

# Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography and for Heart Failure With Preserved Ejection Fraction Diagnosis: An Update From the American Society of Echocardiography



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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 clinical concerns for heart failure. Given the presence of diastolic dysfunction in many cardiovascular diseases, clinical reports should include comments on diastolic function and/or left atrial (LA) pressure whenever possible. Since the publication of the 2016 ASE/EACVI guidelines for assessment of LV diastolic function, new data on additional echocardiographic variables as left atrial strain and their association with LV filling pressures have emerged. Moreover, prognostic data

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from epidemiologic studies have demonstrated the association of echocardiographic measures with the subsequent development of heart failure. This update provides a contemporary approach for the assessment of LV diastolic function and the estimation of LA pressure in the general population of patients in sinus rhythm referred for echocardiographic evaluation, and in special populations that require deviation from the general approach. The update also discusses the application of echocardiography in the diagnosis of patients with heart failure with preserved LV ejection fraction. (J Am Soc Echocardiogr 2025;38:537-69.)

**Keywords:** Diastole, Echocardiography, Doppler, Heart failure

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### Abbreviations

<b>2D</b> = Two-dimensional
<b>AI</b> = Artificial intelligence

### 1. INTRODUCTION

Echocardiographic assessment of left ventricular (LV) diastolic function is an integral part of the

**AR** = Aortic regurgitation

**AS** = Aortic stenosis

**ASE** = American Society of Echocardiography

**AV** = Atrioventricular

**CMR** = Cardiac magnetic resonance

**CRT** = Cardiac resynchronization therapy

**CT** = Computed tomography

**CW** = Continuous-wave

**EF** = Ejection fraction

**ESC** = European Society of Cardiology

**GLS** = Global longitudinal strain

**HCM** = Hypertrophic cardiomyopathy

**HF** = Heart failure

**HFpEF** = Heart failure with preserved left ventricular ejection fraction

**IVRT** = Isovolumic relaxation time

**LA** = Left atrial

**LAP** = Left atrial pressure

**LARS** = Left atrial reservoir strain

**LAV** = LA volume

**LAVi** = Left atrial volume index

**LBBB** = Left bundle branch block

**LV** = Left ventricular

**LVEDP** = Left ventricular end-diastolic pressure

**LVEF** = Left ventricular ejection fraction

routine evaluation of patients presenting with symptoms of dyspnea or clinical concerns for heart failure (HF). Given the presence of diastolic dysfunction in many cardiovascular diseases, clinical reports should include comments on diastolic function and/or LV filling pressures whenever possible. The 2016 American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging guidelines for diastolic function assessment sought to simplify the clinical approach<sup>1</sup> and have been shown to have good accuracy in a large multicenter study.<sup>2</sup> Incomplete data, conflicting parameters, and/or uncertainty about inclusion and exclusion criteria still result in an unacceptably high frequency of unclassifiable or indeterminate cases when using the 2016 guidelines algorithm. New data on additional echocardiographic variables (e.g., left atrial [LA] strain) and their associations with LV filling pressures have emerged.<sup>3</sup> Moreover, prognostic data from epidemiologic studies have demonstrated the association of echocardiographic measures with the subsequent development of HF.<sup>4</sup> Therefore, this update has two primary goals: (1) to provide a more contemporary approach for the assessment of LV diastolic function and the estimation of LV filling pressures and (2) to discuss the application of echocardiography in patients with HF with preserved LV ejection fraction (HFpEF). As this guideline serves as an update to

**MAC** = Mitral annular calcification

**MR** = Mitral regurgitation

**NP** = Natriuretic peptide

**PA** = Pulmonary artery

**PADP** = PA diastolic pressure

**PASP** = Pulmonary artery systolic pressure

**PCWP** = Pulmonary capillary wedge pressure

**PR** = Pulmonary regurgitation

**RAP** = Right atrial pressure

**RV** = Right ventricular

**SR<sub>IVR</sub>** = Strain rate during the isovolumic relaxation period

**STE** = Speckle-tracking echocardiographic

**TDI** = tissue Doppler imaging

**TEER** = Transcatheter edge-to-edge repair

**TR** = Tricuspid regurgitation

**TTR** = Transthyretin

the 2016 diastolic function guideline document, it is important to note that there are several images in the original guideline that show important pathologic or abnormal echocardiographic findings that are not republished in this document but may be of interest to readers of this update. The document has three main sections: one for the general population, a second for specific populations that require deviation from the general approach, and a third focused on the diagnosis of HFpEF. The document also contains a summary and recommendations for artificial intelligence (AI) applications in this field.

### Clinical and Technical Considerations

The application of the guidelines starts with clinical data, including age, heart rate, underlying rhythm, blood pressure, two-dimensional (2D) and Doppler echocardiographic findings with respect to LV volumes and wall thickness, ejection fraction (EF),

LA volumes, and presence and severity of mitral valve disease. The guidelines are based on scientific work concerning diastolic function and LV filling pressure in adults studied in ambulatory and acute hospital care settings and thus should not be applied in children, normal pregnant women, or in intraoperative settings. The quality of the 2D, Doppler, and speckle-tracking echocardiographic (STE) signals as well as the limitations for each parameter should be carefully scrutinized. If a signal is suboptimal, it should not be used in formulating conclusions about LV diastolic function. The presence of a single measurement that falls within the normal range for a given age group does not necessarily indicate normal diastolic function and conclusions should not be based on a single measurement. In an individual patient, consistency among the different indices is of great importance. For the most successful analysis of diastolic function in any given case, the echocardiographer should have a solid understanding of the physiologic rationale behind each variable, the situations that make any given variable less reliable, the proper acquisition technique, and the correct analysis of the echocardiographic variables.

### Key Points

1. The guidelines should not be applied to children, normal pregnant women, or the intraoperative setting.
2. The quality of the 2D echocardiographic images, Doppler waveforms, and STE signals as well as the limitations for each parameter should be carefully assessed.
3. The echocardiographic indices of diastolic function should always be interpreted in the context of clinical status and other echocardiographic parameters.

4. The echocardiographer should have a solid understanding of the physiologic rationale behind each variable, the situations that make any given variable less reliable, and the technical aspects of acquisition and analysis of the variables.

## 2. INVASIVE ASSESSMENT OF LV DIASTOLIC FUNCTION

The invasive assessment of LV diastolic function relies on the estimation of two fundamental parameters, the time constant of LV relaxation and the chamber stiffness constant. These determine LV pressure throughout diastole. The time constant of LV relaxation,  $\tau$ , during the isovolumic relaxation period (isovolumic relaxation time [IVRT]) can be estimated from high-fidelity solid-state manometry of the left ventricle. The resulting time-pressure data can then be analyzed to estimate  $\tau$  (abnormally prolonged  $>48$  ms). The more common ones include monoexponential decay model to zero asymptote, where  $P(t) = P_0 e^{-t/\tau}$  (Supplemental Figure 1), or to nonzero asymptote, where  $P(t) = P_0 e^{-t/\tau} + P_\infty$ , where  $P_0$  is the LV pressure at peak  $-dP/dt$ .<sup>5</sup> Note that  $\tau$  is load dependent. The sensitivity of LV relaxation to changes in afterload is most apparent in patients with systolic LV dysfunction. The relation between  $\tau$  and LV end-systolic pressure is steeper in patients with systolic dysfunction than in hearts with normal LV systolic function.<sup>6,7</sup>

Chamber stiffness affects the rate of LV pressure increase during LV filling. Chamber stiffness is most reliably obtained by analyzing LV end-diastolic volume and LV end-diastolic pressure (LVEDP) obtained from conductance catheters from multiple cardiac cycles as filling is decreased by gradually inflating a balloon in the inferior vena cava. It is determined primarily by the stiffness properties of the sarcomeres, the interstitial space, and LV chamber geometry and wall thickness. It can be characterized by the LV chamber stiffness constant  $k$ . Table 1 presents a summary of invasive measurements that indicate abnormal LV diastolic function.<sup>5,7,8</sup>

The term *LV filling pressures* is frequently used but can refer to several different LV and LA diastolic pressures. These pressures include mean pulmonary capillary wedge pressure (PCWP), mean

**Table 1** Invasive measurement values that diagnose LV diastolic dysfunction and HFpEF<sup>5,8</sup>

Parameter	Value
1. Time constant of LV relaxation ( $\tau$ ), ms	$>48$
2. LV chamber stiffness constant	$>0.015^*$
3. Rest mean PCWP, mm Hg	$>15$
4. Rest LV end-diastolic pressure, mm Hg	$>16$
5. Exercise mean PCWP, mm Hg	$\geq 25$
6. Exercise LV end-diastolic pressure, mm Hg	$\geq 23$
7. PCWP/Cardiac Output slope during supine exercise, mm Hg/L/min	$>2$

\*Value based on the 90th percentile of control group without HFpEF, where pressure and volume data were obtained by conductance catheter, from Kasner M, Westermann D, Steendijk P, et al. Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation. 2007;116:637-647.

LA pressure (LAP), LV pre-A pressure, mean LV diastolic pressure, and LVEDP<sup>1</sup> (Figure 1). In the early stages of diastolic dysfunction, LVEDP is the only abnormally elevated pressure, while mean PCWP and LAP remain normal. During tachycardia and/or increased LV afterload or intravascular volume, mean PCWP and LAP increase, which is the basis for diastolic stress testing (invasive and noninvasive). Some Doppler variables correlate with an increase in LVEDP, whereas others reflect an increase in mean LAP or its surrogate (Table 2).

## Key Points

1. LV impaired relaxation is defined as a time constant of LV relaxation  $>48$  ms.
2. Increased LV chamber stiffness is defined by a chamber stiffness constant  $>0.015$ .
3. Invasive criteria for HfPEF, in addition to the time constants of LV relaxation and LV chamber stiffness, include mean PCWP at rest  $>15$  mm Hg, LVEDP at rest  $>16$  mm Hg, and mean PCWP with exercise  $\geq 25$  mm Hg.
4. Doppler measurements that correlate better with mean LAP or PCWP include mitral E velocity, E/A ratio, and E/e' ratio.
5. Echocardiographic measurements that correlate better with LVEDP include mitral A velocity, pulmonary vein Ar velocity, the time difference between Ar duration and that of mitral A duration (Ar–A), and LA pump strain.
6. Throughout this document, the term *LV filling pressure* refers to mean LAP or its correlates (mean PCWP, LV pre-A pressure). It should be noted that LVEDP and LAP are not the same, and although elevated LAP is always associated with elevated LVEDP in patients with diastolic dysfunction, elevated LVEDP may be present when LAP is normal.

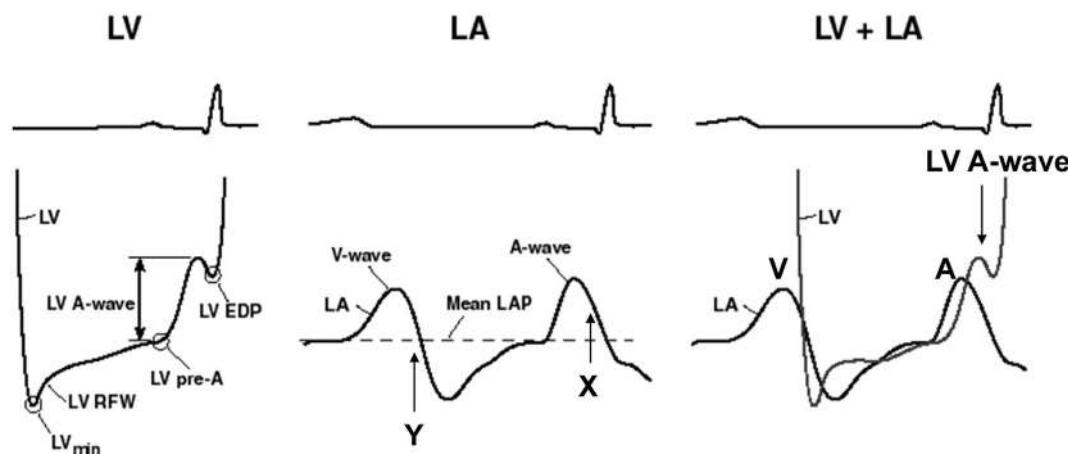
Tables 3 and 4 summarize the technical aspects, hemodynamic determinants, and clinical utility including advantages and limitations of each parameter used in the echocardiographic evaluation of LV diastolic function.

**Table 2** Echocardiographic correlates with mean PCWP and with LVEDP

PCWP, mean LAP, LV pre-A, and mean LV diastolic pressure correlates	LVEDP correlates
1. Mitral peak E velocity	1. Mitral peak A velocity at tips level
2. Mitral E/A ratio	2. A-wave duration at the annulus
3. Mitral E velocity deceleration time	3. Mitral A velocity (tips level) deceleration time
4. Mitral E/e' ratio	4. Pulmonary vein peak Ar velocity
5. Pulmonary vein systolic-to-diastolic velocity ratio	5. Pulmonary vein Ar duration – mitral A duration
6. Peak TR velocity and PASP	6. LA minimum volume
7. End-diastolic velocity of PR and PADP	7. Tissue Doppler-derived mitral annular a' velocity
8. LARS	8. LA pump (or contractile) strain

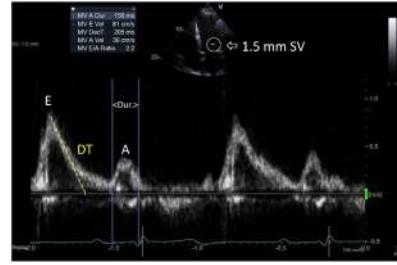
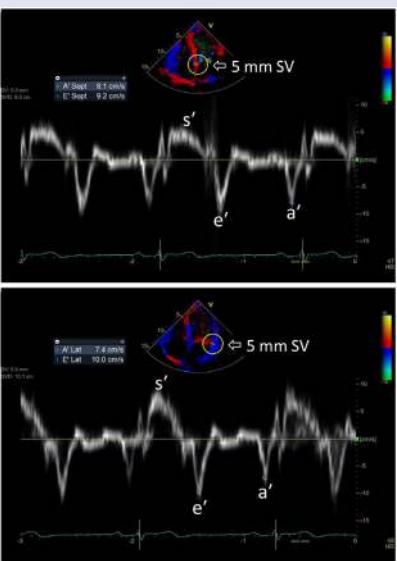
## 3. NORMAL RANGES FOR DIASTOLIC MEASUREMENTS

Numerous studies have demonstrated the association between age and echocardiographic measurements of LV diastolic function (a list of these studies is included in the *Supplemental Appendix*). Some studies have further suggested that prognostic thresholds for diastolic measurements may differ by age. The purpose of this section is to describe current estimates of normal ranges of diastolic measurements by age, on the basis of the observed range of values among subjects believed to be free of cardiovascular disease and without known risk factors. Importantly, such normal ranges are not necessarily equivalent to "optimal" values, as the aging process itself may affect diastolic function. However, the use of age-specific normal ranges can enhance clinical interpretation of diastolic indices and has become standard for echocardiographic measurements of cardiac structure and function.



**Figure 1** (Left) LV diastolic pressure 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) LA pressure recording showing "V" and "A" waves marked along with Y and X descent. (Right) Simultaneous LV pressure and LAP recording showing early and late trans-mitral pressure gradients. Notice that LA "A-wave" pressure precedes the late diastolic rise (LV A wave) in LV pressure.

**Table 3** Parameters required for the assessment of LV diastolic function via transthoracic echocardiography

Parameter/variable	Acquisition	Measurements
<b>Primary measurements</b>		
Transmitral Inflow	<ol style="list-style-type: none"> <li>Apical four-chamber <math>\pm</math> color Doppler imaging to aid optimal alignment.</li> <li>PW Doppler sample volume (1-3 mm) placed at MV leaflet tips.</li> <li>Lower zero baseline and adjust velocity scale so signal above the zero baseline is as large as possible.</li> <li>Use low wall filter setting (100-200 MHz) and low signal gain.</li> <li>Sweep speed at 100 mm/s.</li> <li>Optimal spectral waveforms should display minimal spectral broadening and not display spikes or feathering.</li> <li>For A duration, when end of A-wave is not well defined, sample volume may be lowered a few millimeters toward the mitral annulus.</li> </ol>	<p><b>Peak E-wave velocity (cm/s):</b> peak early diastolic modal velocity after ECG T wave</p> <p><b>Deceleration time (ms):</b> time interval from peak E-wave velocity along the deceleration slope to the zero baseline</p> <p><b>Peak A-wave velocity (cm/s):</b> peak late diastolic modal velocity after ECG P wave</p> <p><b>E/A ratio:</b> peak E-wave velocity divided by peak A-wave velocity</p> <p><b><math>\pm</math> A duration (ms)*:</b> Time interval from the onset to the offset of the A-wave signal at zero baseline</p> 
TDI at mitral annulus	<ol style="list-style-type: none"> <li>Apical four-chamber with TDI preset (detection of low velocity, high amplitude signals).</li> <li>PW sample volume (5-10 mm) at septal and lateral insertion site of the mitral leaflets (larger sample size required to ensure sampling of annular excursion over systole and diastole).</li> <li>Angle of interrogation should be as parallel as much as possible to annular motion.</li> <li>Adjust zero baseline and velocity scale to display the full spectral signal above and below the zero baseline as large as possible.</li> <li>Sweep speed at 100 mm/s.</li> <li>Optimal spectral waveforms should be sharp and not display signal spikes, feathering or ghosting.</li> </ol>	<p><b>e' velocity (cm/s):</b> peak early diastolic modal velocity after ECG T-wave</p> <p><b>a' velocity (cm/s):</b> peak late diastolic modal velocity after ECG P-wave</p> <p><b>MV E/e' ratio:</b> MV peak E-wave divided by the TDI e' velocity</p> <p><b>Average E/e':</b> MV peak E-wave divided by the average of the TDI septal e' and lateral e' velocities</p> 

(Continued)

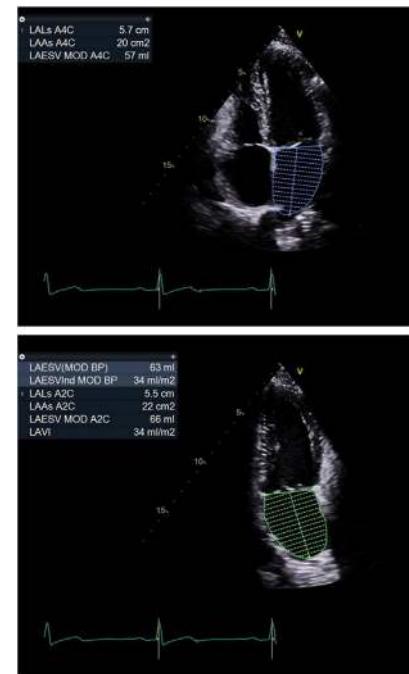
LAVi (mL/m<sup>2</sup>)

1. Apical four- and two-chamber views.
2. Each view optimized for left atrium.
3. Avoid foreshortening by maximizing the width of the LA base (mitral annulus) and by maximizing the LA long axis. This typically requires an anterior tilt, demonstrating the pulmonary veins entering the left atrium.
4. Acquire and freeze end-systolic frames (one or two frames before MV opening).

From each view, trace the LA area (excluding the PVs and LAA) and measure the LA length from the center of the MV annulus to the center of the superior LA wall. Ensure long-axis lengths are within 5 mm of each other.

**LAV (mL):** calculated via the method of disks or area-length method.

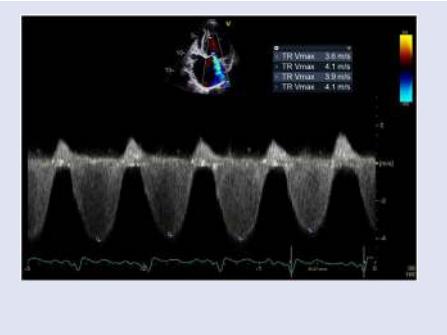
**LAVi (mL/m<sup>2</sup>):** LAV divided by BSA.



## Peak TR velocity (m/s)

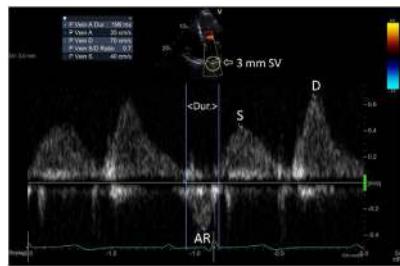
1. Acquired from any view that aligns TR jet parallel with the ultrasound beam as noted via the color Doppler images.
2. CW Doppler cursor is aligned parallel to the TR jet.
3. Adjust zero baseline and velocity scale to ensure TR signal is displayed as large as possible.
4. Optimize gain, compression and/or reject to obtain a complete profile with minimal spectral “bearding.”
5. Sweep speed at 50-100 mm/s.

**Peak TR velocity (m/s):** averaged over the respiratory cycle



PV inflow

1. Apical four-chamber with color Doppler imaging at a reduced Nyquist limit to aid optimal alignment and identification of venous flow (anterior tilt may be required).
2. PW Doppler sample volume (3-5 mm) placed approximately 5-10 mm into the right upper or right lower PV.
3. Use low wall filter setting (100-200 MHz) and low signal gain.
4. Adjust zero baseline and velocity scale to display the full spectral signal above and below the zero baseline as large as possible.
5. Sweep speed at 100 mm/s.
6. Optimal spectral waveforms should not display spikes or feathering.
7. Note: High PRF may be required when peak velocities exceed the Nyquist limit. In this instance, be aware of the second sample volume position (if placed at the mitral valve level, PV and MV signals will be superimposed, and PV S-wave and D-wave measurements will not be accurate).



IVRT (ms)

1. Apical long-axis or five-chamber view.
2. CW Doppler through LVOT to simultaneously display the end of aortic ejection and the onset of transmитral inflow.
3. Use low wall filter setting (100-200 MHz) and low signal gain.
4. Adjust zero baseline and velocity scale to display the full spectral signal above and below the zero baseline as large as possible.
5. Sweep speed at 100 mm/s.
6. Optimal spectral waveforms should display AV closing click and clear onset of transmитral inflow in early diastole

**Peak S-wave velocity (cm/s):** peak systolic velocity at ECG T wave. When two systolic peaks (S1 and S2), the peak S2 should be measured for the S/D ratio

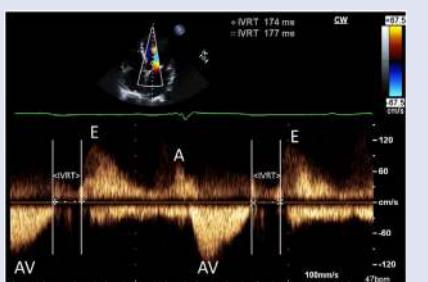
**Peak D-wave velocity (cm/s):** peak early diastolic velocity after ECG T wave

**S/D ratio:** peak S-wave velocity divided by peak D-wave velocity

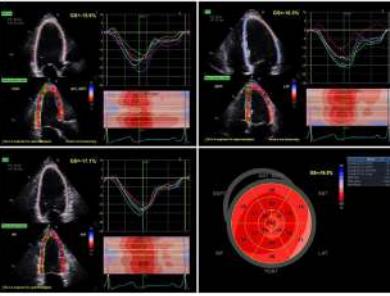
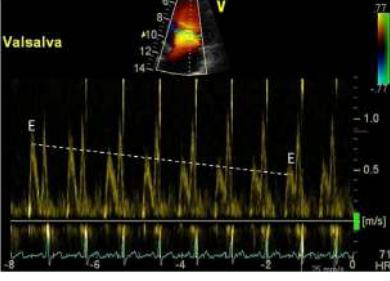
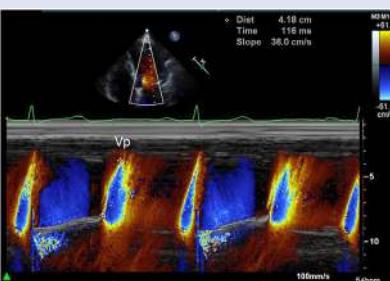
**± Peak AR velocity (cm/s)\*:** peak late diastolic velocity after ECG P wave

**± AR duration (ms)\*:** Time interval from the onset to the offset of the AR-wave signal at zero baseline

**IVRT (ms):** measured as the time interval between aortic valve closure and MV opening.



(Continued)

LV GLS (%)	<ol style="list-style-type: none"> <li>Optimize the apical four-chamber, two-chamber, and long-axis of the left ventricle, avoiding foreshortening.</li> <li>Increase 2D gains to increase speckles.</li> <li>Narrow image sector and decrease image depth for optimal frame rate (40-80 frames/s). Ensure sector wide enough to include full wall thickness and apex and depth to extend beyond annulus to allow capture of entire left ventricle throughout the cardiac cycle.</li> <li>Region of interest should include 90% of the myocardium but not the pericardium/epicardium.</li> <li>Confirm good-quality electrocardiogram.</li> <li>Acquire three to five cardiac cycles for each view ensuring similar heart rates for each view.</li> </ol>	<p><b>LV GLS (%):</b> calculated using dedicated LV strain software to track the LV endocardial wall and to calculate LV GLS. Ensure correct ECG gating for end-systole based on aortic valve closure. Confirm tracking and adjust contour and region of interest if needed.</p>	
Secondary measurements			
Valsalva maneuver <sup>†</sup>	<ol style="list-style-type: none"> <li>See above in primary measurements section for transmитral flow for the proper technique of acquiring transmитral inflow signals.</li> <li>Patients should be instructed to bear down against a closed glottis and practice this technique before recording.</li> <li>Transmитral inflow signal should be continuously recorded for 10 to 12 s during the strain phase of the maneuver.</li> <li>Use a slower sweep speed (50 mm/s or slower) to display the transmитral signal at rest and during peak strain and/or during peak strain and after release.</li> <li>The acquired trace should be annotated to indicate the use of the Valsalva maneuver.</li> <li>An adequate Valsalva maneuver may be defined as a &gt;10% reduction in maximal E-wave velocity from baseline.</li> </ol>	<p><b>Valsalva positive:</b> E/A ratio &lt; 1 or increase in A-wave velocity  <b>Valsalva negative:</b> E/A ratio &gt; 1</p>	
Color M-mode Vp (cm/s) <sup>†</sup>	<ol style="list-style-type: none"> <li>Apical four-chamber with color Doppler imaging of transmитral inflow (variance mode off).</li> <li>M-mode cursor placed well aligned with the path of transmитral inflow.</li> <li>Lower the color Nyquist limit by either decreasing the color velocity scale or by moving the color baseline upward in the direction of MV inflow to enhance the early diastolic slope.</li> </ol>	<p><b>Vp (cm/s):</b> measured from the level of the mitral annulus to 4 cm into the LV cavity along the early diastolic slope of first aliasing velocity (red-blue interface)</p>	

$T_{E-e'}$  time interval (ms)<sup>†</sup>

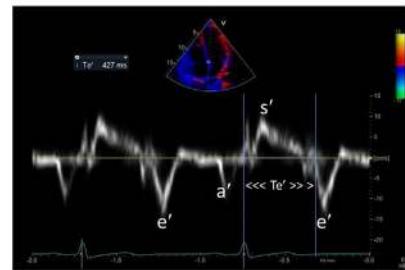
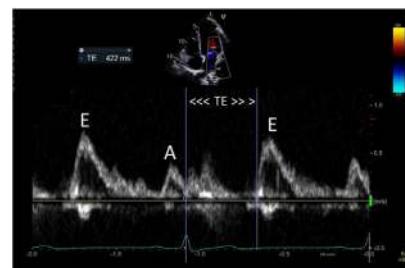
See above in the primary measurements section for transmital flow for proper technique of acquisition of transmital E-wave and TDI e' velocities.

**$T_E$  (ms):** time interval between the peak R wave on ECG and the onset of transmital E-wave velocity

**$T_{e'}$  (ms):** time interval between the peak R-wave on ECG and the onset of TDI e' velocity.

R-R intervals should be matched.

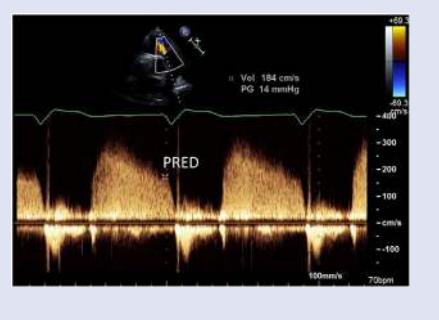
**$T_{E-e'}$  (ms):**  $T_{e'}$  minus  $T_E$



Peak PR end-diastolic velocity (m/s)

1. Acquired from any view that aligns PR jet parallel with the ultrasound beam as noted via the color Doppler images.
2. CW Doppler cursor is aligned parallel to the PR jet.
3. Adjust zero baseline and velocity scale to ensure PR signal is displayed as large as possible.
4. Optimize gain, compression and/or reject to obtain a complete profile with minimal spectral “bearding.”
5. Sweep speed at 50-100 mm/s.

**Peak PR end-diastolic velocity (cm/s):**  
measured at end-diastole



(Continued)

## Advanced techniques

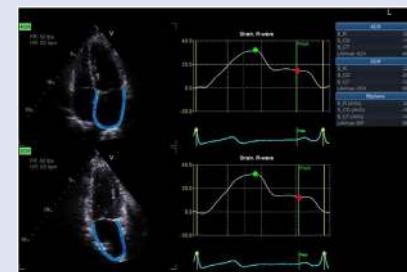
## LA strain (%)

1. See above in the primary measurements section for LA volumes for the proper technique for optimizing apical four-chamber and two-chamber dedicated LA views.
2. Decrease gain and compression to optimize clean blood pool and LA tissue border, minimizing artifact.
3. Narrow image sector for optimal frame rate (50-70 frames/s, preferably on higher end).
4. Confirm good quality ECG with a well-visible P wave. Use R-R gating method to provide reservoir, conduit, and contractile LA strain values.
5. Acquire three to five cardiac cycles for each view ensuring similar heart rates for each view.
6. Use dedicated LA strain software to track LA wall in both apical views (excluding pulmonary veins and LAA).
7. Confirm tracking is on the underside of each annular point, following the tissue boundary and extrapolating the fossa ovalis, LAA and PVs to the roof of the left atrium. Minimally adjust contour if needed.

**LARS (%)**: peak positive strain value during ventricular systole.

**LASct (%)**: measured in sinus rhythm as 0 minus strain value at the onset of AC (pre-A wave on ECG), where 0 = strain value at end-diastole (negative value).

**LAScd (%)**: 0 minus strain value at AC (negative value).



Green dots, peak of the strain curve; red dots, peak strain at onset of AC or at pre-A, S\_R, LARS; S\_CT, LASct; S\_CD, LAScd.

AC, Atrial contraction; AR, atrial reversal; BSA, body surface area; CD, LA conduit strain; ECG, electrocardiography; LARS = S\_R, LA reservoir strain; LAScd = S\_CD, LA conduit strain; LASct = S\_CT, LA contractile or pump strain; MV, mitral valve; PV, pulmonary vein; PW, pulsed-wave; Vp, early diastolic flow propagation velocity.

\*Additive value when suspected elevated LVEDP and normal LAP (e.g., grade 1 diastolic dysfunction with elevated LVEDP and normal LAP).

<sup>†</sup>May be attempted when pseudonormalization of the transmural inflow profile is suspected. The Valsalva maneuver may also be performed to identify reversible and irreversible grade 3 diastolic dysfunction.

**Table 4** Utility, advantages, and limitations of variables used to assess LV diastolic function

Variable	Utility and physiologic background	Advantages	Limitations
Mitral E-wave velocity	Reflects the LA-to-LV pressure gradient during early diastole and is affected by changes in the rate of LV relaxation and LAP.	1. Feasible and reproducible. 2. In patients with DCM and reduced LVEF, mitral velocities correlate better with LVFPs, functional class, and prognosis than LVEF.	1. In patients with CAD and patients with HCM in whom LVEF is >50%, transmural velocities correlate poorly with LVFPs. 2. More challenging to apply in patients with arrhythmias. 3. Preload dependent. 4. Age dependent (decreasing with age).
Mitral A-wave velocity	Reflects the LA-to-LV pressure gradient during late diastole (atrial contraction) and is affected by LV compliance and LA contractile function.	Feasible and reproducible.	1. Sinus tachycardia, first-degree AV block and paced rhythm can result in fusion of the E and A velocities. If E at onset of A is >20 cm/s, A velocity may be higher than if diastole was longer. 2. Not applicable in AF/atrial flutter. 3. Age dependent (increases with aging).
Mitral E/A ratio	Along with the DT, this ratio may be used to identify filling patterns: normal, impaired relaxation, PN, and restrictive filling.	1. Feasible and reproducible. 2. Increased ratio usually predicts elevated LVFP in patients with myocardial disease but is not useful in normal subjects. 3. Provides diagnostic and prognostic information. 4. In patients with DCM, LV filling pattern correlates better with LVFPs, functional class, and prognosis than LVEF. 5. 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 DCM.	1. Preload-dependent. A normal transmural profile may be difficult to differentiate from a PN transmural profile, particularly with normal LVEF, without additional variables. 2. When E velocity at onset of A is >20 cm/s, E/A ratio will be reduced (see above). 3. Not applicable in AF/atrial flutter. 4. Age dependent (decreases with aging).
Mitral DT	Influenced by the rate of decline in LA-LV pressure gradient after mitral valve opening, and therefore LV relaxation and LV stiffness.	1. Feasible and reproducible. 2. A short DT (<140 ms) in patients with reduced LVEFs indicates increased LVEDP with high accuracy both in sinus rhythm and in AF.	1. Preload-dependent. 2. DT does not relate to LVEDP in normal LVEFs. 3. Should not be measured with E and A fusion or E at onset of A >20 cm/s because of potential inaccuracy. 4. Age dependent (increases with aging). 5. Not applicable in atrial flutter.
Mitral A duration	Reflection of LV compliance in late diastole. Shortening occurs when there is reduced LV compliance resulting in a rise in LV pressure with atrial contraction, which abruptly terminates transmural inflow. Best used in conjunction with pulmonary venous AR duration (see below).	1. In patients with cardiac disease, a longer A duration for age is usually associated with normal LVFPs. 2. A shorter A duration (<120 ms) in patients with cardiac disease indicates elevated LVFPs. 3. When the ECG PR interval is normal, termination of the A duration before the peak ECG QRS complex is a reliable indicator of elevated LVEDP.	1. Cannot be reliably measured or used when there is E and A fusion, sinus arrhythmias, second- and third-degree AV block, or a short PR interval (<120 ms).
Changes to mitral inflow profile with Valsalva maneuver	Helps distinguish normal from PN transmural patterns by reducing preload. 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 LVFPs.	When performed adequately under standardized conditions (keeping 40 mm Hg intrathoracic pressure constant for 10 s) accuracy in diagnosing increased LVFPs is good.	1. Not every patient can perform this maneuver adequately. The patient must generate and sustain a sufficient increase in intrathoracic pressure, and the sample volume position needs to be maintained at the mitral leaflet tips during the maneuver. 2. It is difficult to assess if it is not standardized.

(Continued)

**Table 4 (Continued)**

Variable	Utility and physiologic background	Advantages	Limitations
MV L-wave velocity	Triphasic transmural inflow profile with mid-diastolic flow indicates markedly delayed LV relaxation in the setting of elevated LVFPs and reflects a continued LA-LV pressure gradient during diastasis.  May also be seen on the TDI trace between the $e'$ and $a'$ velocities.	1. When present in patients with known cardiac disease (e.g., LVH, HCM), it is specific for elevated LVFPs. However, its sensitivity is overall low.  2. Presence in AF may be associated with increased LVFPs.	May rarely be seen with normal LV diastolic function when the subject has bradycardia; however, when present, the velocity is usually $<40$ cm/s.
TDI $e'$ velocity	$e'$ velocity is an index of LV relaxation. The hemodynamic determinants of $e'$ velocity include LV relaxation, restoring forces and filling pressure. $e'$ is decreased across all grades of diastolic dysfunction.	1. Feasible and reproducible. 2. LVFPs have a minimal effect on $e'$ in the presence of impaired LV relaxation. 3. Less load dependent than other conventional PW Doppler parameters. 4. Helps distinguish PN from normal transmural inflow profiles.	1. Limited accuracy in patients with CAD and regional dysfunction in the sampled segments, significant MAC, surgical mitral rings or prosthetic mitral valves and pericardial disease. 2. Need to sample at least two sites with precise location and adequate size of sample volume. 3. Different cutoff values depending on the sampling site. 4. Age dependent (decreases with aging).
E/ $e'$ ratio	$e'$ velocity can be used to correct for the effect increased preload on the transmural E velocity, E/ $e'$ ratio can be used to predict increased LVFPs.	1. Feasible and reproducible. 2. Values for average E/ $e'$ ratio $<8$ usually indicate normal LVFPs, values $>14$ have high specificity for increased LVFPs.	1. Not accurate in patients with heavy MAC, or prosthetic MV and pericardial disease. 2. "Gray zone" of values (E/ $e'$ between 8 and 14) in which LVFPs are indeterminate. 3. Accuracy is reduced in patients with CAD and regional dysfunction at the sampled segments. 4. Different cutoff values depending on the sampling site.
LAVi	LA volume reflects the cumulative effects of increased LVFPs over time. It is directly but weakly related to LVFP. Increased LA volume is an independent predictor of death, HF, AF, and ischemic stroke.	1. Feasible and reproducible. 2. Provides diagnostic and prognostic information about LV diastolic dysfunction and chronicity of disease. 3. Apical 4-chamber view provides visual estimate of LA and RA size which confirms LA is enlarged. 4. A normal LA size suggests normal LVFPs.	1. LA dilatation, in the absence of diastolic dysfunction, may be seen in patients with high-output states, heart transplants with biatrial technique, atrial flutter/fibrillation, significant MV disease, and in well-trained athletes. 2. Suboptimal image quality, including LA foreshortening, in technically challenging studies precludes accurate tracings. 3. It can be difficult to measure LA volumes in patients with ascending and descending aortic aneurysms and large interatrial septal aneurysms.
TR velocity	Can be used to estimate the PASP in the absence of PS or RVOT obstruction (RVSP = PASP). A significant correlation exists between PASP and noninvasively derived LAP in group II PH. In the absence of pulmonary disease, increased PASP suggests elevated LAP.	1. PASP is passively elevated when the LAP is increased due to left heart PH; thus, an elevated PASP infers an elevated LAP.  2. Increased PASP indicates PH which has prognostic implications.	1. Indirect estimate of LAP. 2. Adequate recording of a full envelope is not always possible, though intravenous agitated saline or UEs increase yield. 3. Accuracy of calculation of PASP is dependent on the reliable estimation of RAP. 4. With very severe TR and a low systolic RV-RA pressure gradient, PASP cannot be accurately estimated. 5. RVSP does not equal PASP when there is PS or RVOT obstruction.

*(Continued)*

**Table 4 (Continued)**

Variable	Utility and physiologic background	Advantages	Limitations
PR end-diastolic velocity	Can be used to estimate the PAEDP when TR velocity cannot be accurately measured. A significant correlation exists between PAEDP and invasively, as well as noninvasively, derived PCWP. In the absence of pulmonary disease, the PAEDP approximates the PCWP.	1. PAEDP is closely related to PCWP. 2. Increased PAEDP indicates PH which has prognostic implications.	1. Adequate recording of a full PR jet envelope is not always possible though UEs increases yield. 2. Accuracy of calculation of PAEDP is dependent on the reliable estimation of RAP. 3. PAEDP overestimates PCWP by >5 mm Hg when there is increased PVR.
Pulmonary veins: S velocity, D velocity and S/D ratio	S-wave velocity (sum of S1 and S2) is influenced by LAP, LA contractility and relaxation, LA stiffness, and LV and RV contractility. D-wave velocity is influenced by changes in LAP in early diastole and LV relaxation and it changes in parallel with the transmural E-wave velocity. AR velocity is determined by LA contractility and LV compliance.  Decrease in LV compliance and increase in LAP is associated with decrease in S velocity, increase in D velocity, and an increase in AR velocity and a longer AR duration. The S/D is inversely related to LAP.	1. Reduced S velocity, an S/D ratio <1 and systolic filling fraction (systolic VTI/total forward flow VTI) < 40% indicate increased LAP in patients with reduced LVEFs. 2. In patients with AF, DT of the D-velocity can be used to estimate mean PCWP. 3. AR velocity > 35 cm/s indicates an increased LVEDP.	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 EF, AF, MV disease, and HCM. 3. AR velocity is absent in patients with AF.
Ar-A duration	The time difference between durations of PV flow and transmural inflow during atrial contraction is associated with the LVEDP. The longer the time difference, the higher LVEDP.	1. AR duration > mitral A duration by 30 ms indicates an increased LVEDP. 2. Independent of age and EF. 3. Accurate in patients with MR and patients with HCM.	1. Adequate recordings of AR duration may not be feasible in many patients (comparing the end of AR and transmural A signals to the ECG QRS may be helpful in identifying a shortening of the transmural A duration). 2. Not applicable in patients with atrial arrhythmias, sinus tachycardia or heart block. 3. Transmural A duration cannot be reliably measured in certain cases (see above).
IVRT	Reflects the time interval aortic valve closure and MV opening and the crossover between LA and LV pressures.  Duration is directly related to LV relaxation and inversely related to LAP (i.e., prolonged in patients with impaired LV relaxation and normal LVFPs, shortened with increased LAP).	1. Overall feasible and reproducible. 2. IVRT can be combined with other transmural inflow parameters such as E/A ratio to estimate LVFPs in patients with HFrEF. 3. Helpful in identifying elevated LVFPs in patients with MAC. 4. When IVRT markedly prolonged (>110 ms), LAP likely normal. 5. A short IVRT (<70 ms) has a high specificity for elevated LAP in patients with cardiac disease. 6. In patients with MS or MR, IVRT can be combined with $T_{E-e'}$ to estimate LVFPs.	1. Limited use in isolation 2. Age-dependent (shorter in young patients with rapid LV filling and lengthens as relaxation slows with age) 3. Preload-dependent (normalizes with increasing LAP) 4. IVRT is in part affected by heart rate and arterial pressure. 5. More challenging to measure and interpret with tachycardia. 6. Identification of the onset of MV opening can be challenging.

(Continued)

**Table 4 (Continued)**

Variable	Utility and physiologic background	Advantages	Limitations
LV GLS	Measure of LV systolic function. Impaired LV GLS is common in some patients with HFpEF indicating subclinical LV dysfunction.	<ol style="list-style-type: none"> <li>1. A more sensitive index of myocardial systolic performance than EF.</li> <li>2. Provides earlier detection of myocardial disease in the setting of a normal EF.</li> <li>3. Can be more reproducible than EF.</li> <li>4. May be a superior discriminator of outcomes in patients with HFrEF and HFpEF.</li> </ol>	<ol style="list-style-type: none"> <li>1. Requires dedicated software package which is not available in all institutions.</li> <li>2. Suboptimal image quality in technically challenging studies precludes accurate measurements.</li> <li>3. Load-dependent.</li> <li>4. Values may vary between vendors; hence, results may not be interchangeable.</li> </ol>
Color M-mode Vp: Vp, and E/Vp ratio	Vp indirectly related to the time constant of LV relaxation ( $\tau$ ); (the longer it takes for the LV to relax, the slower the Vp). Vp can be used to correct for the effect increased preload on the transmural E velocity, E/Vp ratio is directly related to the LAP.	<ol style="list-style-type: none"> <li>1. Relatively load-independent.</li> <li>2. Vp is reliable as an index of LV relaxation in patients with depressed LVEFs and dilated LV but not in patients with normal EFs.</li> <li>3. Helps distinguish PN from normal transmural inflow profiles.</li> <li>4. The ratio of the transmural E to Vp (E/Vp) <math>\geq 2.5</math> predicts PCWP <math>&gt;15</math> mm Hg with reasonable accuracy in patients with depressed EFs.</li> </ol>	<ol style="list-style-type: none"> <li>1. In patients with normal LV volumes and EF but elevated LVFPs, Vp can be misleadingly normal.</li> <li>2. Vp pseudonormalization may also be seen in patients with small, hypertrophied ventricles.</li> <li>3. Lower feasibility and reproducibility.</li> <li>4. Suboptimal alignment between M-mode cursor and transmural inflow results in erroneous measurements.</li> </ol>
$T_{E-e'}$ time interval	Can identify patients with diastolic dysfunction due to delayed onset of $e'$ velocity compared with onset of the transmural E velocity.	<ol style="list-style-type: none"> <li>1. Helps distinguish PN from normal transmural inflow profiles.</li> <li>2. Ratio of IVRT to <math>T_{E-e'}</math> (IVRT/<math>T_{E-e'}</math>) can be used to estimate LVFPs in normal subjects and patients with MV disease.</li> <li>3. 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>	<ol style="list-style-type: none"> <li>1. Non-simultaneous measurements (important to match R-R intervals).</li> <li>2. More challenging to acquire satisfactory signals with close attention needed to sampling location, gain, and filter settings.</li> <li>3. Time intervals are numerically quite small so any error in measurement may prove significant.</li> </ol>
LAS	<p>LAS in diastolic function primarily focused on LARS. LARS shows a direct correlation with the degree of diastolic dysfunction (LARS worsens as the degree of diastolic dysfunction worsens) and is inversely related to LVFP (the lower the LARS, the higher the LVFP).</p> <p>As a late diastolic parameter, LASct (pump strain) is inversely related to LVEDP (the less negative the LASct, the higher the LVEDP).</p>	<ol style="list-style-type: none"> <li>1. LARS provides an estimate of LVFPs in patients with reduced EF.</li> <li>2. LARS may be helpful in distinguishing between degrees of diastolic dysfunction.</li> <li>3. LARS may be used as a substitute for missing standard variables.</li> <li>4. LARS provides prognostic value in patients with HF, AF, ischemic heart disease, and valvular heart disease.</li> <li>5. LA dysfunction identified with LARS may show abnormalities before anatomic changes occur.</li> </ol>	<ol style="list-style-type: none"> <li>1. Requires dedicated LAS software package which is not available in all institutions.</li> <li>2. Suboptimal image quality in technically challenging studies precludes accurate measurements.</li> <li>3. Values are age dependent (LARS decreases with age).</li> <li>4. LARS dependent on LV systolic function (may be normal despite elevated LVFP in patients with normal EF with preserved LV GLS).</li> <li>5. R-R gating may be an inaccurate substitution for end-diastole (e.g., when there is a BBB).</li> <li>6. May be inaccurate when there is a mobile atrial septum or a thin-walled LA or when tracking does not follow the mitral annulus or follows speckles outside of the imaging plane.</li> <li>7. LARS should not be used to assess LVFP in patients with AF, significant MR, heart transplant recipients, patients with normal EF and GLS <math>&gt; 18\%</math>, or suspected LA stunning.</li> </ol>

AF, Atrial fibrillation; AR, atrial reversal velocity in pulmonary veins; BBB, bundle branch block; CAD, coronary artery disease; DCM, dilated cardiomyopathy;  $E@A$ , mitral velocity at the start of atrial contraction; HFrEF, HF with reduced EF; ICU, intensive care unit; LARS, LA reservoir strain; LAS, LA strain; LASct, LA contractile strain; LVFP, LV filling pressure; Mitral DT, E-wave deceleration time; MV, mitral valve; PAEDP, PA end-diastolic pressure; PH, pulmonary HTN; PN, pseudonormal; PS, pulmonary stenosis; PV, pulmonary vein; PVR, pulmonary vascular resistance; RA, right atrial; ROI, region of interest; RVOT, RV outflow tract; RVSP, RV systolic pressure; UEA, ultrasound enhancing agent; Vp, early diastolic flow propagation velocity; VTI, velocity time integral.

**Table 5** Normal reference ranges for diastolic measurements by age category

Diastolic measure	Age, y		
	20-39	40-60	60-80
E wave, m/s	0.54 (0.52-0.57) to 1.11 (1.07-1.16)	0.47 (0.46-0.49) to 1.02 (0.99-1.05)	0.39 (0.37-0.42) to 0.92 (0.88-0.96)
A wave, m/s	0.24 (0.21-0.27) to 0.68 (0.63-0.72)	0.33 (0.32-0.35) to 0.82 (0.80-0.84)	0.43 (0.40-0.45) to 0.97 (0.93-1.00)
E/A ratio	0.88 (0.82-0.94) to 2.73 (2.66-2.81)	0.69 (0.66-0.73) to 2.07 (2.03-2.11)	0.50 (0.45-0.56) to 1.40 (1.34-1.47)
e' lateral (cm/s)	9.9 (9.4-10.4) to 22.1 (21.5-22.8)	7.5 (7.3-7.8) to 17.5 (17.1-17.9)	5.2 (4.8-5.6) to 13.0 (12.4-13.5)
e' septal (cm/s)	7.2 (6.8-7.7) to 16.4 (16.0-16.9)	5.7 (5.4-5.9) to 13.5 (13.2-13.8)	4.1 (3.7-4.5) to 10.6 (10.1-11.0)
e' average (cm/s)	8.7 (8.2-9.2) to 19.1 (18.6-19.7)	6.7 (6.4-7.0) to 15.4 (15.1-15.7)	4.7 (4.3-5.1) to 11.7 (11.2-12.2)
E/e' lateral	2.5 (2.0-3.0) to 6.3 (5.3-7.2)	3.6 (3.4-3.9) to 9.4 (8.9-10.0)	4.8 (4.5-5.0) to 12.6 (12.0-13.2)
E/e' septal	4.0 (3.3-4.7) to 9.1 (8.2-9.9)	4.9 (4.6-5.3) to 12.1 (11.7-12.6)	5.9 (5.5-6.3) to 15.2 (14.7-15.7)
E/e' average	4.0 (3.8-4.3) to 9.1 (8.5-9.7)	4.6 (4.4-4.8) to 11.5 (11.2-11.9)	5.2 (4.9-5.4) to 14.0 (13.4-14.5)
LAVi, mL/m <sup>2</sup>	12.1 (10.9-13.2) to 39.4 (34.6-44.2)	12.9 (12.2-13.5) to 38.3 (35.4-41.1)	13.7 (12.7-14.6) to 37.1 (33.0-41.3)
LAVi, Simpson, mL/m <sup>2</sup>	12.5 (12.0-13.0) to 41.9 (38.1-45.6)	13.3 (13.0-13.6) to 41.0 (38.5-43.4)	14.2 (13.7-14.6) to 40.0 (36.5-43.6)
LAVi, A-L, mL/m <sup>2</sup>	8.9 (3.9-13.9) to 20.9 (12.9-28.8)	11.0 (8.9-13.0) to 27.1 (24.0-30.3)	13.0 (9.9-16.0) to 33.4 (28.6-38.2)
TR velocity, m/s	1.3 (1.1-1.5) to 2.7 (2.6-2.7)	1.5 (1.4-1.6) to 2.7 (2.7-2.7)	1.7 (1.5-1.8) to 2.8 (2.7-2.8)
LA strain, %	29.5 (27.6-31.3) to 63.2 (59.9-66.5)	26.8 (25.6-28.0) to 57.7 (55.6-59.9)	24.1 (22.2-26.0) to 52.3 (48.9-55.7)
LAS, TomTec, %	29.9 (27.0-32.9) to 60.5 (57.6-63.4)	27.5 (25.7-29.4) to 55.4 (53.6-57.2)	25.1 (22.6-27.6) to 50.3 (47.9-52.7)
LAS, EchoPAC, %	29.5 (27.9-31.1) to 64.9 (59.7-70.2)	25.3 (24.0-26.5) to 61.5 (57.4-65.6)	21.1 (18.7-23.4) to 58.1 (50.3-65.8)

Reference values are based of fifth and 95th percentile values derived from regression equations to fit summary data from persons free of cardiovascular disease or risk factors (see [Supplemental Appendix](#)). Values displayed are: fifth percentile limit (95% confidence limits) to 95th percentile limit (95% confidence limit).

Summary-level data were extracted from publications of several population-based studies reporting the distribution of diastolic function measurements among subjects known to be free of cardiovascular diseases within specified age ranges and, when available, stratified by sex. These studies generally excluded individuals with known cardiovascular disease (e.g., coronary artery disease, atrial fibrillation, HF) or cardiovascular risk factors (e.g., hypertension, diabetes, obesity, renal dysfunction). Not all measurements were available in all studies. Using summary data on values by age group, we identified the normal ranges for diastolic measurements on the basis of their fifth and 95th percentile limits. Details of the data extraction, harmonization, and statistical analysis used to derive these limits are provided in the [Supplemental Appendix](#). A list of studies used for data extraction is provided in [Supplemental Table 2](#).

[Supplemental Figures 5 to 16](#) display the resulting estimated fifth and 95th percentile limits of diastolic measurements by age and sex, while [Table 5](#) provides the estimated normal ranges for each diastolic measurement by decade of life. Expanded data are provided in the [Supplemental Appendix](#). [Supplemental Table 3](#) provides fifth and 95th percentile reference limits for each diastolic measurement by age decade. [Supplemental Figures 17 to 32](#) provide additional plots of the fifth and 95th percentile limits of each diastolic measure by age, including 95% CIs and the associated scatterplot of the source data.

Differences in normal ranges by age were observed for measurements on the basis of transmural flow velocities (E velocity, A velocity, E/A ratio), tissue Doppler imaging (TDI) early diastolic velocity (e'), E/e' ratio, tricuspid regurgitation (TR) peak velocity, and LA volume (maximum LA volume index [LAVi]) and function (LA reservoir strain [LARS];  $P < .001$  for all). Statistical differences in fifth and 95th percentile limits were observed by sex for E and A

velocities but not for E/A ratio or the other measurements assessed. For LAVi, differences were also observed by method of measurement: biplane method of disks vs area-length method ([Supplemental Figures 27 and 28](#)). For LARS, differences were noted on the basis of the speckle-tracking strain software vendor used ([Supplemental Figures 31 and 32](#)).

#### 4. REFERENCE RANGES COMPARED WITH PROGNOSTIC VALUES FOR DIASTOLIC FUNCTION MEASUREMENTS

The values provided in this section are based on an estimate of the most extreme 10% of values from individuals of varying ages free of known cardiovascular disease or traditional risk factors. It is important to recognize that prognostically relevant alterations in diastolic measurements can occur within the range of normal values defined in this way. Among >5,700 older adults (>65 years of age) in the ARIC (Atherosclerosis Risk in Communities) study, increases in the incidence of HF or death were observed at values of septal e' velocity < 6 cm/s (lower 10th percentile limit 4.6 cm/s) and lateral e' velocity < 7 cm/s (lower 10th percentile limit 5.2 cm/s). Additionally, in this study E/e' ratio and LAVi demonstrated monotonic and near linear associations with incidence of HF or death, without evidence of a clear threshold with respect to prognosis. Additional studies with greater power and inclusion of individuals of broader age range will be necessary to determine if similar patterns are seen in younger individuals, and to refine estimates of prognostically relevant thresholds for diastolic measurements. As noted above, these data also do not address "optimal" values for these diastolic measurements, which may be obscured by their population-level age-related changes.

## Key Points

1. Numerous studies have demonstrated the association between age and echocardiographic measurements of LV diastolic function.
2. Normal ranges are not necessarily equivalent to “optimal” values, as the aging process itself may affect diastolic function.
3. E/e' ratio and LAVi have near linear associations with incidence of HF or death, without evidence of a clear threshold with respect to prognosis.

## 5. AGE-INDEPENDENT INDICES OF ELEVATED LV FILLING PRESSURES

Some indices of LV diastolic pressures are age independent. These indices are changes in mitral inflow velocities with Valsalva maneuver, and the difference in duration between pulmonary vein Ar velocity and mitral A velocity.<sup>1</sup> 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  $\geq 50\%$  is highly specific for increased LV filling pressures.<sup>1</sup> The procedure should be standardized by continuously recording mitral inflow using pulsed-wave Doppler for 10 seconds during the strain phase of the maneuver.

An increase in Ar-A duration is consistent with increased LVEDP. Pulmonary artery systolic pressure (PASP) identifies patients with increased LV filling pressures, provided pulmonary vascular disease is excluded.<sup>1</sup> The presence of a triphasic transmural inflow profile with mid-diastolic flow (L-wave) velocity  $\geq 50$  cm/s occurs in patients with markedly delayed LV relaxation and increased LAP.<sup>1</sup> A similar pattern may be seen on mitral annular velocity recordings and with mitral valve M-mode tracings.

## 6. LV STRUCTURE AND LA VOLUME AND FUNCTION

In many patients with diastolic dysfunction, LV and LA structural changes are present. LA enlargement, in the absence of chronic atrial arrhythmia and mitral valve disease, is a marker of chronic elevation of LAP.<sup>1,7,9</sup> However, this conclusion should be reached only after exclusion of other reasons for LA enlargement, including anemia, heart transplant recipients with biatrial technique, hyperdynamic state, or athletic status. Hence it is important to pay attention to the clinical setting.

Pathologic LV hypertrophy is usually associated with increased LV chamber stiffness. The presence of increased LV mass index and LA enlargement are among the criteria for the diagnosis of HFpEF, as will be discussed later.<sup>5,7,9</sup>

## 7. LV GLOBAL LONGITUDINAL STRAIN

In some patients with diastolic dysfunction and normal EF, including those with and those without HFpEF, LV global longitudinal function is reduced.<sup>7,9</sup> Abnormal LV longitudinal systolic function can be detected by using speckle-tracking to measure global longitudinal strain (GLS, *Supplemental Figure 2*). Although not an index of LV diastolic function, reduced LV GLS is one of the criteria used for HFpEF evaluation and is associated with worse outcomes in many cardiovascular diseases associated with diastolic dysfunction, including cardiomyopathies and left sided valvular heart disease (see the

*Supplemental Appendix* for technical aspects of acquisition and measurement).

## 8. LA STRAIN

LA strain has emerged as a useful parameter for estimating LV filling pressures. Additional details pertaining to acquisition and measurements can be found in *Supplemental Table 1* and *Supplemental Figures 3* and *4*. Obtained by STE imaging, LA strain is available on most ultrasound systems, and offline analysis is also possible. Accuracy for LAP estimation is highest in patients with depressed LVEF.<sup>10</sup> In addition, it is possible to divide LARS by the E/e' ratio to yield a noninvasive index of LA stiffness.<sup>11</sup> This index has the highest accuracy in comparison with other echocardiographic measurements in identifying patients with HFpEF<sup>12</sup> and in identifying patients with HFpEF who are most likely to be hospitalized for HF management.<sup>13</sup>

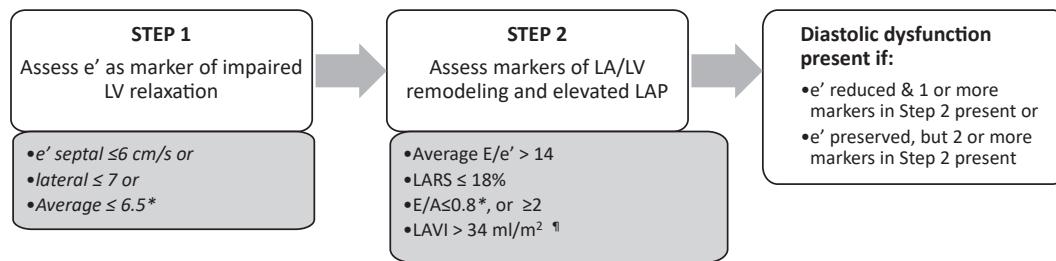
## 9. OTHER IMAGING MODALITIES FOR ASSESSMENT OF LV DIASTOLIC FUNCTION

Radionuclide angiography, cardiac magnetic resonance (CMR), and cardiac computed tomography (CT) can be used to measure LV filling rates. In addition, CT and CMR have been applied to measure mitral annular diastolic velocities, albeit with consistent underestimation in comparison with TDI. As a result, the other imaging modalities are not routinely applied for evaluation of LV diastolic function. However, they can provide valuable insights into LV structural changes including more precise measurement of LV mass and volumes. Using CMR, it is possible to identify and to quantify the extent of replacement and interstitial fibrosis.<sup>14,15</sup> Importantly, the fibrosis burden adds incremental value to echocardiographic assessment of LV diastolic function for risk stratification of patients with, or at risk for, HF.<sup>16</sup>

## 10. DEFINITION OF LV DIASTOLIC DYSFUNCTION USING ECHOCARDIOGRAPHY

LV diastolic function is assessed on the basis of LV relaxation and myocardial stiffness. Patients with diastolic dysfunction can have normal or elevated LV filling pressures. The existing echocardiographic surrogates of LV relaxation and LV chamber stiffness are not perfect and thus patients with diastolic dysfunction can be missed by echocardiography if one were to rely on a single variable. Accordingly, the working group recommends a combination of echocardiographic measurements for diagnosis of diastolic dysfunction. These include an index of LV relaxation, echocardiographic variables of reduced early diastolic LV filling relative to late diastolic filling, and functional and structural changes related to elevated LAP and LV diastolic pressures (*Figure 2*).

For LV relaxation, the best indices are mitral annular e' velocity and LV diastolic strain rate during isovolumic relaxation and early diastole.<sup>9</sup> Of the three indices, e' velocity has the highest feasibility and reproducibility for daily application. Ideally, cutoff values that are associated with clinically relevant events should be sought and considered in the definition of normal function. However, data with respect to association with outcomes is available only for individuals  $>65$  years of age and not younger subjects. Thus, the working group chose normal ranges for subjects  $<65$  years of age and prognostically low-risk features in subjects



\* : can also consider age specific cutoff values to identify abnormally reduced e' velocity or abnormally reduced E/A ratio

: after excluding LA enlargement in athletes, or due to anemia, atrial fibrillation or flutter, and mitral valve disease

① : another finding consistent with diastolic dysfunction: LV mass index >95 g/m<sup>2</sup> in women or 115 g/m<sup>2</sup> in men, after exclusion of increased LV mass in athletes

**Figure 2** Steps for diagnosing LV diastolic dysfunction.

>65 years of age. Of note, the cutoff values based on normal ranges in subjects >65 years of age are very similar to the ones that are associated with worse outcomes. The recommended cutoffs for e' velocity, which are based on reported normal values, are shown in [Table 6](#).

Mitral annular e' velocity is determined by LV relaxation, restoring forces, and lengthening load.<sup>9,17,18</sup> On a cellular level, the rate of LV relaxation reflects the decay of active force developed during systole. The restoring forces account for diastolic suction and can be represented by the behavior of an elastic spring that is compressed to a dimension less than its resting length during systole, and recoils back to the resting length during diastole when the compression is released. The lengthening load is the pressure in the left atrium at the mitral valve opening, which "pushes" blood into, and thereby lengthens the LV. The dependence of e' on LAP is most prominent in the presence of normal LV relaxation, whereas the effect of LAP on e' velocity is absent or reduced in the presence of diastolic dysfunction.<sup>17</sup> This is due to the delay in e' velocity such that it occurs when LV pressure equals or exceeds LAP.<sup>19,20</sup>

For surrogates of LAP, E/A and E/e' ratios and LARS are the recommended measurements. For structural surrogates, LAVi and LV mass index are the recommended indices. Given the direct dependence of e' velocity on LV relaxation, it is the first index in the algorithm. If abnormally reduced, only one additional variable is needed from the functional and structural variables discussed above. If e' velocity is not reduced, then two abnormal variables as shown in [Figure 2](#) are needed to diagnose the presence of diastolic dysfunction. A reduced E/A ratio for age is due to impaired LV relaxation leading to reduced early diastolic LV filling relative to late diastolic LV filling, whereas E/A ≥ 2, average E/e' > 14, and LARS < 18% are consistent with elevated LAP.

## Key Points

1. LV diastolic dysfunction is identified on the basis of mitral annulus e' velocity measurements, reduced early diastolic LV filling relative to late diastolic filling, and structural and functional surrogates of LAP and LV diastolic pressures.
2. Septal e' velocity < 6 cm/s, lateral e' velocity < 7 cm/s, or average e' velocity < 6.5 cm/s indicates abnormal LV relaxation irrespective of age.
3. Age-independent indices of LV filling pressure include changes in mitral inflow velocities with the Valsalva maneuver and the

difference in duration between pulmonary vein Ar velocity and mitral A velocity.

4. Patients with diastolic dysfunction and HFrEF frequently have abnormalities in LV structure and systolic function as well as in LA volume and function.
5. LV filling rates and LA volume and function can be assessed using cardiac CT and CMR. CMR determination of replacement and interstitial fibrosis provides incremental prognostic value to the echocardiographic assessment of LV diastolic function.

## 11. ALGORITHM FOR ESTIMATION OF MEAN LAP AT REST

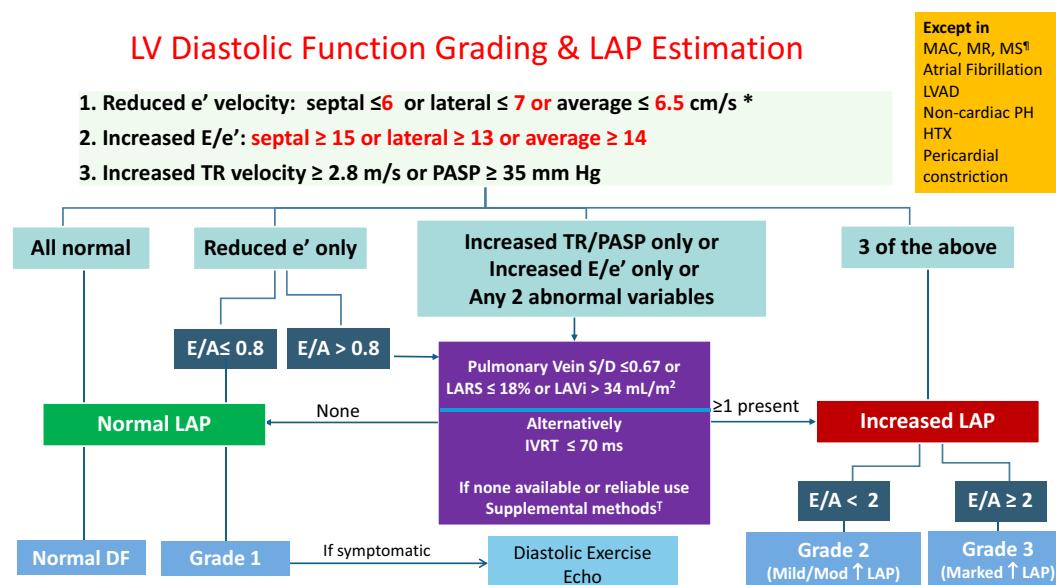
Echocardiography can estimate mean LAP using several parameters. During echocardiographic determination of diastolic function and filling pressure, the patient's rhythm, heart rate, and blood pressure should be recorded as they affect both LV diastolic function and the Doppler indices used in the algorithm ([Figure 3](#)). No single approach can estimate mean LAP in all clinical situations. [Figure 3](#) presents the validated main algorithm (21), irrespective of LVEF, in a practical approach that can be applied to most patients. The algorithm in [Figure 3](#) applies to all patients in sinus rhythm except for cases described in the special population sections. In subsequent sections, specific recommendations for special groups are discussed.

In clinical studies, LAVi is often inconsistent with other indices of LAP. True LA volume is often overlooked, and in some patients, this measurement is technically challenging. Furthermore, the correlation between LAP and LA volumes is not strong and LA volumes fail to track changes in LAP.<sup>2,21</sup> In addition, there are other causes for LA enlargement including anemia, athletic heart, high cardiac output states, atrial arrhythmias, and mitral valve disease. Therefore, unlike

**Table 6** Mitral annular e' velocity values for diagnosis of impaired LV relaxation

	20-39 y	40-65 y	>65 y
1. Septal e', cm/s	<7	<6	<6
2. Lateral e', cm/s	<10	<8	<7
3. Average e', cm/s	<9	<7	<6.5

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**Figure 3** Algorithm for estimation of mean LAP for patients in sinus rhythm and who do not have severe primary MR, any degree of mitral stenosis (MS), or moderate or severe MAC. The algorithm should also not be applied to patients in atrial fibrillation, heart transplant (HTx) recipients, noncardiac PH, pericardial constriction or LV assist device (LVAD). \*For annular e' velocity, age-adjusted lower limits of normal values shown in Table 6 can be applied in place of the values shown in this figure. †The algorithm should also not be applied to patients with mitral valve repair, mitral valve replacement, or mitral-transcatheter edge-to-edge repair. DF, Diastolic function;  $\dot{T}$ , PR end-diastolic velocity  $\geq 2$  m/s, PA diastolic pressure  $\geq 16$  mm Hg, mitral inflow L-wave velocity  $\geq 50$  cm/s, Ar-A duration  $> 30$  ms, and/or a decrease in mitral E/A ratio of  $\geq 50\%$  with Valsalva maneuver.

the 2016 guidelines, the algorithm in Figure 3 includes LAVi in the second stage, if needed.

The algorithm in Figure 3 begins with mitral annular  $e'$  velocity,  $E/e'$  ratio, and peak TR velocity or PASP. When the right atrial pressure (RAP) can be estimated, decisions about LAP should be based on whether PASP is  $\geq 35$  mm Hg or not. If RAP cannot be estimated, then peak TR velocity should be relied on, and a peak velocity  $\geq 2.8$  m/s in the absence of pulmonary parenchymal or vascular disease supports the conclusion that LAP is elevated. The TR jet should be obtained from multiple windows and the use of intravenous saline or ultrasound enhancing agents is encouraged in cases with incomplete TR jet, to enhance the jet and obtain a complete TR envelope. Caution should be exercised to avoid measuring the peak velocity from blooming artifacts.

For estimation of LAP at rest, the presence of all three findings of reduced  $e'$  velocity, increased  $E/e'$  ratio, and  $\text{PASP} \geq 35 \text{ mm Hg}$  or peak TR velocity  $\geq 2.8 \text{ m/s}$  when RAP cannot be estimated, supports the conclusion of elevated LAP. Subsequently, diastolic function is classified as grade 2 if the  $E/A$  ratio is  $<2$  or grade 3 if the  $E/A$  ratio is  $\geq 2$ . If all three variables do not meet the cutoff values for elevated LAP in [Figure 3](#), then LAP is normal, and the patient has normal diastolic function.

Grade 1 diastolic dysfunction is present when  $e'$  velocity is reduced with normal  $E/e'$  ratio and normal PASP, along with  $E/A$  ratio  $\leq 0.8$ . When  $e'$  velocity is reduced and the  $E/A$  ratio is  $>0.8$ , then additional variables should be considered as LAP can be elevated in some of these patients. Likewise, if only PASP or only  $E/e'$  ratio, or any two of the three variables ( $e'$  velocity,  $E/e'$  ratio, and PASP) are consistent with elevated LAP, then additional variables should be evaluated.

The additional variables recommended are LARS, pulmonary vein systolic to diastolic velocities ratio, LAVi, or alternatively IVRT. If LARS, pulmonary vein systolic to diastolic velocities ratio, IVRT.

and LAVi do not meet the cutoff threshold for elevated LAP, then LAP is likely normal. In symptomatic patients, diastolic exercise echocardiography is recommended when LAP at rest is normal to increase the sensitivity of detecting patients with HFrEF when there are indicators of abnormal LA/LV morphology and/or function (Figure 3).

LARS can be readily obtained in most patients with satisfactory 2D apical views (see the *Supplemental Appendix* for technical details). If LARS is  $\leq 18\%$ , then LAP is elevated. LARS  $\leq 18\%$  has high specificity, but can have low sensitivity in patients with normal LVEF for detecting elevated LAP.<sup>3,10,22</sup> On the other hand, relying on LARS cutoff values of 19% to 24%, which is in the low normal range,<sup>10</sup> leads to higher sensitivity and lower specificity for detecting elevated LAP.

For pulmonary venous flow velocities, previous work showed that a systolic filling fraction (systolic velocity-time integral [VTI]/systolic VTI + diastolic VTI) of  $\leq 40\%$  has good accuracy in identifying patients with elevated mean LAP.<sup>1</sup> The corresponding value for pulmonary vein systolic velocity-to-diastolic velocity ratio of  $\leq 0.67$  is equal to  $\leq 40\%$  systolic filling fraction and is therefore recommended. The ratio is most reliable in patients with LV systolic dysfunction and should not be considered in normal subjects with normal echocardiographic results, when the ratio can be  $\leq 0.67$ . In patients with normal LVEF, the ratio can be  $>0.67$  despite elevated LV filling pressures. In these patients, confirmation should be sought with IVRT, and if IVRT is not available, then other parameters discussed in the "Supplemental Parameters" section below should be analyzed to reach a conclusion about LAP. IVRT  $\leq 70$  ms is consistent with elevated LAP. If the findings indicate elevated LAP, then grading diastolic function should be pursued on the basis of E/A ratio (Figure 3).

## Supplemental Parameters

These can be relied on in the absence of the three parameters in the section above.

- a. Pulmonary regurgitation (PR) end-diastolic velocity: An end-diastolic velocity  $\geq 2$  m/s or pulmonary artery (PA) diastolic pressure  $\geq 16$  mm Hg is consistent with elevated LAP in the absence of pulmonary disease. Ultrasound enhancing agents can facilitate recording of a complete PR jet.
- b. Mitral inflow L-wave velocity: This is a mid-diastolic velocity that occurs after the mitral E wave. It was initially described in normal healthy young individuals with bradycardia with peak velocity  $<40$  cm/s. Later, it was also noted in patients with marked delay in myocardial relaxation and increased filling pressure. Because of delayed relaxation, LV diastolic pressure falls after the initial rise from LV filling, resulting in a mid-diastolic LA-LV pressure gradient, leading to blood flow into the left ventricle with peak velocity  $\geq 50$  cm/s. Therefore, the presence of an L-wave velocity  $\geq 50$  cm/s is an indicator of both impaired LV relaxation and elevated LAP.
- c. Premature termination of mitral inflow before QRS complex and diastolic mitral regurgitation (MR): Diastolic MR is recognized as diastolic flow from the left ventricle to the left atrium and can be indicative of increased LVEDP. It is analogous to the "B" bump on a mitral valve M-mode trace. However, this can also happen when the electrocardiographic PR interval is  $>200$  ms with sufficient atrial relaxation before systole. Therefore, one should be careful to exclude advanced atrioventricular (AV) block, atrial flutter, and organized atrial fibrillation activity before attributing diastolic MR to increased LV diastolic pressures.
- d. Pulmonary vein atrial reversal velocity: In the evolution of diastolic dysfunction, there is an early stage when LVEDP is elevated but mean LAP is normal. This stage is diagnosed on the basis of a high amplitude ( $>35$  cm/s) and long duration of pulmonary vein Ar velocity, along with an Ar-A duration  $>30$  ms.
- e. Changes in mitral inflow with Valsalva: A decrease in E/A ratio of  $\geq 50\%$  with the Valsalva maneuver is specific for elevated LAP.

The evaluation of LV diastolic function should not stop at the algorithm above in symptomatic patients with grade 1 diastolic dysfunction. These patients should be referred for diastolic exercise echocardiography.

## 12. REPORTING ON DIASTOLIC FUNCTION

All echocardiographic reports should include an assessment of diastolic function grading and filling pressure, indicating whether diastolic function is normal or abnormal with grade 1, 2 (mild to moderate increase in LAP), or 3 (marked increase in LAP). If the interpreting cardiologist is unable to determine the grade of diastolic dysfunction, the status of LV filling pressure should be mentioned in the report (whether LAP is normal or elevated). An isolated increase in LVEDP should be reported, as it predisposes patients to elevated mean LAP with exercise, faster heart rate, or increased afterload. Whenever possible, the report should mention whether a change has occurred in LV diastolic function grade in comparison with previous studies.

Measurements that should be included in the report are mitral inflow velocities, mitral annular e' velocity, peak TR velocity, E/A ratio, and average E/e' ratio (unless only one side is acquired or satisfactory). LARS, pulmonary vein S/D ratio or systolic filling fraction, mitral inflow A duration, pulmonary vein Ar duration, and/or IVRT should be included in the report if relied on to arrive at the conclusions pertaining to diastolic function grade and mean LAP.

## 13. DIASTOLIC EXERCISE ECHOCARDIOGRAPHY

LV filling pressure at rest may not be sufficient to evaluate a patient with dyspnea that happens mostly with exertion. Importantly, up to 50% of patients with HFpEF have normal LV filling pressure at rest that in-

creases rapidly with exercise or even leg raising.<sup>23</sup> Echocardiography can determine the status of LV relaxation by measuring e' velocity.<sup>9,17,18</sup> In normal subjects, mitral e' increases about 3 to 5 cm/s on average with exercise,<sup>24</sup> but in subjects with diastolic dysfunction, e' velocity does not increase as much as in a normal subject, or not at all. In patients with diastolic dysfunction, mitral inflow E velocity increases with exercise and e' does not change as much, such that E/e' ratio increases. Normal E/e' values have been published for middle-age and young subjects using treadmill or supine bicycle exercise with remarkably similar values of 6 to 8 at rest and with exercise. It rarely becomes higher than 10. Several studies have shown a good correlation between E/e' ratio and invasively obtained PCWP, LAP, or LV mean diastolic pressure with variable levels of effort, including day-to-day activity as well as during supine bicycle exercise in the catheterization laboratory.<sup>23,25-27</sup>

### A. Indications

Diastolic stress testing is most valuable when resting echocardiography does not explain the symptoms of HF or exertional dyspnea. In general, patients with completely normal diastolic function at rest with preserved e' velocity need not undergo stress testing as it is highly unlikely that they will develop 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 is already 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 the presence of delayed myocardial relaxation and normal mean LAP at rest. The diagnostic evaluation of symptomatic patients with indeterminate diastolic function or filling pressure at rest can also benefit from diastolic stress testing. LARS has been reported to identify patients who are more likely to develop increased filling pressure with exercise.<sup>28</sup>

### B. Performance

Diastolic stress testing can be performed using either supine bicycle or treadmill exercise echocardiography. The use of dobutamine stress testing for the assessment of diastolic function is strongly discouraged. For supine bicycle exercise, there is sufficient time during each stage of exercise to acquire 2D images, mitral inflow velocities, annular velocities, and peak TR velocity. For treadmill exercise, 2D images are obtained first to assess wall motion for myocardial ischemia. Mitral inflow velocities are usually fused during exercise, and it would be most helpful to obtain TR velocity first, immediately after wall motion analysis, followed by mitral inflow and annular velocities when E and A velocities are not fused. When LV filling pressure is elevated with exercise, it usually remains elevated for several minutes, providing sufficient time to acquire Doppler velocities after acquisition of parasternal and apical views for LV wall motion and volume analysis. As soon as mitral E and A velocities are separated, mitral annular and mitral inflow velocities (in this order) are acquired. In patients with atrial fibrillation, diastolic function parameters can be obtained immediately after recording 2D views. Recently, lung scanning to detect "B" lines, which indicates water in the lung or pulmonary venous congestion, was introduced as a part of diastolic exercise stress echocardiography.<sup>29</sup> In some patients, similar information can be obtained with simple leg raising for 1 minute using a regular echocardiographic examination table. However, this simple method lacks sufficient sensitivity.<sup>30</sup>

### C. Interpretation

The results are considered definitely abnormal, indicating increased LV filling pressure when the following conditions are met: average E/e' ratio  $\geq 14$  or septal E/e' ratio  $\geq 15$  and peak TR velocity  $> 3.2$  m/s. The test indicates normal filling pressure when average (or septal) E/e' is  $<10$  and peak TR velocity is  $<2.8$  m/s. HFpEF diagnosis is not supported by an E/e' ratio  $<14$ , even with an increase in peak TR velocity to  $>3.2$  m/s. HFpEF diagnosis is considered likely when E/e' ratio is  $>14$  and the peak TR velocity is  $>2.8$  but  $<3.2$  m/s. One should be cautious in drawing conclusions on the basis of an isolated increase in exercise peak TR velocity, as normal subjects can have significant increases in peak TR velocity related to increased pulmonary blood flow. After analysis of  $>14,000$  diastolic exercise echocardiograms, it was found that 17% of patients develop increased LV filling pressure with exercise, while 28% have evidence of myocardial ischemia.<sup>31</sup> Patients with increased filling pressure after exercise but no ischemia have a worse prognosis than patients with isolated ischemia.<sup>31</sup> In addition, PASP  $> 50$  mm Hg or TR velocity  $> 3.2$  m/s portends a worse outcome,<sup>31</sup> hence the recommendation for this cutoff value. An invasive hemodynamic investigation, including the use of exercise, may be necessary when exercise echocardiographic assessment is negative or indeterminate in a patient with a clinical presentation concerning for HFpEF.

### Key Points

1. Diastolic exercise stress testing is indicated in patients with dyspnea and grade 1 diastolic dysfunction at rest and in patients with indeterminate LV filling pressure at rest. It is performed using supine bicycle or treadmill exercise stress testing.
2. At rest, mitral E and e' velocities should be recorded, along with the peak velocity of TR, using agitated saline if needed. The same parameters are recorded during exercise or 1 to 2 minutes after termination of exercise when E and A velocities are not merged, because increased filling pressures usually persist for a few minutes.
3. The result is considered positive when during exercise, average E/e' ratio is  $\geq 14$  (or septal E/e' ratio is  $\geq 15$ ) and peak TR velocity is  $\geq 3.2$  m/s.

## 14. APPLICATION OF AI TO THE ASSESSMENT OF LV DIASTOLIC FUNCTION

Given the complexity of diastolic function assessment, both in terms of the need to measure numerous parameters and the requirement of data integration to grade the severity, the application of AI to streamline these processes through automating both parameter measurement and severity grading would be highly valuable. This type of application has been demonstrated in few studies that used a rule-based algorithm to grade diastolic function on the basis of measurements obtained by experts or by machine learning models, including some studies that used electrocardiographic findings relying on data from close to 100,000 paired echocardiograms and electrocardiograms.<sup>32,33</sup> Interestingly, electrocardiographic findings showed good accuracy in identifying the three grades of diastolic dysfunction, with similar prognostic value to echocardiography.<sup>33</sup>

Several approaches have been tested for AI-assisted diastolic function assessment. Multiple-view approaches involve the use of machine

learning models to automate view classification, view segmentation, and input of the machine-derived measurements into a rule-based decision tree algorithm for severity classification using the 2016 guidelines as a reference.<sup>33-35</sup> Single-view approaches have also been studied. These often involve the segmentation of LA and LV volumes, measurement of LVEF and longitudinal strain, and training the model to identify which combination of LA and LV metrics provides the most accurate grading of diastolic function.<sup>33,35-37</sup> Other single-view approaches use a deep-learning neural network to train models to identify and grade diastolic function directly from the 2D apical four-chamber videos without segmentation.<sup>33-35</sup> All these approaches have used the 2016 guideline as a reference, and thus, they are similarly prone to grading several cases as indeterminate.

Machine learning models based on clinical outcomes<sup>38,39</sup> offer a more evidence-based approach to optimizing the classification of diastolic function with both reduction of "indeterminate" cases and improvement of the clinical relevance of diastolic function classification. Recognizing that diastolic function represents a continuum from normal function to the most severe diastolic dysfunction grade, the ability to accurately assess where a patient is in that continuum is important for prognostication and management purposes. To that end, a continuous diastolic function score has been developed on the basis of inputs of traditional diastolic parameters on echocardiography, even for cases that would have been labeled indeterminate according to the reference guidelines.<sup>32</sup> Further validation of this model and other models using invasive hemodynamics and clinical outcomes is needed to establish precision, reproducibility, and clinical relevance. Vendor reporting systems based on AI that incorporate several echocardiographic measurements to arrive at a conclusion regarding LV diastolic function are needed as they have the potential of increasing the incorporation of diastolic function assessment results in clinical reports.

### Key Points

1. The application of AI can enhance the noninvasive assessment of LV diastolic function by automating parameter measurement and severity grading.
2. There are multiple- and single-view approaches. Single-view approaches involve the segmentation of LA and LV volumes, measurement of LVEF and longitudinal strain, and training the model to identify which combination of LA and LV metrics provides the most accurate grading of diastolic function.
3. Machine learning models based on clinical outcomes offer a more evidence-based approach to optimize the classification of diastolic function.
4. Validation of AI models using invasive hemodynamics and clinical outcomes is needed to establish their precision, reproducibility, and clinical relevance.

## 15. ASSESSMENT OF LV DIASTOLIC FUNCTION AND ESTIMATION OF LV FILLING PRESSURES IN SPECIAL POPULATIONS

In the following sections we 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 7)<sup>40-58</sup>.

**Table 7** Indicators of elevated LV filling pressures in special populations

Disease	Echocardiographic measurements indicative of elevated LV filling pressure
1. Atrial fibrillation <sup>40-42</sup>	1. DT < 160 ms in patients with depressed LVEF 2. Peak acceleration rate of mitral E velocity ( $\geq 1,900 \text{ cm/s}^2$ ) 3. IVRT ( $\leq 65 \text{ ms}$ ) 4. DT of pulmonary venous diastolic velocity ( $\leq 220 \text{ ms}$ ) 5. E/Vp ratio ( $\geq 1.4$ ) 6. Septal E/e' ratio ( $\geq 11$ ) 7. Peak TR velocity $> 2.8 \text{ m/s}$
2. Sinus tachycardia <sup>43,44</sup>	1. Predominant early LV filling pattern with depressed LVEF 2. IVRT $\leq 70 \text{ ms}$ is specific (79%) 3. Pulmonary vein systolic filling fraction $\leq 40\%$ is specific (88%) 4. Average E/e' ratio $> 14$ (high specificity but low sensitivity) 5. 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
3. HCM <sup>45</sup>	1. Average E/e' ( $> 14$ ) 2. Ar-A ( $\geq 30 \text{ ms}$ ) 3. Peak TR velocity ( $> 2.8 \text{ m/s}$ ) 4. LA maximum volume index ( $> 34 \text{ mL/m}^2$ )
4. Restrictive cardiomyopathy <sup>46-49</sup>	1. Average E/e' ( $> 14$ ) 2. DT $< 140 \text{ ms}^*$ 3. E/A ratio $> 2.5^*$ 4. IVRT $< 50 \text{ ms}^*$
5. PH <sup>50,51</sup>	1. E/A $\geq 2$ favors postcapillary PH 2. E/A $\leq 0.8$ favors precapillary PH 3. When E/A ratio is $> 0.8$ but $< 2$ , lateral E/e' ratio $> 13$ , LA maximum volume index $> 34 \text{ mL/m}^2$ , and LARS $< 18\%$ favor the diagnosis of postcapillary PH.
6. Mitral stenosis <sup>52</sup>	1. IVRT $< 60 \text{ ms}^*$ 2. Mitral A peak velocity $> 1.5 \text{ m/s}$ 3. IVRT/T <sub>E-e'</sub> ratio $< 4.2$
7. MR <sup>52-54</sup>	1. IVRT $< 60 \text{ ms}^*$ 2. Ar-A ( $\geq 30 \text{ ms}$ ) 3. IVRT/T <sub>E-e'</sub> ratio $< 5.6$ 4. Average E/e' ratio $> 14$ in patients with depressed EF
8. Moderate/severe MAC <sup>55</sup>	1. LV filling pressure normal when mitral E/A ratio is $< 0.8$ 2. LV filling pressure elevated when mitral E/A ratio is $> 1.8$ 3. E/A ratio $> 0.8$ but $< 1.8$ , IVRT should be measured. LV filling pressure normal when IVRT is $\geq 80 \text{ ms}$ , whereas it is elevated if IVRT $< 80 \text{ ms}$ .
9. LV assist device <sup>56,57</sup>	1. E/A ratio $> 2$ 2. RAP $> 10 \text{ mm Hg}$ 3. PASP $> 40 \text{ mm Hg}$ 4. Average E/e' ratio $> 14$ or septal E/e' ratio $\geq 15$ 5. LA maximum volume index $> 33 \text{ mL/m}^2$ 6. Interatrial septum position <sup>†</sup>
10. Cardiac transplant recipients <sup>58</sup>	1. Average E/e' ratio $< 7$ denotes normal LV filling pressures 2. Average E/e' ratio $> 14$ denotes elevated LV filling pressures 3. For E/e' ratio $> 7$ and $< 14$ , SR <sub>IVR</sub> , from all three apical views, is measured, and the ratio of mitral E velocity to SR <sub>IVR</sub> is derived. A ratio $\leq 200 \text{ cm}$ is consistent with normal LV filling pressure, but $> 200 \text{ cm}$ denotes elevated LV filling pressure. 4. In patients in whom SR <sub>IVR</sub> cannot be measured, peak TR velocity is relied on. Peak TR velocity $\leq 2.8 \text{ m/s}$ is consistent with normal LV filling pressures, but $> 2.8 \text{ m/s}$ denotes elevated LV filling pressures.

\*Specific but not sensitive indicators of elevated LV filling pressure.

<sup>†</sup>LAP = RAP if the interatrial septum position is neutral. If septum bulges to right, then LAP is 5 mm Hg higher than RAP. If septum bulges to left, then LAP is 5 mm Hg lower than RAP.

#### A. Assessment of LV Diastolic Function in Patients With Valvular Heart Disease

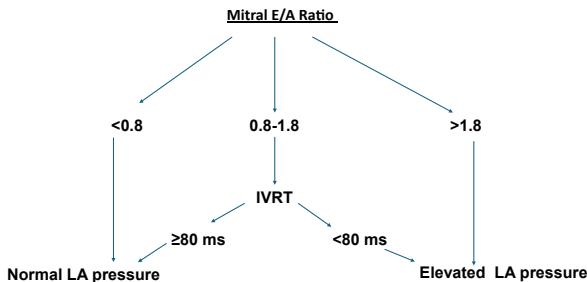
a. Mitral stenosis: Usually, patients with mitral stenosis have normal or reduced LV diastolic pressures, except for the rare occurrence of coexisting myocardial disease. The same hemodynamic findings are present in patients

with other etiologies of LV inflow obstruction, such as a large LA tumor obstructing LV inflow, or cor triatriatum. A short IVRT ( $< 60 \text{ ms}$ ) and mitral A velocity  $> 1.5 \text{ m/s}$  are usual findings in patients with increased LAP. The time interval between the onset of mitral E and annular e' velocities (T<sub>E-e'</sub>) can be applied to estimate LV filling pressures in patients with mitral valve disease. In the presence of impaired LV relaxation, e' velocity is reduced and

delayed such that it occurs at the second LA-LV pressure crossover point. In comparison, mitral E velocity occurs earlier with elevated LAP. Thus,  $T_{E-e'}$  is prolonged and can correct for the effect of LV relaxation on IVRT. IVRT/ $T_{E-e'}$  correlates well (inversely) with mean PCWP and LAP in patients with mitral stenosis.<sup>1,52</sup> However, E/e' ratio is not useful.

b. MR: Primary MR leads to LA and LV enlargement and an increase in the compliance of both chambers, which attenuates the increase in LAP. Later, with increased LA stiffness, mean LAP and PA pressures increase, which is related to MR, not LV myocardial disease. However, with LV diastolic dysfunction, the increased LV diastolic pressures contribute to the increase in LAP. The sequence is opposite to that seen in primary myocardial disease such as dilated cardiomyopathy, which leads to increased LV diastolic pressures initially 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 increase in mitral E velocity and a decrease in pulmonary vein systolic velocity, and the S-to-D ratio. In severe MR, systolic pulmonary venous flow reversal can be seen. Thus, MR can induce changes in transmural and pulmonary venous flow patterns resembling advanced LV diastolic dysfunction. Irrespective of MR severity, Ar-A duration remains a good indicator of increased LVEDP.<sup>53</sup> A continuous-wave (CW) Doppler MR velocity profile showing early peaking and reduced late LV-LAP gradient is a highly specific, though not sensitive, sign of increased LAP. The utility of E/e' ratio in predicting LV filling pressures in the setting of moderate or severe MR is more complex. In patients with depressed EF, an increased E/e' ratio has a direct significant relation with LAP and predicts hospitalizations and mortality.<sup>54</sup> However, E/e' ratio does not appear to be useful in patients with primary MR and normal EF,<sup>55</sup> though some investigators have noted a good correlation between E/e' ratio and mean PCWP as well as PASP in this population. Likewise, LARS has been shown to have no significant relationship with LA "v" wave or mean pressure in patients with significant MR and could not detect changes in "v" pressure after transcatheter edge-to-edge repair (TEER).<sup>60</sup> In comparison, IVRT/ $T_{E-e'}$  ratio correlates reasonably well with mean PCWP, regardless of EF. An IVRT/ $T_{E-e'}$  ratio  $<3$  readily predicts PCWP  $> 15$  mm Hg in this patient population.<sup>52</sup> In patients with atrial fibrillation and MR, the use of matched intervals (necessitating acquisition of many cycles) is necessary. It is challenging to assess LV relaxation and LV filling pressures after mitral valve repair or replacement, although time intervals and PA pressures could be of value for drawing inferences about LV filling pressures.<sup>52</sup>

c. Mitral annular calcification (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 transmural velocities, while lateral e' velocity may be decreased because of reduced annular excursion. Thus, an increase in E/e' ratio can occur because of the mechanical effects of MAC. Although data are limited, LV filling pressures are usually normal when mitral E/A ratio is  $<0.8$  but elevated when the ratio is  $>1.8$ . When E/A is 0.8 to 1.8, IVRT should be measured (Figure 4). LV filling pressure is usually normal when IVRT is  $\geq 80$  ms, whereas it is elevated if IVRT is  $<80$  ms.<sup>55</sup>



**Figure 4** Algorithm for estimation of mean LAP in patients with moderate or severe MAC.

d. LAP estimation after TEER: Flow across an iatrogenic atrial septal defect after TEER can be detected from multiple views using color Doppler. When flow is aligned with the ultrasound beam (usually from the subcostal view), CW Doppler can be used to record the peak flow velocity across the interatrial septum in late diastole in patients in sinus rhythm, corresponding to the LA "a" wave, and the peak velocity at end-systole corresponding to the LA "v" wave. The modified Bernoulli equation is then used to estimate the corresponding LAP as follows:

$$\text{LAP (mm Hg)} = 4V^2 + \text{RAP},$$

where  $V$  is the peak velocity of flow across the interatrial septum in meters per second. RAP is estimated on the basis of inferior vena cava diameter, its change with respiration and sniffing, and hepatic vein flow.<sup>1</sup> When interatrial left-to-right shunt velocity is  $>1.7$  m/s, LAP is usually elevated. However, in patients with biventricular HF, the interatrial velocity may not be helpful in estimating LAP. The aforementioned approach can also be applied in other situations with residual shunt across the interatrial septum after ablation procedures for atrial fibrillation, LA appendage occlusion, other procedures involving transseptal access, and also congenital atrial septal defects.

e. Aortic stenosis and aortic regurgitation: The presence of diastolic dysfunction, including elevated LV filling pressures, predicts worse outcomes in patients with moderate or severe aortic stenosis (AS).<sup>61</sup> Furthermore, the improvement of diastolic dysfunction after surgical and transcatheter aortic valve replacement is associated with lower rates of adverse outcome events.<sup>62,63</sup> It is therefore recommended that assessment of LV diastolic function status be carried out in all patients with AS and be included in the report. There are usually no major challenges to the application of the guidelines in patients with AS. If moderate or severe MAC is present, then the recommendations pertaining to patients with significant MAC should be applied.

For patients with severe aortic 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 elevated LV filling pressures. In chronic severe AR, the mitral inflow pattern often shows predominant early diastolic filling with short deceleration time of mitral E velocity,<sup>64</sup> but 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'  $> 14$ , LARS  $< 18\%$ , and peak TR velocity  $> 2.8$  m/s support the presence of increased LV filling pressures.

## Key Points

1. Mitral stenosis renders assessment of LV diastolic function more challenging, but IVRT,  $T_{E-e'}$ , and mitral E and A velocities can be of value in the semiquantitative prediction of mean LAP.
2. Ar-A duration  $> 30$  ms and IVRT/ $T_{E-e'}$   $< 5.6$  may be applied 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. In patients with moderate and severe MAC, LV filling pressures are usually normal when mitral E/A ratio is  $<0.8$  but elevated when the ratio is  $>1.8$ . When E/A is 0.8 to 1.8, IVRT should be measured. LV filling pressure is usually normal when IVRT is  $\geq 80$  ms, whereas it is elevated if IVRT  $<80$  ms.

4. The guidelines in patients without valvular heart disease can be applied to patients with AS, irrespective of severity of valvular stenosis. This excludes patients with moderate or severe MAC.
5. Flow across atrial septal defect (congenital or iatrogenic after TEER and other procedures) can be recorded by CW Doppler. The modified Bernoulli equation is used to estimate the corresponding LAP as LAP (mm Hg) =  $4V^2 + RAP$ , where  $V$  is the peak velocity of flow across the interatrial septum in meters per second.
6. In patients with acute or chronic severe AR, premature closure of the mitral valve, diastolic MR, LA enlargement, average  $E/e' > 14$ , and TR peak velocity  $> 2.8$  m/s are consistent with elevated LV filling pressures.

## B. Heart Transplant Recipients

The transplanted heart is affected by many factors that influence LV diastolic function, making the interpretation of diastolic function more difficult. The donor heart is denervated, leading to sinus tachycardia, which can lead to fusion of mitral E and A velocities. Pulmonary venous flow is usually not helpful in estimating LV filling pressures as the S-to-D ratio is reduced given the young age of most donor hearts.

For mitral inflow, an E/A ratio  $\geq 2$  in patients with preserved EF is a common finding after heart transplantation and can be observed in patients with normal LV diastolic function as donor hearts are usually obtained from healthy individuals. It is most pronounced in the early weeks after surgery, and in some patients is likely related to myocardial edema. This inflow pattern changes at follow-up. Although LV diastolic pressures can be normal at rest, a large increase in LV minimal pressure and LVEDP has been noted during exercise in heart transplant recipients with diastolic dysfunction.<sup>65</sup> This is due to lack of shortening or prolongation of the time constant of LV relaxation with exercise in addition to increased LV chamber stiffness.<sup>65</sup> Mitral annular  $e'$  velocity is influenced by the pronounced translational motion of the heart and may not detect the changes in LV relaxation status with exercise. 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. 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.<sup>1</sup> Later, myocardial fibrosis seen with chronic graft rejection can lead to a restrictive LV filling pattern and markedly reduced annular velocities. However, no single diastolic parameter is reliable enough to predict graft rejection.

A recently validated simplified approach may be used in transplant recipient patients in sinus rhythm, whereby average  $E/e' < 7$  denotes normal LV filling pressures, and  $E/e' > 14$  denotes elevated LV filling pressures.<sup>58</sup> For average  $E/e'$  between 7 and 14, LV strain rate during the isovolumic relaxation period ( $SR_{IVR}$ ), from all 3 apical views, is measured, and the ratio of mitral E velocity to  $SR_{IVR}$  is derived. A ratio  $\leq 200$  cm is consistent with normal LV filling pressures, but  $> 200$  cm denotes elevated LV filling pressures (Figure 5). In patients in whom  $SR_{IVR}$  cannot be measured, peak TR velocity is used. A peak TR velocity  $\leq 2.8$  m/s is consistent with normal LV filling pressures, but  $> 2.8$  m/s denotes elevated LV filling pressures.<sup>58</sup>

## Key Points

1. Predominant early diastolic filling in patients with preserved EF 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 individuals.
2. No single diastolic parameter is reliable enough to predict graft rejection.
3. A simplified approach may be used whereby average  $E/e' < 7$  denotes normal LV filling pressures, but  $E/e' > 14$  supports the conclusion of elevated LV filling pressures. For  $E/e'$  between 7 and 14,  $SR_{IVR}$ , from all three apical views, is measured, and the ratio of mitral E velocity to  $SR_{IVR}$  is derived. A ratio  $\leq 200$  cm is consistent with normal LV filling pressures, but  $> 200$  cm denotes elevated LV filling pressures. In patients in whom  $SR_{IVR}$  cannot be measured, peak TR velocity is used. A peak TR velocity  $\leq 2.8$  m/s is consistent with normal LV filling pressures, but  $> 2.8$  m/s denotes elevated LV filling pressures.

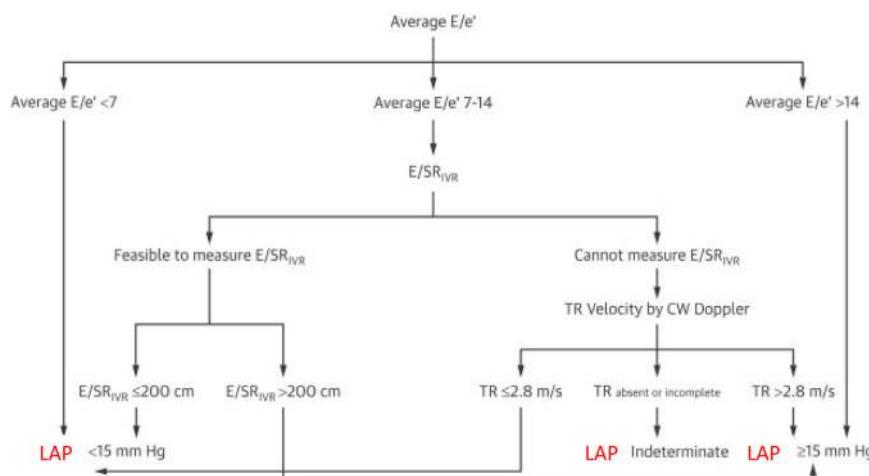


Figure 5 Algorithm for estimation of mean LAP in heart transplant recipients in sinus rhythm.

### C. Pulmonary Hypertension

Evaluation of LV filling pressure in patients with moderate or severe pulmonary hypertension (PH) group I and groups III to V requires a different approach than in patients with PH due to left-sided heart disease or group II PH.<sup>1</sup> Because PH is associated with elevated right ventricular (RV) systolic and diastolic pressures, there is often septal flattening, and therefore lateral E/e' rather than the average of septal and lateral E/e' should be used to evaluate LV filling pressure. In patients with PH, lateral E/e' > 13 reflects elevated LV filling pressure, and values <8 are consistent with normal filling pressure.<sup>50</sup> In a recent study looking at noninvasive evaluation of LV filling pressure in PH, these observations were confirmed, and it was observed that E/e' in the range of 8 to 13 had weak or no association with LV filling pressure.<sup>51</sup> Therefore, the use of lateral E/e' as a marker of LV filling pressure can result in indeterminate cases. However, the combination of lateral E/e' with either mitral E/A ratio or LARS (<16%) readily identified patients with elevated PCWP with good accuracy and high feasibility (Figure 6).

### Key Points

1. Reliable variables for estimation of LV filling pressure in patients with PH include lateral E/e', mitral E/A, LAVi, and LARS.
2. An E/A value  $\leq 0.8$  is usually seen in patients with noncardiac PH, whereas a ratio  $\geq 2$  is seen in patients with group II PH.
3. LAVi  $> 34 \text{ mL/m}^2$ , lateral E/e'  $> 13$ , and LARS  $< 18\%$  favor the presence of group II PH.
4. The recommended algorithm in patients with PH begins with mitral E/A, where a ratio  $\leq 0.8$  favors the diagnosis of precapillary PH, and a ratio  $\geq 2$  favors the diagnosis of postcapillary PH. For E/A  $> 0.8$  but  $< 2$ , lateral E/e'  $> 13$ , LAVi  $> 34 \text{ mL/m}^2$ , and LARS  $\leq 16\%$  favor the diagnosis of group II PH.

### D. AV Block, Bundle Branch Block, and Electronic Pacing

Normal subjects have near simultaneous contraction and relaxation of all ventricular segments, which is demonstrated as synchronous systolic shortening and diastolic lengthening as seen with strain imaging.

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 capacity by altering LV systolic and diastolic function, and thus the 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 ms is usually well tolerated if 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  $> 280$  ms usually results in fusion of E and A velocities. If atrial contraction occurs before early diastolic mitral flow velocity has decreased toward zero (defined as  $\leq 20 \text{ cm/s}$ ), E/A is reduced because of a higher A-wave velocity.<sup>66</sup> This fusion of early and late diastolic filling waves with an E/A  $< 1$  can be misinterpreted as impaired relaxation filling pattern. In addition, with mitral E and A fusion, the larger atrial stroke volume increases the mitral A-wave duration. Diastolic fusion of filling waves can limit exercise capacity because LV end-diastolic volume is reduced, lowering maximal cardiac output. At PR values  $> 320$  ms, E and A velocity fusion leads to filling only with atrial contraction (uniphasic A velocity), and diastolic MR is seen.<sup>67</sup> In these patients, maximal exercise capacity is almost always limited because of the inability to increase LV filling with increasing heart rate. If there is complete fusion, peak TR velocity and LA volume and strain can be used to draw inferences about LV filling pressures. Albeit the accuracy of LARS has not been critically examined in this setting.

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 (LBBB) can be associated with prolongation of IVRT, which leads to shortening of LV filling time,<sup>68,69</sup> which in turn limits stroke volume. This can be a challenge during exercise when the rapid heart rate further reduces diastolic filling time. LBBB can be associated with

## LAP Estimation in Patients with Pulmonary Hypertension

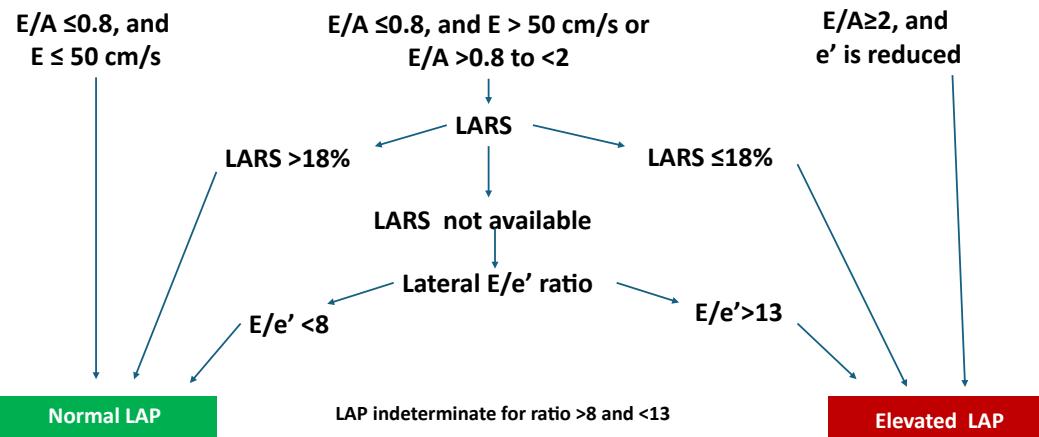


Figure 6 Algorithm for estimation of mean LAP in patients with PH.

abnormal function of the interventricular septum leading to a reduction in septal  $e'$  velocity. Therefore, septal and average  $E/e'$  may not reflect LV filling pressure reliably in patients with LBBB. Lateral  $E/e'$  may still be a valid indicator of filling pressure. There is a need for further studies to determine how lateral  $E/e'$  may be used in patients with LV dyssynchrony caused by LBBB, RV pacing, and in patients with cardiac resynchronization therapy (CRT).

RV pacing often leads to LV mechanical dyssynchrony resembling the contraction pattern in LBBB. Therefore, RV pacing can impair LV filling and limits utility of septal  $e'$  as a marker of diastolic dysfunction. Patients who mostly need atrial pacing have no alterations in LV systolic and diastolic function. In patients who are not dependent on ventricular pacing to maintain heart rate, pacemaker settings are often set with a long AV delay to encourage fusion or native QRS beats to minimize RV pacing. 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 LBBB, RV pacing, and in patients who have received CRT.<sup>21,70</sup>

## Key Points

1. In patients with first-degree AV block, the variables used to evaluate diastolic function and filling pressures are valid if there is no fusion of mitral E and A velocities.
2. The accuracy of mitral annular velocities and  $E/e'$  is less in the presence of LBBB, RV pacing, and in patients who have received CRT.
3. If only mitral A velocity is present, peak TR velocity ( $>2.8$  m/s) can be used as an indicator of LV filling pressures. The accuracy of LARS in this setting has not been examined.

## E. Restrictive Cardiomyopathy

Restrictive cardiomyopathies are composed of a heterogeneous group of heart muscle diseases including but not limited to such diseases as idiopathic restrictive cardiomyopathy, cardiac amyloidosis, and sarcoidosis. These diseases are often characterized by restrictive pathophysiology, which is defined as a rapid rise in diastolic ventricular pressure with only a small increase in LV volume due to increased myocardial stiffness.<sup>71</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 hypertrophic cardiomyopathy (HCM), and restrictive cardiomyopathy.

A common restrictive cardiomyopathy is cardiac amyloidosis, an infiltrative cardiomyopathy most commonly caused by either immunoglobulin light chain deposition or by misfolding in the hepatic-derived transthyretin (TTR) protein into amyloid fibrils. 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 with markedly elevated LV filling pressures.<sup>46</sup> In contemporary diagnostic approaches, there has been an evolution of the diastolic function techniques applied in studying these patients, initially using mitral inflow and pulmonary vein flow, to TDI of the mitral annulus and now STE imaging, including LV GLS, LA strain, and RV strain.<sup>47</sup> 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  $E/A > 2.5$ , deceleration time of E velocity  $< 150$  ms, IVRT  $< 50$  ms, decreased septal and lateral  $e'$  velocities (3-4 cm/s), decreased GLS with preserved radial and circumferential strain,<sup>72</sup> and reduced LA strain.<sup>47</sup> In advanced cardiac amyloidosis, mitral annular velocity tracings may show the "5-5-5" sign with systolic, early diastolic, and late diastolic velocities all  $< 5$  cm/s.<sup>47</sup> Grade 3 diastolic dysfunction is associated with a poor outcome.<sup>73</sup> For cardiac amyloidosis (TTR or light chain type), there are "red flags" suggestive of cardiac involvement, such as increased LV and RV wall thickness, batrial enlargement, preserved EF with low stroke volume index, an association with paradoxical low-flow, low-gradient AS, and diastolic dysfunction ( $E/A$  ratio  $> 2$  with increased filling pressures and markedly reduced annular velocities.<sup>22</sup> In addition, speckle-tracking of the LV myocardium in patients with cardiac amyloidosis has shown a distinctive phenotype of apical sparing using a polar plot of LV longitudinal strain compared with hypertensive heart disease, HCM, and AS.<sup>74</sup> There have been several ratios to evaluate apical sparing, including a ratio of apical strain to mid and basal strain ( $>1$ ),<sup>74</sup> the septal apical-to-basal ratio using the four-chamber septal apical and basal segmental longitudinal strain values with a value  $>2.1$ ,<sup>75</sup> as well as EF/strain ratio  $>4.1$ .<sup>76</sup>

## F. Pericardial Constriction

Pericardial constriction is characterized by dissociation of intrathoracic and intracardiac pressures as well as interventricular dependence due to the effect of the constricting pericardium on the LV and the RV. This results in respirophasic shift of the ventricular septum, septal bounce, mitral and tricuspid inflow variation with respiration ( $>25\%$  and 40%, respectively), and expiratory reversal of end-diastolic flow within the hepatic veins (end-diastolic reversal velocity/forward flow velocity  $\geq 0.8$ ).<sup>77,78</sup> In addition, mitral septal  $e'$  velocity is often  $>7$  cm/s, whereas it is usually  $\leq 5$  cm/s in restrictive cardiomyopathy. Tethering of the LV lateral and RV free walls contributes to the constrictive physiology and is demonstrated by an increased ratio of mitral septal to lateral  $e'$  (annulus reversal).<sup>79</sup> Similarly, the lateral LV and RV free wall peak systolic strain is diminished compared with the septal peak systolic strain (strain reversal).<sup>80</sup> Figure 7 shows a validated algorithm based on data from the Mayo Clinic comparing pericardial constriction with restrictive cardiomyopathy.<sup>78,81</sup> This algorithm was corroborated in a similar study.<sup>82</sup> The presence of a normal septal (or medial) annular  $e'$  velocity in a patient referred with HF diagnosis should raise suspicion of pericardial constriction.

## Key Points

1. Patients with early disease restrictive cardiomyopathy usually have grade 1 diastolic dysfunction that progresses to grade 2 and grade 3 as the severity of the disease increases.
2. In patients with advanced disease, grade 3 diastolic dysfunction is present and is characterized by mitral inflow  $E/A > 2.5$ , deceleration time of E velocity  $< 150$  ms, IVRT  $< 50$  ms, and decreased septal and lateral  $e'$  velocities (3-4 cm/s), as well as decreased LV GLS, RV strain, and LA reservoir and pump strain.
3. Strain imaging of the LV myocardium in patients with cardiac amyloidosis can have a distinctive phenotype of apical sparing.

4. Patients with pericardial constriction usually have respirophasic shift of the interventricular septum, septal bounce, mitral and tricuspid inflow variation with respiration (>25% and 40%, respectively), normal to increased medial annular early diastolic velocity (>7 cm/s), increased expiratory reversal of end-diastolic flow within the hepatic veins (end-diastolic reversal velocity/forward flow velocity  $\geq 0.8$ ), as well as annulus and strain reversus.

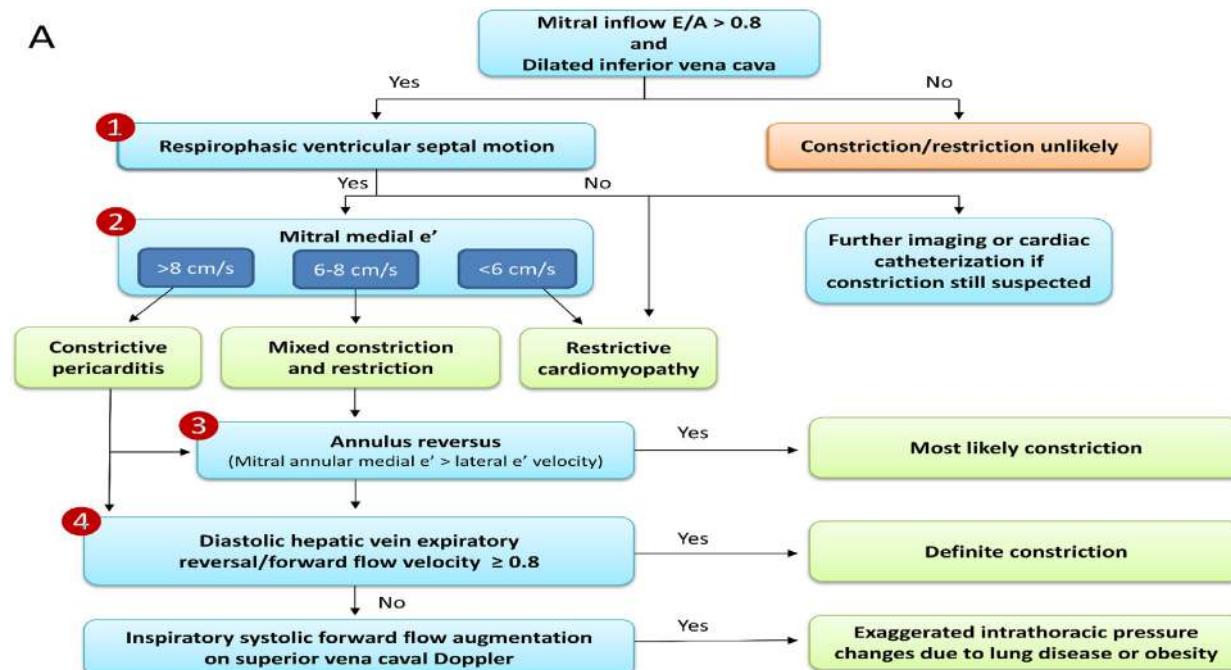
## G. HCM

Impaired LV relaxation is an early finding in subjects carrying pathogenic mutations for HCM that occurs before the development of LV hypertrophy.<sup>45</sup> Furthermore, diastolic dysfunction is a ubiquitous finding in HCM patients irrespective of the hypertrophy pattern and contributes to their symptoms even in the absence of dynamic obstruction.<sup>45</sup> The Doppler variables that are recommended are mitral inflow velocities, pulmonary vein velocities, mitral annular velocities, peak TR velocity by CW Doppler, and biplane LA volumes. Significant MR can lead to elevated LAP, LA volumes, and peak TR velocity with a decrease in the pulmonary vein systolic to diastolic

velocity ratio. However, MR does not affect pulmonary vein Ar velocity. Ar peak velocity and duration can be used to draw inferences about LVEDP in the absence of atrial myopathy and first-degree AV block.<sup>45,53</sup> In addition, LA reservoir and pump strains in patients with HCM have been associated with functional capacity and development of atrial fibrillation, though there is need to study their specific application for LAP estimation. A restrictive LV filling pattern with increased E/e' is associated with HF hospitalizations, reduced exercise tolerance in children and adults, and sudden cardiac death.<sup>45</sup>

## Key Points

1. A comprehensive approach is recommended for the evaluation of diastolic function in patients with HCM.
2. The Doppler variables that are recommended are mitral inflow velocities, pulmonary vein velocities, mitral annular velocities, peak TR velocity by CW Doppler, and biplane LA volumes.
3. Restrictive LV filling with increased E/e' is associated with reduced functional capacity and HF hospitalizations in patients with HCM.



**B**

	Sensitivity	Specificity	PPV	NPV
1	94%	73%	93%	77%
2	81%	91%	97%	58%
3	71%	79%	93%	45%
4	73%	66%	86%	42%
1 and 2	80%	96%	99%	58%
1 with both 2 and 4	67%	99%	100%	50%

**Figure 7** (A) Algorithm for differentiation of pericardial constriction from restrictive cardiomyopathy. (B) Sensitivity, specificity and predictive values of the algorithm. Reprinted with permission from Klein et al.<sup>78</sup> NPV, Negative predictive value; PPV, positive predictive value.

## H. Atrial Fibrillation

Atrial fibrillation is a common finding in patients with diastolic dysfunction and HFpEF. Atrial fibrillation poses several challenges due to tachycardia in some cases, the absence of organized atrial contraction, the variability in cycle length, and the frequent presence of LA enlargement. Several echocardiographic parameters have been suggested as markers of LV filling pressure in patients with atrial fibrillation and smaller single-center studies have shown promising results.<sup>40,41,83</sup> In a recent multicenter study, it was found that no single echocardiographic parameter had sufficiently strong association with LV filling pressure to be recommended as a stand-alone marker. When using a multiparametric approach, the accuracy in differentiating between normal and elevated LV filling pressure was moderate (Figure 8).<sup>42</sup>

When assessing LV filling pressure in atrial fibrillation, one should use average values from several cardiac cycles, and the selected heart cycles should be reflective of the average heart rate.<sup>40</sup> For E/e' and ratios that rely on timing of mitral E onset and e' velocity onset, the use of a dual Doppler probe can enable the recording of both velocities from the same cardiac cycle, with a much higher accuracy for estimation of PCWP than averaging velocities or time intervals from several cardiac cycles.<sup>84,85</sup> Looking at variability of mitral inflow with varying cycle length is a practical method to determine whether LV filling pressure is elevated. This necessitates recording several cardiac cycles with a sweep speed of 50 mm/s. Patients with less beat-to-beat mitral inflow variability usually have elevated LV filling pressure.<sup>40</sup>

## Key Points

1. In patients with atrial fibrillation, several echocardiographic parameters are associated with LAP, but no single parameter has a strong association.
2. A decision algorithm that combines multiple echocardiographic parameters can differentiate between normal and elevated LV filling pressure with moderate accuracy.
3. One should use average values from several cardiac cycles and the selected heart cycles should be reflective of the average heart rate.

## 16. HFpEF DIAGNOSIS

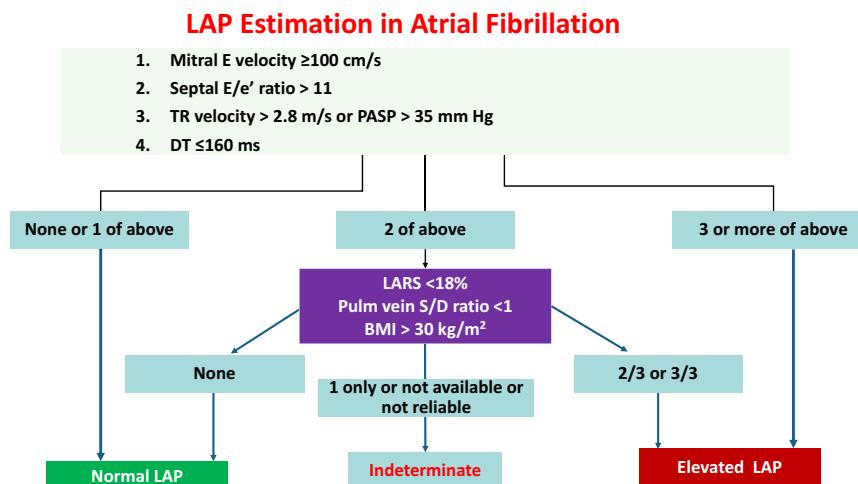
HFpEF constitutes half of all HF hospitalizations, with a growing prevalence relative to HF with reduced EF.<sup>86-88</sup> This is multifactorial because of an aging population with an increasing burden of comorbidities such as hypertension, diabetes, obesity—predominantly metabolic syndrome—associated comorbidities—that contribute to the development of HFpEF.<sup>89</sup> The guidelines present a stepwise guide to the diagnosis of HFpEF, including clinical diagnosis, and guide for noninvasive and invasive testing (Figure 9).

### A. Clinical Diagnosis of HFpEF

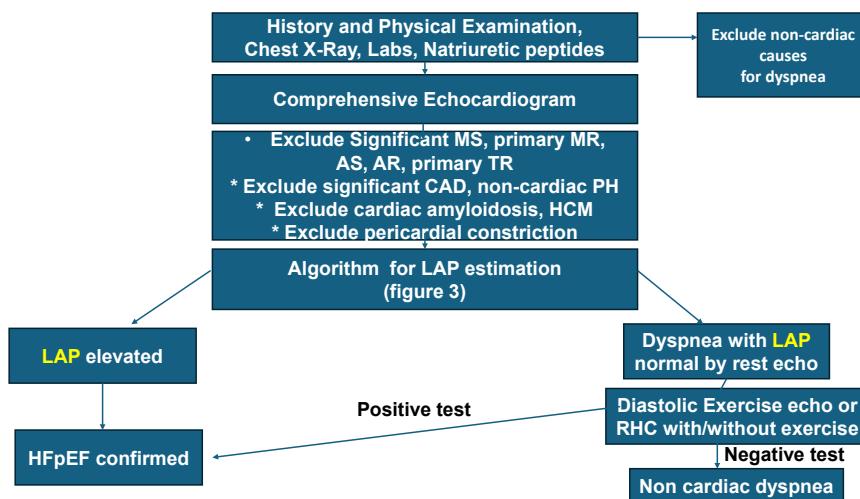
The clinical diagnosis of HFpEF is reached by establishing the presence of signs and symptoms of congestive HF as well as an echocardiographic determination of normal LVEF (generally accepted to be  $\geq 50\%$ ) in the absence of other cardiac or noncardiac causes for the patient's symptoms. The American College of Cardiology/American Heart Association/Heart Failure Society of America and European Society of Cardiology (ESC) each provide definitions of HFpEF and suggested diagnostic evaluation<sup>22,90-92</sup> (Table 8).

The recognition of the clinical HF syndrome is the first step in diagnosing HFpEF. Several criteria have been proposed to diagnose HF including the Framingham, Boston, Gothenburg, and ESC criteria.<sup>93-95</sup> The Framingham criteria are among the most widely accepted criteria for diagnosis of HF in epidemiologic studies. Although the Framingham criteria demonstrate excellent specificity for the diagnosis of HF, they lack sensitivity, particularly in elderly patients who may have not had acute HF decompensation.<sup>96,97</sup> Therefore, a patient may have HFpEF even in the absence of satisfying specific clinical criteria for HF.

Early presenting symptoms of HFpEF may be relatively nonspecific, including exertional dyspnea, exercise intolerance, or fatigue. Clinical suspicion should be further raised if a patient presenting with these symptoms has one or more risk factors commonly associated with HFpEF. The most commonly associated comorbidities with HFpEF that may raise pretest probability of the diagnosis include the history of hypertension, elderly age ( $>60$  years), obesity (body mass index  $> 30 \text{ kg/m}^2$ ), history of diabetes mellitus, or history of atrial fibrillation.<sup>8,98</sup>



**Figure 8** Algorithm for estimation of mean LAP with atrial fibrillation. *BMI*, Body mass index; *Pulm*, pulmonary.



**Figure 9** Algorithm for HFrEF diagnosis. \*Multimodality imaging and cardiac catheterization should be used as needed to establish the presence of alternative diagnoses to HFrEF. CAD, Coronary artery disease; MS, mitral stenosis; RHC, right heart catheterization.

Physical examination may demonstrate signs of congestion, including elevated jugular venous pressure, presence of an S3 gallop, pulmonary crackles or rales, hepatomegaly, ascites, or lower extremity edema. Electrocardiography should be performed in all patients with suspected HFrEF. Although there are no pathognomonic or diagnostic signs to identify HFrEF on electrocardiography per se, patients may have features of LV hypertrophy or LA enlargement. Furthermore, electrocardiographic evaluation can screen for atrial

fibrillation, which may be occult in HFrEF and is prevalent in 15% to 41% of patients.<sup>99,100</sup> Last, chest radiography should be performed in the evaluation of HFrEF, particularly in patients presenting with dyspnea. Chest radiography may show signs of volume overload (Kerley B-lines, pleural effusion, pulmonary congestion) or reveal other noncardiac causes of dyspnea. Radiographic findings appear to have low sensitivity in detecting patients with HFrEF compared with PCWP measurements by cardiac catheterization.<sup>101</sup>

**Table 8** Consensus definitions of HFrEF

	ACC/AHA/HFSA	ESC
Definition of HFrEF	EF $\geq$ 50% and: <ul style="list-style-type: none"> <li>Clinical symptoms and/or signs of HF and</li> <li>Diastolic dysfunction</li> </ul>	EF $\geq$ 50% and: <ul style="list-style-type: none"> <li>Clinical symptoms and/or signs of HF and</li> <li>Elevated NP levels and at least one of the following:               <ul style="list-style-type: none"> <li>Relevant structural heart disease (LVH and/or LAE)</li> <li>Diastolic dysfunction</li> </ul> </li> </ul>
Clinical signs	<ul style="list-style-type: none"> <li>Obtain detailed history and physical examination</li> <li>Assess volume status and vital signs to determine evidence of congestion</li> </ul>	<ul style="list-style-type: none"> <li>Obtain detailed history and physical</li> <li>Assess symptoms and signs of HF for evidence of congestion</li> </ul>
NPs	<ul style="list-style-type: none"> <li>Can guide the diagnosis of HF, especially in the setting of clinical uncertainty</li> </ul>	<ul style="list-style-type: none"> <li>Can guide the diagnosis or exclusion of HF</li> <li>Normal levels exclude HF</li> </ul>
Echocardiography	<ul style="list-style-type: none"> <li>EF measurement and assessment of valvular or myocardial abnormalities</li> <li>Evidence of LV diastolic dysfunction may be considered to define the syndrome of HFrEF</li> </ul>	<ul style="list-style-type: none"> <li>Evaluate for evidence of functional or structural abnormalities</li> <li>Key structural abnormalities:               <ul style="list-style-type: none"> <li>LAVi <math>&gt; 34 \text{ mL/m}^2</math></li> <li>LVMI <math>\geq 115 \text{ g/m}^2</math> for men and <math>\geq 95 \text{ g/m}^2</math> for women</li> </ul> </li> <li>Key functional abnormalities:               <ul style="list-style-type: none"> <li>E/e' <math>\geq 13</math></li> <li>Mean e' (mean of septal and lateral e') <math>&lt; 9 \text{ cm/s}</math></li> </ul> </li> </ul>
Invasive testing	<ul style="list-style-type: none"> <li>RHC if refractory to initial therapy or if a specific clinical question needs to be addressed</li> <li>LHC is recommended if HF and angina present</li> </ul>	<ul style="list-style-type: none"> <li>RHC at rest followed by exercise hemodynamics if below the threshold of PCWP 15 mm Hg, may be considered in cases of clinical uncertainty</li> </ul>

ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; LAE, LA enlargement; LHC, left heart catheterization; LVH, LV hypertrophy; LVMI, LV mass index; RHC, right heart catheterization.

**Table 9** Differential diagnosis of HFrEF

Cardiac, myocardial
Restrictive cardiomyopathy
Cardiac amyloidosis
Endomyocardial fibrosis
Systemic sclerosis
Radiation fibrosis
Hemochromatosis
Fabry disease
Glycogen storage disease
Metastatic cancer
HCM
Arrhythmogenic RV cardiomyopathy
Myocardial ischemia
HF with recovered EF
Pulmonary arterial hypertension
Cardiac, nonmyocardial
Valvular heart disease (>mild stenosis or $\geq$ moderate regurgitation)
Pericardial disease
Constrictive or effusive constrictive pericarditis
Cardiac tamponade
High-output HF
Noncardiac
Pulmonary disease
Anemia
Venous insufficiency

## B. Echocardiographic Imaging

Once the clinical diagnosis of HFrEF is suspected in the appropriate clinical setting, physical examination findings, and/or the presence of risk factors, the next step in the diagnostic evaluation of HFrEF should be imaging. Echocardiography is the most common initial imaging modality in the evaluation of HFrEF, providing information on structural changes and hemodynamic parameters that may support a diagnosis of HFrEF, while also useful for the evaluation of other cardiac causes of dyspnea, such as valvular disease, infiltrative cardiomyopathy, or pericardial disease. Though different EF cutoff points have been proposed for the diagnosis of HFrEF, an LVEF of  $\geq$ 50% is accepted as normal or preserved and is consistent with a diagnosis of HFrEF.<sup>8</sup>

Patients with HFrEF often have morphologic and functional abnormalities on the echocardiogram (e.g., LV hypertrophy, concentric remodeling, LA enlargement, diastolic dysfunction, reduced LV GLS, reduced LARS), though by themselves these findings are not diagnostic of HFrEF. Diastolic function is assessed as recommended in the previous sections (see algorithms in Figures 2 and 3). A comprehensive echocardiographic examination with measurement of these parameters should be performed in the initial diagnostic evaluation of a patient with suspected HFrEF. If the resting echocardiogram shows increased LV filling pressure (grade 2 or 3 diastolic dysfunction), the diagnosis of HFrEF is confirmed in the appropriate clinical setting. However, if only diastolic function grade 1 is present at rest in a patient with exertional dyspnea, diastolic exercise echocardiography or cardiac catheterization should be performed (see the following discussion). For patients in atrial fibrillation, the specific recommenda-

tions for estimation of LV filling pressures for these groups should be followed.

Although echocardiography remains at the cornerstone of HF evaluation, CMR is a robust imaging modality to characterize myocardial tissue abnormalities.<sup>15</sup> CMR can be considered in the workup of patients with HFrEF, particularly if echocardiographic imaging quality is suboptimal or if there are concerns for an infiltrative myopathic process such as amyloidosis.

## C. Natriuretic Peptides

Levels of natriuretic peptides (NPs), including brain NP and N-terminal pro-B-type NP, should be checked in patients presenting with suspected HFrEF or undifferentiated dyspnea.<sup>102</sup> NP levels are generally higher in patients with HFrEF compared with subjects without HF and have useful prognostic implications.<sup>102</sup> Of note, NP levels are known to be lower in patients with HFrEF compared with those with HF with reduced EF, and obesity, a common comorbidity associated with HFrEF, is well known to be associated with lower NP levels.<sup>103</sup> Prior studies have indicated that up to 30% of patients with HFrEF can have normal NP levels despite signs and symptoms of HF, echocardiographic abnormalities, and elevated LV filling pressures on invasive hemodynamic testing.<sup>104</sup> Therefore, although important in the evaluation of HFrEF, a normal NP level does not necessarily rule out a diagnosis of HFrEF, particularly in obese patients with HFrEF.

## D. Role of HFrEF Prediction Scores

For patients with an uncertain probability of HFrEF, a few scoring systems have been developed to aid in predicting the likelihood of the disease. Reddy *et al*<sup>98</sup> developed the H<sub>2</sub>FPEF score by retrospectively comparing clinical findings in 414 patients referred for evaluation of unexplained dyspnea who underwent invasive hemodynamic exercise testing. The H<sub>2</sub>FPEF score is a weighted score ranging from 0 to 9 and based on six clinical variables: heavy (body mass index  $>30 \text{ kg/m}^2$ , 2 points), hypertensive (two or more antihypertensive medications, 1 point), atrial fibrillation (paroxysmal or persistent, 3 points), PH (Doppler echocardiographic estimated PASP  $> 35 \text{ mm Hg}$ , 1 point), elder (age  $> 60$  years, 1 point), and filling pressure (septal E/e'  $> 9$ , 1 point). A score of 0 to 2 is indicates a low probability of HFrEF. An intermediate score of 2 to 5 is correlated with a 40% to 80% likelihood of HFrEF, whereas a score  $>5$  indicates high HFrEF probability. Although the H<sub>2</sub>FPEF score was formulated on the basis of a relatively small referral population, it has been validated in a test cohort and showed good discrimination of HFrEF from noncardiac dyspnea.<sup>98</sup> Additionally, the clinical variables are commonly assessed for, allowing wide applicability in various clinical settings.

The Heart Failure Association of the ESC also recently published a consensus recommendation for the diagnosis of HFrEF, the HFA-PEFF diagnostic algorithm.<sup>8</sup> The HFA-PEFF algorithm is a stepwise approach to the diagnosis of HFrEF meant to be performed in the ambulatory setting. It begins with a pretest probability assessment (signs and symptoms of HF, presence of comorbidities or risk factors, electrocardiography, echocardiography, NP levels, and functional testing such as the 6-minute walk test or cardiopulmonary exercise testing). If pretest assessment is overall suggestive of a HFrEF diagnosis, further testing, including comprehensive echocardiography and NP levels, are used to tabulate a likelihood score. If a diagnosis of HFrEF is intermediate, noninvasive or invasive exercise stress

testing is recommended for further evaluation. The HFA-PEFF diagnostic algorithm highlights the importance of a combination of abnormal structural and functional echocardiographic parameters in the diagnosis of HFpEF. Although NP levels are incorporated in this algorithm, a diagnosis of HFpEF does not rely only on elevated NP levels.

These scores may be used in the initial evaluation of patients with possible HFpEF but confirmation of elevated LV filling pressures (noninvasive estimation or invasive measurement) is needed. In borderline cases with either approach, exercise stress testing should be pursued to determine if mean PCWP is abnormally increased with exercise ( $\geq 25$  mm Hg).

## E. Alternative Diagnoses

Certain cardiac and noncardiac conditions that mimic HFpEF should be ruled out (Table 9). The prevalence of TTR cardiac amyloidosis in HFpEF is estimated to be 5% to 13%; though this is based on limited data from autopsy studies and nuclear scan-based screening of patients with HFpEF.<sup>105,106</sup> In the only prospective study using endomyocardial biopsy in the evaluation of HFpEF, 14% of patients were found to have cardiac amyloidosis, the majority being TTR cardiac amyloidosis.<sup>107</sup>

## F. Exercise and Invasive Hemodynamic Testing

Although many patients with HFpEF present with clear HF syndrome and echocardiographic findings consistent with HFpEF, some present with little more than dyspnea on exertion and fatigue. These patients often require additional testing to further evaluate for a diagnosis of HFpEF. Exercise stress echocardiography, typically performed with supine bicycle or treadmill exercise, is the primary modality of noninvasive stress testing to evaluate for occult HFpEF. Compared with invasive hemodynamic testing, exercise echocardiography is less expensive, with less risk, and may be more accessible. Additionally, exercise stress testing may be useful to assess for concomitant obstructive coronary artery disease.

Right heart catheterization is considered the gold-standard test to establish the diagnosis of HFpEF, during which exercise hemodynamics can often be obtained. PCWP  $> 15$  mm Hg at rest, or  $\geq 25$  mm Hg with exercise, measured at end-expiration, is consistent with the diagnosis of HFpEF.<sup>108,109</sup> The use of exercise invasive hemodynamics has been shown to significantly increase the diagnostic yield of HFpEF, particularly for patients presenting at an earlier stage of the disease.<sup>108</sup> In patients who are unable to exercise, saline loading during right heart catheterization can be considered as an alternative diagnostic modality but has been shown to be less sensitive compared with exercise in the diagnosis of HFpEF.<sup>110</sup>

## G. Research Needs

A novel method for prediction of LV diastolic pressures using ultrasound enhancing agent microbubbles and subharmonic-aided pressure estimation has been reported in a single-center study.<sup>111</sup> High-frame rate echocardiography was used to measure shear wave elastography to gain insight into myocardial stiffness.<sup>112</sup> The clinical feasibility, accuracy, and incremental value of these new techniques await evaluation in multicenter studies. There are several AI models for the assessment of LV diastolic function. Validation of these and future models using invasive hemodynamics and clinical outcomes in multicenter studies is needed to establish their accuracy and clinical relevance. For HFpEF diagnosis, the existing approaches relying on

scores have a high yield of an indeterminate category where stress testing or right heart catheterization is needed. The utility of comprehensive echocardiography (at rest) in the indeterminate category using LA strain, LA stiffness, pulmonary vein flow, IVRT and PA diastolic pressure should be evaluated. If successful, it can decrease the need for additional testing.

## Key Points

1. Clinical data, radiographic findings, and NP levels should be considered in trying to determine whether there is a cardiac cause for dyspnea.
2. The next step is a comprehensive echocardiographic examination that includes the acquisition and measurement of LV GLS and LARS.
3. Before reaching a diagnosis of HFpEF, valvular heart disease, noncardiac PH, significant coronary artery disease, infiltrative and HCM, and pericardial constriction should be excluded.
4. Apply the algorithm for the estimation mean LAP shown in Figure 3. If LAP is elevated at rest in symptomatic patients, HFpEF diagnosis is reached.
5. If LAP at rest is normal in a symptomatic patient, the next step is diastolic exercise stress echocardiography. If positive, HFpEF diagnosis is reached. If negative, then noncardiac cause of dyspnea is present. If the test is inconclusive, then the next step should be right heart catheterization.

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## REVIEWERS

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## SUPPLEMENTARY DATA

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