Test

Exercise echocardiography<sup>156</sup> is usually performed to detect reduced LV systolic and/or diastolic reserve capacity in the setting of coronary disease or diastolic dysfunction, as patients with diastolic dysfunction may have a similar hemodynamic profile (in terms of cardiac output and filling pressure) at rest as healthy individuals who have normal diastolic function. When normal subjects exercise, they are able to increase stroke volume without significantly increasing filling pressures because of augmented myocardial relaxation along with more powerful early diastolic suction. Reduced LV relaxation is one of the earliest manifestations of myocardial dysfunction. Myocardial relaxation is consistently reduced in all forms of myocardial disease, including hypertensive heart disease, myocardial ischemia and HCM.<sup>157</sup> More important, patients with diastolic dysfunction may not be able to augment myocardial relaxation with exercise compared with normal subjects (Figure 29). Hence, these patients can only achieve the required cardiac output at the expense of increased LV filling pressures. In normal subjects, mitral early diastolic



**Figure 29** Mitral septal annulus (left), mitral inflow (middle), and TR velocity (right) at rest (top) and immediately after treadmill exercise test (bottom). It shows E/e' of 10 and normal PASP at rest. With exercise, e' remains the same and E velocity increased such that E/e' ratio increased to 19 along with an increase of PASP to  $\geq 49$  mm Hg with TR velocity of 3.5 m/sec.

E velocity increases with the augmented LV suction. Mitral annular e' velocity likewise increases proportionally with E velocity with exercise so that E/e' ratio remains unchanged from resting state to exercise.<sup>158</sup> Normal E/e' values have been published for middle-age and younger age subjects using treadmill and bicycle exercise with remarkably similar values of 6 to 8 at rest and with exercise.<sup>159,160</sup> Previous studies showed exercise diastolic parameters correlate better with exercise capacity than resting parameters. Overall, the faster the myocardial relaxation (e') is, the higher the exercise capacity. Since augmentation of myocardial relaxation as reflected in e' velocity is limited in patients with diastolic dysfunction, the E/e' ratio increases with exercise. Several studies have shown a good correlation between E/e' ratio and invasively obtained pulmonary capillary pressure, LAP or LV mean diastolic pressure with variable levels of effort, including day-to-day activity as well as supine bike exercise in the catheterization laboratory.<sup>161–163</sup>

### 6.1. Indications

Diastolic stress testing is indicated when resting echocardiography does not explain the symptoms of heart failure or dyspnea, especially with exertion. In general, patients with completely normal hearts and diastolic function at rest with preserved e' velocity ( $>7$  cm/sec for septal e',  $>10$  cm/sec for lateral e') need not undergo stress testing as it is highly unlikely that they will develop diastolic dysfunction and elevated filling pressures with exercise. Likewise, patients with abnormal findings at baseline consistent with elevated LV filling pressures should not be referred for stress testing as the cardiac etiology for dyspnea has already been established and their filling pressures will almost certainly increase further with exercise. The most appropriate patient population for diastolic exercise testing is the group of patients with grade 1 diastolic dysfunction, which indicates delayed myocardial relaxation and normal LA mean pressure at rest.

### 6.2. Performance

Diastolic stress testing is best performed with exercise and not using dobutamine as the administration of the drug does not simulate the

day-to-day physiologic stress. It is easier to perform the test using supine bike protocol which allows ample time to acquire 2D and Doppler data. During the supine bicycle test, 2D images, mitral inflow velocities, mitral annulus tissue Doppler velocities, and peak TR velocity by CW Doppler are acquired at baseline, during each stage including peak exercise and in recovery. In addition, diastolic stress testing can be part of exercise treadmill testing and data are acquired at baseline and in early recovery. Of note, mitral inflow and annular early and late diastolic velocities are frequently fused at peak exercise. This is particularly true during treadmill tests wherein patients usually achieve higher heart rates than those reached during supine bike testing. Nevertheless, it is possible to acquire Doppler signals later during recovery when the heart rate is slower and merging is less of a problem. This applies to both modalities of stress testing.

When the indications for stress testing are chest pain and dyspnea, including patients with known or suspected coronary artery disease, it is important to prioritize the collection of 2D images for wall motion analysis. If echocardiographic contrast is used for LV cavity opacification, tissue Doppler signals are not useful and only TR velocity can be of value. The provider can consider two separate tests in this setting. Whether contrast is used or not, one should proceed immediately after treadmill exercise is terminated to acquire 2D images so as to ideally visualize all LV segments within 60 sec for assessment of myocardial ischemia. Subsequently, Doppler echocardiography can be obtained when there is a separation of early and late diastolic mitral flow and annular velocities. If merging is noted still, one should proceed to record peak TR velocity by CW Doppler and then re-attempt recording mitral inflow and annular tissue Doppler velocities when the heart rate has decreased further.

### 6.3. Interpretation

The successful acquisition of Doppler signals during exercise and the interpretation of the diastolic stress test require a higher level of experience than that needed for evaluation of diastolic function at rest. The test is considered definitely abnormal indicating diastolic dysfunction when all of the following three conditions are met:

average  $E/e' > 14$  or septal  $E/e'$  ratio  $> 15$  with exercise, peak TR velocity  $> 2.8$  m/sec with exercise and septal  $e'$  velocity is  $< 7$  cm/sec or if only lateral velocity is acquired, lateral  $e' < 10$  cm/sec at baseline. The results are normal when average (or septal)  $E/e'$  ratio is  $< 10$  with exercise and peak TR velocity is  $< 2.8$  m/sec with exercise. One should be cautious in drawing conclusions on the basis of an isolated increase in exercise peak TR velocity as normal subjects can have a significant increase in peak TR velocity related to the increased pulmonary blood flow. In the absence of these results, the test is considered indeterminate. In these patients, an invasive hemodynamic investigation, including the use of exercise, maybe necessary if clinical assessment warrants determination of LV filling pressures.

#### 6.4. Detection of Early Myocardial Disease and Prognosis

There is a paucity of data on the prognostic utility of diastolic stress testing. It has been demonstrated that increased LV filling pressure ( $E/e' > 13$ ) with exercise has an incremental prognostic power to clinical parameters as well as 2D findings diagnostic of myocardial ischemia.<sup>164</sup> Regarding detection of subclinical disease, the increment in systolic and diastolic longitudinal velocities of the mitral annulus is generally reduced in patients with myocardial disease as in patients with diabetes mellitus compared with control subjects<sup>165</sup> and exercise induced diastolic dysfunction appears promising in identifying these patients for targeted treatment. Although the use of dobutamine for diastolic stress testing is discouraged, one report noted that the presence of a persistent restrictive LV filling pattern with dobutamine was associated with poor long-term outcomes in patients with ischemic cardiomyopathy.<sup>166</sup>

##### Key Points

- (1) Diastolic stress testing is indicated in patients with dyspnea and grade 1 diastolic dysfunction at rest. It is performed using supine bike or treadmill stress testing.
- (2) At rest, mitral  $E$  and annular  $e'$  velocities should be recorded, along with the peak velocity of TR jet from multiple windows. The same parameters are recorded during exercise or 1 to 2 min after termination of exercise when  $E$  and  $A$  velocities are not merged, because increased filling pressures usually persist for few minutes.
- (3) The test is considered positive when all of the following three conditions are met during exercise: average  $E/e' > 14$  or septal  $E/e'$  ratio  $> 15$ , peak TR velocity  $> 2.8$  m/sec and septal  $e'$  velocity  $< 7$  cm/sec.

### 7. Novel Indices of LV Diastolic Function

Several indices of LV and LA systolic and diastolic function have been proposed in recent years as indices of LV relaxation and LV and LA filling pressures. In general, patients with HFpEF usually have abnormally depressed LV GLS such that LVEDP varies directly with LV GLS. Lower absolute value for GLS denotes more impaired LV global longitudinal function. However, there is wide scatter in such data so the relation cannot be used for estimation of LV filling pressures. LV global longitudinal diastolic strain rate measurements during the isovolumic relaxation period and during early diastole by STE have a

significant association with the time constant of LV relaxation ( $\tau$ ). These novel parameters have been used in conjunction with mitral  $E$  velocity to estimate LV filling pressures and to predict outcomes in several disease states.<sup>167–174</sup> Notwithstanding the encouraging results reported by several investigators, the technical challenges and the variability in strain rate measurements on the basis of the ultrasound system and the software used for analysis limit day-to-day application of these parameters.

LV untwisting rate<sup>175,176</sup> is another parameter that has garnered interest as a surrogate of LV relaxation.<sup>177,178</sup> Both animal and human studies have shown that LV relaxation is not the sole determinant of this measurement. LV filling pressures, LV recoil and thus LV systolic function affect it as well.<sup>179–183</sup> In fact, there are several studies that have shown normal LV untwisting rate in patients with HFpEF. However, the timing of peak untwisting rate can be of more value in diagnosing patients with diastolic dysfunction and normal LV volumes and EF.<sup>177,182</sup> In the latter group of patients, delayed peak of LV untwisting rate is often present as might be expected with delayed LV relaxation. Given the complexity of the measurement and the difficulty in deciphering the contribution of each of the underlying variables that affect it, more studies are needed to prove it has a role in the day-to-day clinical practice.

Recently there have been a number of observational studies demonstrating an inverse correlation between LA systolic strain and mean wedge pressure. It appears that the relation is better in patients with HFrEF, though significant correlations were also noted in patients with HFpEF.<sup>184</sup> LA systolic strain can be combined with invasive and noninvasive measurements of LAP to estimate LA stiffness, which appears to be a promising variable in distinguishing patients with HFpEF from those with diastolic dysfunction who are not in heart failure.<sup>185</sup> Likewise, assessment of LA conduit function appears promising.<sup>186</sup> Although promising, there are technical challenges for accurate LA strain measurements in patients with marked LA enlargement and LA areas with echo dropout.

##### Key Points

- (1) LV global longitudinal diastolic strain rate measurements during the isovolumic relaxation period and during early diastole by STE have a significant association with the time constant of LV relaxation ( $\tau$ ). These parameters have been used in conjunction with mitral  $E$  velocity to estimate LV filling pressures and to predict outcome in several disease states.
- (2) The timing of peak untwisting rate can be of value in diagnosing patients with diastolic dysfunction and normal LV volumes and EF. In the latter group of patients, delayed peak of LV untwisting rate is often present.
- (3) An inverse correlation is present between LA systolic strain and mean wedge pressure. Although promising, there are technical limitations, and experience is essential.

### 8. Diastolic Doppler and 2D Imaging Variables for Prognosis in Patients with HFrEF

Diastolic dysfunction with impaired LV relaxation develops early in most cardiac diseases and can progress to include increased



LV stiffness which leads to the elevation of LV filling pressures. Echocardiographic measurements of diastolic function reflect tissue changes and therefore provide important prognostic information. Clinical studies have shown the association of short mitral DT (indicating increased LV chamber stiffness) with heart failure symptoms, death and hospitalization in patients presenting with acute myocardial infarction and those with HFrEF. In this population, DT provided incremental prognostic information to clinical parameters, wall motion score index and LVEF.<sup>73–86,88–91</sup> Importantly, a meta-analysis of 12 post-acute myocardial infarction studies involving 1,286 patients confirmed the prognostic power of restrictive diastolic filling in patients with LV dysfunction,<sup>86</sup> as did an echocardiographic substudy of 620 patients with acute myocardial infarction from the OASIS-6 study.<sup>187</sup> In addition, the less abnormal pseudonormal filling pattern has also been shown to portend poor outcomes in patients with heart failure, which was similar to that seen with restrictive LV filling in some studies.<sup>188</sup> Pulmonary venous velocities<sup>189–191</sup> and  $V_p$ <sup>30,192–194</sup> were less frequently examined but were still predictive of clinical events. Given the variability in measuring DT,  $V_p$ , and pulmonary venous flow velocity duration, more recent studies have examined the prognostic power of  $E/e'$  ratio. Several studies have shown that  $e'$  velocity and  $E/e'$  ratio are highly predictive of adverse events after acute myocardial infarction and in patients with and without heart failure.<sup>102,132,194–204</sup> A recent study has shown that low values of both global tissue Doppler-derived mitral annular  $s'$  and  $e'$  velocities were independent predictors of higher risk for death in patients after myocardial infarction.<sup>205</sup> Doppler-estimated PASP has also been shown to be a robust predictor of outcome in heart failure patients.<sup>206,207</sup> Likewise, increased LA and right atrial volume indices have been shown to portend an adverse prognosis in patients with myocardial infarction and heart failure.<sup>208–211</sup>

More recently, novel echocardiographic indices (longitudinal and circumferential strain and diastolic strain rate by STE) have been shown to predict outcomes in patients after myocardial infarction, and in patients with systolic heart failure, above and beyond LVEF and  $E/e'$  ratio.<sup>172–174,212–216</sup> Similarly, LA strain, a measure of LA deformation related to LAP, has also been shown to portend an adverse prognosis in patients with myocardial infarction that is incremental to LA maximum volume index.<sup>217,218</sup>

### Key Points

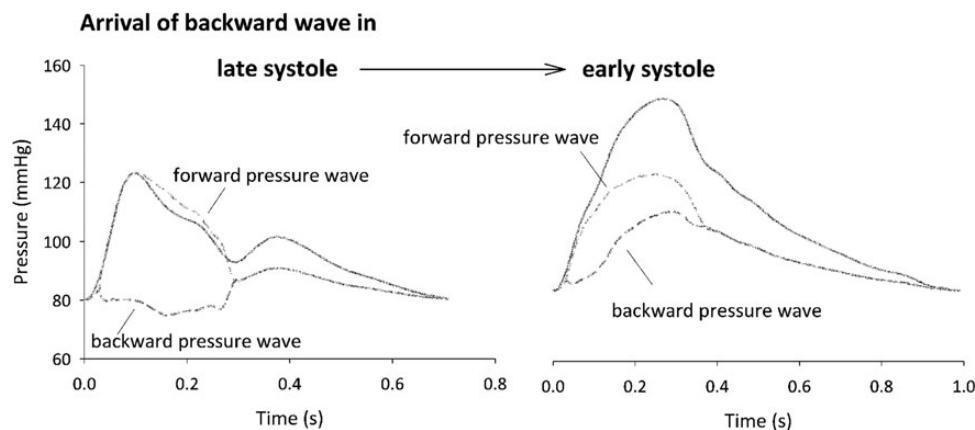
- (1) Mitral inflow velocities and pulmonary vein velocities and time intervals provide important prognostic data in patients with LV systolic dysfunction that is incremental to clinical and LV volumetric variables.
- (2) Mitral annular velocities, including  $E/e'$  ratio, have likewise been reported to predict outcomes in these patient groups.
- (3) Grade II or grade III diastolic dysfunction that does not improve despite adequate medical therapy are highly predictive of worse outcomes in this patient population.
- (4) There is growing literature showing LV strain and diastolic strain rate signals as well as LA strain providing incremental prognostic information in several disease states, including patients presenting with acute myocardial infarction, AF and HFpEF.

## 9. Prediction of Outcomes in Patients with HFpEF

In patients with HFpEF, the prognostic relevance of diastolic dysfunction has been evaluated in a framework, including clinical, laboratory and echocardiographic indicators of prognosis and outcome. For clinical and laboratory variables, the most powerful prognostic parameters were N-terminal pro-B-type natriuretic peptide, age, diabetes mellitus and previous hospitalization for heart failure in the I-PRESERVE study. Other independent factors associated with poor outcome were quality of life, chronic obstructive lung disease, neutrophil count, heart rate and estimated glomerular filtration rate.<sup>219</sup> Similarly, in the Karolinska-Rennes (KAREN) study, the independent predictors of prognosis were age, history of non-cardiovascular syncope (a proxy for frailty), valvular heart disease, anemia, lower sodium, and higher potassium levels (impaired renal function). Of note, the use of renin-angiotensin system antagonists and mineralocorticoid receptor antagonists independently predicted improved prognosis.<sup>220</sup> Other studies looked at the value of specific parameters such as worsening of renal function (I-PRESERVE data), albuminuria independently from renal function, and anemia.<sup>221–223</sup>

For echocardiographic parameters, RV dysfunction was present in a significant subset of patients with HFpEF from Olmsted County, Minnesota, and was associated with worse outcomes. Importantly, RV dysfunction provided important prognostic information, which was independent from the prognostic information of PASP.<sup>224</sup> In the I-PRESERVE echocardiographic substudy, LV mass and LA size remained independently associated with an increased risk of morbidity and mortality.<sup>225</sup> In the TOPCAT echocardiographic substudy, neither LV volumes nor EF was predictive of worse outcomes. However, LV hypertrophy, septal  $E/e'$  ratio, and TR peak velocity were predictive of outcome beyond clinical and laboratory characteristics. Because LV hypertrophy, elevated filling pressures, and elevated PASP frequently coexist, a greater number of these abnormalities is associated with a higher risk for incident hospitalization for heart failure<sup>226</sup> as is the presence of a reduced GLS.<sup>227</sup> Another potentially useful parameter is the pulmonary vein S/D ratio, which proved to have an added prognostic significance in an observational study,<sup>228</sup> likely related to the dynamics of systolic pulmonary venous flow, which are determined by mechanisms that are different from those that affect diastolic venous flow velocities.<sup>229</sup> These observations have triggered interest in further study of existing and novel echocardiographic parameters.<sup>230</sup>

Arterial function with its resistive and pulsatile aspects may further refine the prognostic evaluation of patients with HFpEF. In general, the best validated parameter is pulse-wave velocity.<sup>231</sup> An emerging parameter is pathologic wave reflection in the arterial tree (Figure 30), and hence late systolic wall stress.<sup>232</sup> The magnitude of wave reflection appears to be independently associated with diastolic dysfunction<sup>233–235</sup> and increased LV mass.<sup>236</sup> It is an independent predictor of cardiovascular events, specifically incident heart failure<sup>237</sup> and mortality.<sup>238</sup> The prognostic value of wave reflection is independent of and as potent as systolic blood pressure. Late systolic wall stress is associated with population characteristics opposite to those seen with early systolic wall stress. This provides



**Figure 30** A forward and a backward-traveling (reflected) wave contribute to pressure changes in the central aorta. In the young and healthy subject on the left, the backward-traveling wave arrives at end-systole, contributes to closing the aortic valve and to increasing diastolic perfusion pressure. In the hypertensive subject on the right, the backward-traveling wave reaches the proximal aorta in early systole and contributes to the late systolic peak in pressure. The magnitude of the reflected wave (and the late systolic pressure) has a well-validated and independent prognostic significance as summarized in the guidelines.

an original, novel clue to distinct hemodynamic triggers of physiologic and pathologic hypertrophy including diastolic dysfunction. Of note, early systolic load triggers physiologic adaptations, while late systolic load induces maladaptive cardiac changes that are associated with adverse outcomes.

#### Key Points

- (1) Echocardiographic data adds incremental prognostic information in patients with HFpEF. They include LV hypertrophy, LA volumes,  $E/e'$  ratio, peak velocity of TR jet, RV function, and GLS.
- (2) Arterial function with its resistive and pulsatile aspects further refines the prognostic evaluation of patients with HFpEF.

## 10. Reviewers

This document was reviewed by members of the 2015–2016 ASE Guidelines and Standards Committee, the 2015–2016 ASE Board of Directors, the EACVI Scientific Documents Committee, and external reviewers.

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## 12. Abbreviations

2D, Two-dimensional; AR, Aortic regurgitation; ASE, American Society of Echocardiography; AV, Atrioventricular; CW, Continuous-wave; DT, Deceleration time; EACVI, European Association of Cardiovascular Imaging; EF, Ejection fraction; GLS, Global longitudinal strain;

HCM, Hypertrophic cardiomyopathy; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; IVRT, Isovolumic relaxation time; LA, Left atrial; LAP, Left atrial pressure; LV, Left ventricular; LVEDP, Left ventricular end-diastolic pressure; LVEF, Left ventricular ejection fraction; MAC, Mitral annular calcification; MR, Mitral regurgitation; PASP, Pulmonary artery systolic pressure; PCWP, Pulmonary capillary wedge pressure; RV, Right ventricular; STE, Speckle-tracking echocardiography; TR, Tricuspid regurgitation; Vp, Flow propagation velocity

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