Pathophysiology and Echocardiographic Diagnosis of Left Ventricular Diastolic Dysfunction



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Echocardiography is the primary imaging modality used for the clinical evaluation of left ventricular (LV) diastolic function. Using two-dimensional together with transmitral, mitral annular, and pulmonary venous Doppler data, conclusions may be drawn regarding the relaxation and compliance properties of the ventricle that can be used for estimating LV filling pressure. Echocardiographic estimation of LV filling pressure has been shown to be especially useful for evaluating patients with dyspnea of unknown etiology as well as those with heart failure with preserved ejection fraction. Moreover, echocardiographic estimation of LV filling pressure can be used for clinical decision making on day-to-day basis. This article discusses the pathophysiology of diastolic dysfunction and provides a comprehensive review of its echocardiographic evaluation. (J Am Soc Echocardiogr 2019;32:216-32.)

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Evaluation of left ventricular (LV) diastolic function has become a routine component of the standard echocardiographic examination. Using data obtained from two-dimensional and Doppler imaging, conclusions may be drawn regarding the relaxation and compliance properties of the ventricle that can be used for estimating LV filling pressures (LVFPs). Echocardiographic estimation of LVFP has proved especially useful in evaluating patients with dyspnea of unknown etiology¹ as well as those with heart failure with preserved ejection fraction (HFpEF).² Moreover, it has become increasingly accepted that echocardiographically based estimates of LVFP can be used for clinical decision making on a day-to-day basis. This article discusses the pathophysiology of diastolic dysfunction and provides a comprehensive review of its echocardiographic evaluation.

DIASTOLIC DYSFUNCTION AND LVFP

LV filling during diastole ensures delivery of a normal stroke volume through the Starling mechanism. However, when LV filling is accompanied by an abnormal rise in LVFP, diastolic heart failure results. It is important to note that the term "LVFP" fails to distinguish LV enddiastolic pressure (LVEDP) from mean left atrial pressure (LAP; Figure 1), although there are important pathophysiologic differences between them. Mean LAP may be regarded as the downstream pres-

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Copyright 2018 by the American Society of Echocardiography. https://doi.org/10.1016/j.echo.2018.11.011 sure "seen" by the pulmonary circulation throughout all of diastole, which when elevated results in pulmonary venous (PV) hypertension, pulmonary vascular congestion, and dyspnea. In contrast, an isolated increase in LVEDP (with normal mean LAP) does not increase PV pressure. The echocardiographic representations of increased mean LAP and LVEDP differ accordingly, as is discussed below.

PHYSIOLOGY OF LV DIASTOLE

LV diastole is conventionally divided into four periods: the isovolumic relaxation period, the rapid filling period (RFP), diastasis, and atrial systole.

Isovolumic Relaxation Period

The isovolumic relaxation period extends from aortic valve closure to mitral valve opening, during which LV pressure, but not volume, decreases. However, it is worth noting that LV pressure actually starts falling during the systolic ejection period, well before aortic valve closure, and normally reaches its nadir, LV minimal pressure (LVmin), during the RFP (Figure 2).

Several studies have used a monoexponential decay assumption to compute τ , the time constant of relaxation (Figure 3). Tau is the time it takes for LV pressure, measured at the peak rate of LV pressure decay (just after aortic valve closure), to decrease by approximately one third.³ In the normal heart, τ lasts approximately 30 to 40 msec, and LV relaxation is nearly complete by $3.5 \times \tau$, during the RFP. However, when LV relaxation is impaired, τ lengthens, and complete relaxation may not be achieved until later in diastole. In extreme cases, relaxation may remain incomplete at end-diastole, a state known as contracture.³

Rapid Filling Period

The phase of rapid LV filling begins at mitral valve opening (Figure 2). Filling during this period is thought to be mediated by

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Abbreviations

A dur = Duration of the mitral A wave

AF = Atrial fibrillation

A_R dur = Duration of PV A-wave flow reversal

 $A_R - A dur = Difference$ between A_R dur and A dur

CAD = Coronary artery disease

DT = Deceleration time

 ϵ_{IVR} = Global longitudinal strain rate measured during isovolumic relaxation

GLS = Global longitudinal strain

HCM = Hypertrophic cardiomyopathy

HFpEF = Heart failure with preserved ejection fraction

IVRT = Isovolumic relaxation time

LA = Left atrial

LAP = Left atrial pressure

LV = Left ventricular

LVEDP = Left ventricular end-diastolic pressure

LVEF = Left ventricular ejection fraction

LVFP = Left ventricular filling pressure

LVmin = LV minimal pressure

MAC = Mitral annular calcification

MR = Mitral regurgitation

PCWP = Pulmonary capillary wedge pressure

P-V = Pressure-volume

PV = Pulmonary venous

PW = Pulsed-wave

RFP = Rapid filling period

SERCA = Sarcoplasmic/ endoplasmic reticulum Ca⁺⁺ adenosine triphosphatase

T_E-e' = Time offset between mitral E-wave and annular e'

TR = Tricuspid regurgitation

three physiologic processes: active relaxation, elastic recoil, and ventricular lengthening. Active relaxation is brought about by resequestration of Ca⁺⁺ ions in the sarcoplasmic reticulum through the action of the sarcoplasmic/endoplasmic reticulum Ca++ adenosine triphosphatase (SERCA) pump.⁴ Elastic recoil results from the restorative force that is produced when potential energy stored in compressible LV elements (e.g., collagen, titin) in systole is released during diastole.^{5,6} The smaller the LV end-systolic volume, the more robust the elastic recoil. It has been suggested that elastic recoil facilitates ventricular untwisting filling by the myocardium, which, in turn, creates an intraventricular gradient along the long axis of the left ventricle that accelerates blood toward the apex (suction).⁷ The last physiologic process thought to facilitate rapid filling is ventricular lengthening. As actin-myosin crosslinks become uncoupled during the RFP, LV muscle fibers become increasingly responsive to the so-called lengthening load imparted by LAP such that they "stretch," causing the left ventricle to enlarge, thereby facilitating ventricular filling.8

It is convenient to consider the RFP in two parts: an earlier part when LV pressure falls to LVmin ("descending limb") and a later part, during which LV pressure returns to left atrial (LA) levels ("ascending limb"; Figure 2, insert). In the normal ventricle, filling during the descending limb is largely facilitated by suction (an increase in LV volume as pressure decreases).⁹ Filling during the ascending limb, however, comes at the expense of a rise in LV pressure and is influenced largely by ventricular compliance.¹⁰ Hence, when compliance is reduced, there is a more rapid (steeper) climb in LV pressure, resulting in earlier mitral valve closure and a shortened RFP (Figure 2, *insert*). However, it is important to emphasize that LV compliance influences filling not just during the RFP but throughout diastole.

Diastasis

The period from the end of the RFP until the onset of atrial systole is called diastasis (Figure 2). During this period, LA and LV pressures are in near equilibrium, so little ventricular filling takes place. Diastasis shortens as heart rate increases, usually disappearing at 90 to 100 beats/min.

Atrial Systole

The task of achieving an adequate LV preload (LV end-diastolic volume) beyond that provided by rapid filling falls to the left atrium. In young, healthy individuals in whom there is robust LV suction, only 20% of the end-diastolic volume is contributed by atrial contraction (Figure 2). With increasing age, however, perturbations of LV relaxation and compliance leave an increased residuum of blood in the atrium at the end of the RFP. This blood is ejected into the left ventricle by virtue of the Starling mechanism and accounts for the ability of older individuals to contribute as much as 40% of LV enddiastolic volume during atrial systole.¹¹

TRANSMITRAL FLOW DOPPLER

Transmitral Doppler imaging was the first method applied in the echocardiographic study of diastolic function. Transmitral flow can be interrogated using pulsed-wave (PW) Doppler. This is accomplished by placing the sample volume between the tips of the open mitral leaflets in the four-chamber view with alignment the cursor (line of insonation) with the color Doppler LV inflow signal to avoid underestimation of transmitral velocities.¹²

Normal transmitral PW Doppler waveforms are shown in Figure 4. Transmitral E and A waves reflect flow during the RFP and atrial systole, respectively. In young, healthy individuals in whom most of LV filling occurs during the RFP, the peak velocity of the E wave exceeds that of the A wave. The deceleration time (DT), the time required for the peak E-wave velocity to cross the baseline, represents the time it takes for the maximal LA-LV pressure gradient to dissipate such that flow comes to a halt. Normal E-wave DT is 160 to 200 msec, but this increases with age.¹⁰

Delayed Relaxation Filling Pattern (Grade 1)

A delayed relaxation filling pattern is commonly seen after the age of 60 years.¹³ This filling pattern is characterized by prolongation of the E-wave DT (>200 msec), a reflection of slow and prolonged LV pressure decay that achieves only a modest decline in LVmin (Figure 5). As a result, the gradient between the left atrium and the left ventricle narrows, reflected by a low peak E-wave velocity. The small transmitral gradient associated with delayed relaxation limits early diastolic filling resulting in a residuum in the atrium, which is subsequently ejected into the left ventricle during atrial systole. This increases peak A-wave velocity, a measure of LA stroke volume. The combined effects of a decreased E wave and an increased A wave usually results in reversal of the normal E/A ratio, such that E < A (Figure 4).

HIGHLIGHTS

- LV relaxation and compliance properties can be inferred using echo-Doppler imaging.
- Annular e' velocity reflects active relaxation, elastic recoil and lengthening load.
- Increased E/e', LA volume index and TR velocity suggest mean LAP is increased.
- Echo-based predictions of LVFP can be used in day-to-day clinical decision making.
- Novel LA and LV deformation indices predict LVFP and have prognostic significance.

Delayed relaxation is usually associated with normal LVFP. Sometimes, the alphanumeric designation 1 a filling is used to indicate this. In some patients, however, LVEDP may be elevated, in which case the designation grade 1b filling is sometimes used.¹⁴ The increased LVEDP seen with grade 1b filling results from superimposition of reduced compliance on a slowly relaxing left ventricle. Importantly, the reduction in compliance is mild enough that it does not manifest during the RFP, because the ventricle is still relatively underfilled and therefore operates on the flat portion of its pressure-volume (P-V) curve (Figure 6). However, the large increase in LV volume that occurs during atrial systole shifts the P-V relation of the left ventricle upward onto a steeper portion of its P-V curve such that its operational compliance decreases and LVEDP rises.^{10,15} It is important to appreciate that the increase in LVEDP that occurs with the transition from 1a to 1b filling represents the earliest hemodynamic abnormality in the "natural history" of diastolic dysfunction.¹⁴

The steep rise in LV pressure that attends the reduced compliance seen in patients with 1b filling (Figure 7)¹⁵ truncates atrial systole and therefore shortens the duration of the mitral A wave (A dur). Of note, it is preferable to measure A dur at the mitral annulus, rather than between the mitral leaflet tips, so that confounding low-velocity signals at end-diastole are not incorporated into its measurement. As is shown in Figure 7, shortening of A dur is primarily the result of a decrease in A-wave DT. In this respect, it is worth noting that an A-wave DT \leq 60 msec predicts an LVEDP > 18 mm Hg.¹⁶ Last, it is important to appreciate that the left atrium does not usually enlarge in patients with type 1 filling patterns, as the compensatory increase in atrial contractility seen with these filling patterns can readily compensate for the increased LA load.

Pseudonormal Filling Pattern (Grade 2)

Progression from type 1b to type 2 filling (pseudonormalization) is characterized by a rise in mean LAP and largely represents the effects of a further reduction in LV compliance.¹⁰ In contrast to type 1b filling, in which LV operational compliance does not decrease until late diastole, the decrease in operational compliance in type 2 filling occurs in early diastole (at lower LV volume). This causes a steep rise of the ascending limb of the RFP pressure curve (Figure 1, *insert*) which truncates rapid filling. This is reflected by a shortening of the E-wave DT (Figure 4). Such shortening masks

the presence of the manifest relaxation abnormality on the transmitral Doppler tracing.

The reduction in early diastolic LV filling seen with grade 2 filling results in an atrial residuum, which increases LAP. This causes an increase in peak mitral E-wave velocity. Concomitant increase in LVEDP produces shortening of A dur. Finally, the increased load imposed on the left atrium as a result of a poorly compliant left ventricle may, over time, lead to decreased atrial contractile reserve, LA enlargement, and a decrease in peak A-wave velocity (reduced LA stroke volume).¹⁵ The combined effects of a rise in E-wave velocity and a decrease in A-wave velocity result in an E/A ratio that is usually >1 (pseudonormalization; Figure 4).

Restrictive Filling Pattern (Grade 3)

The transition from pseudonormal to restrictive filling is characterized by a further decrease in LV compliance, an additional increase in mean LAP, and the intercession of atrial failure.¹⁵ Worsening compliance causes additional shortening of mitral E-wave DT (to <160 msec). It should, however, be noted that patients with significantly increased E-wave velocity (>1.2 m/sec) may fail to demonstrate DT shortening, because of the increased time required for a higher E velocity to decelerate. Continued rise in LAP further increases the peak E-wave velocity, and increased LVEDP is reflected by a short A dur. The increased load imposed on the left atrium eventually results in atrial systolic failure, further LA enlargement, and decreased mitral A-wave velocity. The combined effects of the foregoing E- and Awave changes further increase the E/A ratio (Figure 4). Last, it is important to note that the filling pattern normally found in healthy individuals <40 years of age is similar to that found in patients with restrictive filling. This is due to the large E wave produced by robust diastolic suction, which almost completely empties the atrium during rapid filling.¹⁷

Dynamic Changes in Transmitral Doppler Filling Patterns

It is important to appreciate that although diastolic dysfunction can progress to more advanced filling grades because of LV fibrosis, hypertrophy, or infiltration,^{10,18} similar changes in filling grades can develop acutely in response to alterations in loading conditions. For example, a patient with heart failure and a delayed relaxation filling pattern who retains fluid may develop a pseudonormal filling pattern. This abrupt change results from an upward shift on the patient's P-V curve (reduced operational compliance; Figure 8). In contrast to shifts along the same P-V curve seen with acute changes in operational compliance, those due to structural alterations of the myocardium, previously described, may be viewed as resulting from a leftward shift onto a less compliant P-V curve, as is illustrated in Figure 8.^{10,18}

Early workers found that the reduction in preload that occurs during the Valsalva maneuver provides a means of distinguishing normal from pseudonormal filling (elevated LAP).¹⁹ With normal filling, the reduction in transmitral flow produced by the Valsalva maneuver affects both E- and A-wave velocities proportionately, such that there is little change in the E/A ratio. With pseudonormal filling, however, reduced transmitral flow increases LV operational compliance such that a delayed relaxation pattern emerges with a reduction in the E/A ratio. It has been suggested that a decrease in the E/A ratio of \geq 50% during the strain phase of the Valsalva maneuver indicates that mean LAP is increased (pseudonormal filling).¹⁹



Figure 1 (A) LV pressure curve. (B) LAP curve. (C) Simultaneous LV and LAP curves. *LVmin*, LV minimal pressure; *TMPG*, transmitral pressure gradient. Reproduced with permission from Nagueh *et al.*⁵⁸



Figure 2 LA, LV, and aortic pressure curves depicting the phases of the cardiac cycle. The *insert* demonstrates the steep rise in LV pressure (*arrows*) that results when LV compliance is reduced. See text. AS, Atrial systole; AVC, aortic valve closure; AVO, aortic valve opening; *IVCP*, isovolumic contraction period; MVC, mitral valve closure; MVO, mitral valve opening; SEP, systolic ejection period.

Additional Transmitral Doppler Findings: L Waves and Isovolumic Relaxation Time

Apart from the E/A ratio, additional transmitral Doppler findings may be useful for determining LAP. These include L waves and isovolumic relaxation time (IVRT), discussed below.

L Waves. L waves, sometimes seen on transmitral Doppler imaging, reliably predict increased mean LAP (Figure 9).²⁰ These waveforms are thought to represent abnormal mid-diastolic flow caused by markedly prolonged LV relaxation. L waves are best appreciated at lower heart rates, when there is adequate separation of E and A waves or when A waves are absent, as in atrial fibrillation (AF; Figure 9).²¹ Those <20 cm/sec are not clinically significant.²²

Isovolumic Relaxation Time. IVRT is an additional measurement useful in determining mean LAP. This can be measured by

positioning the PW sample volume in the LV cavity between the aortic and mitral valves in the apical five-chamber view such that both LV outflow and inflow tract flow profiles can both be recorded. Both flow signals can also be recorded using continuous-wave Doppler. IVRT is measured from the time offset between aortic valve closure, at the end of the outflow tract waveform, and mitral valve opening, at the beginning of the mitral E wave (Figure 10). IVRT prolongation (>110 msec) is seen in patients with grade 1 filling and is the earliest Doppler manifestation of impaired LV relaxation (prolongation of τ ; Figure 10).²³ However, it is important to recognize that increased systemic blood pressure can also prolong IVRT because of the longer time required for LV pressure to reach atrial levels. A short IVRT (<60 msec) indicates that mean LAP is elevated (Figure 10). However, it should be noted that a short IVRT can also result from rapid relaxation seen in young, healthy individuals.24



Figure 3 Calculation of τ , the time constant of relaxation. LV pressure from aortic valve closure to 5 mm Hg above LVEDP is fitted to the monoexponential equation shown. τ is obtained from this equation. *e*, natural logarithm; *P*, pressure; *t*, time. Reproduced with permission from Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. Mayo Clin Proc 1989;64:71–81.

MITRAL ANNULAR TISSUE DOPPLER

Translation of the mitral annulus is thought to play an essential role in facilitating volume transfers into and out of the left atrium. Annular motion can be tracked throughout the cardiac cycle with M-mode imaging by placing the line of insonation across the lateral mitral annulus in the apical four-chamber view (Figure 11). In addition, the velocity of annular motion can be measured with Doppler tissue imaging by placing a sample volume adjacent to the hinge point at the base of posterior mitral leaflet (lateral annulus) or the base of the anterior leaflet (medial annulus) in the four-chamber view.²⁵ This inscribes an S' wave (ventricular systole), an e' wave (early diastole), and an a' wave (atrial systole) as well as biphasic "spikes" before and after the S' wave, coincident with isovolumic contraction and relaxation, respectively (Figure 11).²⁶

During systole, the mitral annulus moves apically (descends), thereby displacing the column of LV blood resting beneath the closed mitral valve.²⁷ This motion has been referred to as the mitral annular plane systolic excursion. The velocity of annular descent is registered by the S' wave on the tissue Doppler recording. In addition to facilitating LV ejection, annular descent simultaneously enlarges the left atrium, increasing its compliance. The resulting drop in LAP promotes PV blood flow into the atrium while the mitral valve is closed (atrial reservoir function). The subsequent return of the annulus to its presystolic position (annular ascent) is accomplished in two "steps." During the first, which encompasses the RFP, the relaxing ventricle draws the annulus away from the apex (early annular ascent), and the accompa-

nying fall in LV pressure allows the mitral valve to open, facilitating ventricular filling (atrial conduit function). The velocity of annular motion during early annular ascent (RFP) is registered by the e' wave which is determined by active relaxation, elastic recoil, and lengthening load.²⁸ Following diastasis, during which the annulus remains immobile, late annular ascent (atrial systole) takes place. This is brought about by contraction of radially oriented atrial fibers,²⁹ which insert into and pull the mitral annulus away from the LV apex, thus inscribing the mitral annular a' waveform. The resulting decrease in the length of the LA major axis is thought to promote LV filling by translocating ("ventricularizing") a column of blood initially present in the left atrium to a position beneath the upward moving mitral leaflets (atrial pump function).³⁰

Mitral E-to-Annular e' Ratio (E/e')

Several authors have found that the E/e' ratio can be used to estimate mean LAP.²⁵ The numerator of the expression, E, may be regarded as a surrogate for the LA-LV pressure gradient, while the denominator, e', may be regarded as the extent to which this gradient is generated by ventricular suction. A high e' velocity indicates the presence of vigorous suction created by robust active relaxation and elastic recoil,²⁸ both of which consort to create a transmitral gradient by reducing LVmin. A low e' velocity, on the other hand, implies that LVmin does not drop significantly, because suction is poor. In this instance, the transmitral gradient is instead generated by a rise in LAP. Thus, patients with low E/e' ratios (<9), sometimes referred to as "suckers," typically have normal LAPs, whereas those with high ratios (>14), sometimes referred to as "pushers," typically have high LAPs. In patients with E/e' ratios between 9 and 14, LAP cannot be determined.

Normal values for e' vary with location. Normal lateral annular velocity is ≥ 10 cm/sec, whereas that of the medial annulus is significantly less (≥ 7 cm/sec), possibly because it is tethered to the central fibrous body. Last, an additional tissue Doppler finding, the L' wave, seen in about half of patients with transmitral L waves, suggests the presence of increased mean LAP (Figure 9).³¹

In patients with regional wall motion abnormalities involving basal LV segments, the motion of adjacent portions of the annulus, and hence their e' velocities, may be reduced. In such situations, it is suggested that e' be recorded from two annular regions (septal and lateral) and averaged, to better reflect global long-axis motion.³²

Caveats in Using E/e'

Recent data suggest that using the E/e' ratio to estimate mean LAP should be avoided in patients with significant mitral regurgitation (MR).³³ In patients with large regurgitant volumes, e' increases,^{28,32} possibly because of the attendant rise in lengthening load,⁸ and therefore cannot be used to "correct" peak E-wave velocity.³³ In patients with rheumatic mitral stenosis, E/e' appears to lose its predictive value for increased LAP because the E-wave velocity is more a reflection of orifice narrowing than abnormalities of relaxation or compliance.³⁴ Moreover, annular e' velocity decreases in mitral stenosis,³⁵ possibly because of reduced diastolic recoil of the posterobasal wall caused by the rigidity of and tethering by the mitral apparatus.³⁶ Finally, it has been suggested that E/e' should not be used in patients with significant mitral annular calcification (MAC), because mitral E-wave velocity may increase because of reduced mitral inflow area. In addition, reduced e' may not reflect abnormal relaxation but rather the local effects of tissue calcification.³⁷



Figure 4 Characteristic hemodynamic pressure and Doppler echocardiographic findings seen with different LV filling patterns. See text.



Figure 5 Characteristic LV pressure curves (A) and transmitral Doppler flow profiles (B) seen with normal (*black*) and grade 1 filling (*red*). Note that LV minimal pressure (*arrows*) occurs later and at a higher pressure when relaxation is delayed.

A number of studies have demonstrated that the E/e' ratio fails to predict mean LAP accurately in patients with native left bundle branch block and right ventricular or biventricular pacing.³⁸⁻⁴⁰ This is thought to be due to underestimation of septal e', caused by inadequate (i.e., tangential) beam alignment with the septum, resulting from paradoxical septal motion.³⁸ In addition, so-called clockwise rotation, an abnormal rocking motion of the left ventricle, described in patients with left bundle branch block, may cause underestimation of lateral e'⁴¹ for similar reasons.

It is also thought that the E/e' ratio should not be used to estimate mean LAP in patients with constrictive pericarditis. In such patients, lateral e' velocity may be reduced because of calcific pericardial adhesions, while the (normally lower) velocity of the medial annulus may be compensatorily increased (annulus reversus).⁴² Using the (hyper-dynamic) medial e' velocity to estimate LAP may suggest, incorrectly, that it is normal (annulus paradoxus).⁴³

Last, the utility of E/e' in estimating mean LAP in patients with acute decompensated systolic heart failure remains controversial, with different series drawing opposite conclusions.^{39,40}

Noninvasive Estimation of τ

As noted previously, IVRT relates both to LAP and to τ (Figure 10). The observation that the time offset between the onset of the mitral E wave and that of mitral annular e' ($T_{E-e'}$) is proportional to τ^{44} provides a means of correcting IVRT for the effects of LV relaxation such that it better relates to LAP. By substituting $T_{E-e'}$ for τ in the formula IVRT $\alpha \tau$ /LAP and solving for LAP, we obtain LAP $\alpha T_{E-e'}$ /IVRT or IVRT/ $T_{E-e'} \alpha$ 1/LAP. In one study, IVRT/ $T_{E-e'} < 2$ was found to have a sensitivity and specificity of 90% for detecting a pulmonary capillary wedge pressure (PCWP) > 15 mm Hg.⁴⁴ A potential advantage of using the IVRT/ $T_{E-e'}$ ratio to estimate PCWP is that unlike measurements that rely on transmitral E-wave velocity, it is not influenced by the confounding influences of relaxation, compliance, LAP, or mitral valve area.³³ A major limitation, however, is the need to obtain three different measurements, including e' averaged from



Figure 6 Operational compliance in early and late diastole in type 1b filling. In early diastole, the P-V relation remains on the flat portion of the P-V curve because the left ventricle is relatively underfilled. The increase in LV volume that occurs with atrial contraction shifts the P-V relationship of the left ventricle upward onto a steeper portion of the curve. As a result, LVEDP increases. ΔP , Change in pressure; ΔV , change in volume.

four annular sites. This requires that measurements be obtained during multiple cardiac cycles, which may vary in length.

Mitral Annular Velocities: e' and a'

Mitral annular e' and a' velocities provide important physiologic information regarding LV filling. As was mentioned previously, the rate of LV relaxation is a determinant of e' velocity.²⁸ The velocity of a' is thought to be a reliable index of atrial contractile function.⁴⁵ In fact, the time-velocity integral of a' equals the excursion of the annulus (the amount of LA major-axis shortening) during atrial systole (Figure 11).

In the normal left ventricle, the velocity of annular e' exceeds that of a' (Figure 4). When LV relaxation is delayed, however, e' velocity decreases while that of a' increases, such that a' > e'. The rise in a' is thought to reflect the compensatory increase in atrial contractility that takes place when early diastolic filling is reduced. As LAP increases with more advanced LV filling grades, both e' and a' decline in tandem. The decrease in e' reflects continued slowing of LV relaxation. The decrease in a' represents the progressive deterioration of atrial contractility that occurs as the load against which the left atrium must contract increases because of worsening LV compliance.

PV FLOW DOPPLER

Adequate transthoracic PV PW Doppler flow recordings can usually be obtained by interrogating the right upper pulmonary vein in the



Figure 7 Type 1a and 1b filling patterns. The *top* and *middle rows* show LA and LV pressure tracings obtained during late diastole *(red circles).* The *bottom row* shows the associated transmitral Doppler flow signals. With type 1b filling, reduced LV operational compliance in late diastole causes a steep rise in LV pressure, which abbreviates atrial systole. This shortens A-wave DT and mitral A-wave duration (A dur).

apical four-chamber view. The PV waveforms are designated A_R, S1, S2, and D (Figure 12). In late diastole, LA contraction simultaneously propels blood forward into the ventricle and backward into the pulmonary veins. The latter inscribes the A_R (retrograde A wave) on the Doppler flow recording. As the left atrium relaxes in early systole, the drop in atrial pressure increases the PV-LA gradient, and the resulting PV inflow inscribes the S1 (early systolic) wave. Later in systole, LV contraction draws the plane of the mitral annulus apically. This descent of the annulus, a reflection of ventricular contractility,⁴⁶ increases LA compliance, and the resulting drop in atrial pressure further promotes PV inflow, which inscribes the S2 (late systolic) wave. Of note, LA filling is also augmented by the forward pressure pulse generated by the right ventricle.⁴⁷ It is important to appreciate that the S1 and S2 waveforms overlap, are additive, and frequently appear as a single fused wave. These waveforms may, however, become separated when first-degree atrioventricular block is present.⁴⁸ Finally, PV flow into the left atrium during early diastole (RFP) inscribes the D wave. Because the PV D wave and the transmitral E wave are both recorded from the same uninterrupted column of blood, they are similarly influenced by downstream perturbations of LV relaxation and compliance.

PV S/D Ratio

In the normal left ventricle, PV S \ge D (Figure 4). Because the velocity of the S wave is determined by the gradient between the pulmonary



LV Volume

Figure 8 The P-V curve on the left demonstrates reduced LV compliance compared with the one on the right. Point A is associated with grade 1 filling, whereas points B and C are both associated with a grade 2 filling pattern. The transition from point A to B (upward shift) is due to an abrupt change in operational compliance resulting from volume overload. In contrast, the transition from point A to C (leftward shift) is due to a structural alteration of the left ventricle. See text. ΔP , change in pressure; ΔV , change in volume.

veins and the left atrium, a rise in LAP will predictably decrease its velocity. It has in fact been shown that a PV S/D ratio < 1 indicates the presence of increased mean LAP (Figure 4).⁴⁹ Importantly, this finding is useful in estimating LAP only when LV ejection fraction (LVEF) is decreased.⁵⁰ When LVEF is preserved, robust mitral annular descent will decrease LAP.

Caveats in Using the PV S/D Ratio

Under certain circumstances, a PV S/D ratio < 1 may fail to predict increased mean LAP. Its lack of utility in patients with preserved LVEFs has already been mentioned. In healthy individuals <40 years of age, a reduced S/D ratio may not reflect increased mean LAP but the effect of vigorous LV diastolic suction that increases PV D-wave velocity.⁵¹ Importantly, significant MR has been shown to cause blunting of the S wave and a decrease in the PV S/D ratio independent of LAP.⁵² Last, the loss of atrial systolic function that occurs with AF causes disappearance of the PV A_R-wave, representing atrial contraction, as well as blunting (or reversal) of the PV S1–wave, representing atrial relaxation. The latter limits the utility of a decreased PV S/D ratio in predicting increased mean LAP in patients with AF.⁵³

Duration of PV A-Wave Flow Reversal (A_R dur)

Atrial contraction generates flow into the left ventricle and the pulmonary veins. Although the onset of flow into both is simultaneous, their durations differ depending upon LV compliance⁵⁴ (Figure 13). When ventricular compliance is normal, the duration of transmitral flow into the lower impedance left ventricle exceeds the duration of flow into the PVs. However, when LV compliance is reduced, A_R dur becomes prolonged and A dur shortens. Once the difference between A_R dur and A dur (A_R – A dur) exceeds 30 msec, the reduction in LV compliance becomes sufficient to increase LVEDP. Finally, it has been shown that A_R – A dur > 30 msec accurately reflects increased LVEDP regardless of LVEF.⁵⁰

Diastolic MR

Apart from increased $A_R - A$ dur, other findings suggest the presence of high LVEDP. Significant elevation of LVEDP may be associated with diastolic MR, which can be identified on transmitral PW recordings,⁵⁵ as is shown in Figure 14. When late diastolic LV operational compliance is significantly reduced, blood entering the ventricle during atrial systole may so increase LV pressure that it exceeds that in the left atrium causing a "puff" of blood to regurgitate (diastolic MR). The B bump seen on M-mode recordings in patients with elevated LVEDP (Figure 14) likely represents the regurgitant orifice through which this blood flows.⁵⁶

THE 2016 AMERICAN SOCIETY OF ECHOCARDIOGRAPHY/ EUROPEAN ASSOCIATION OF CARDIOVASCULAR IMAGING GUIDELINES FOR ECHOCARDIOGRAPHIC EVALUATION OF DIASTOLIC FUNCTION

Guidelines for evaluating diastolic function were first published in 2009.⁵⁷ Their subsequent revision in 2016 was driven in large part by their undue complexity. In an effort to make the newer guidelines more serviceable, the algorithms used to estimate LAP were significantly simplified, importantly without sacrificing their accuracy.⁵⁷ The 2016 guidelines⁵⁸ contain two algorithms, shown in Figures 15 and 16, that are useful for estimating mean LAP in the majority of patients. These algorithms, which were created by expert consensus, have recently been validated in a study using an invasive standard.⁵⁹ The study's reported positive predictive value and specificity of 90% should reassure clinicians that Doppler-based predictions of increased mean LAP can be used with confidence in day-to-day clinical decision making. Moreover, the same study found that a Doppler-based diagnosis of elevated mean LAP was significantly more accurate than that obtained by clinical evaluation.⁵⁹

Estimating Mean LAP

The algorithm in Figure 15 from the 2016 guidelines was designed for estimating mean LAP in patients with known diastolic dysfunction. In this respect, the guidelines recommend that clinical as well as echocardiographic evidence of diastolic dysfunction be considered. Clinical findings that suggest the presence of diastolic dysfunction include hypertensive heart disease, coronary artery disease (CAD), and dilated and infiltrative cardiomyopathy. Although diastolic function is nearly ubiquitous in hypertrophic cardiomyopathy (HCM), the 2016 guidelines nonetheless do not recommend using the algorithm found in Figure 15^{,58} to estimate LVFP in patients with this disorder. Echocardiographic findings that suggest the presence of diastolic dysfunction include reduced LVEF, pathologic LV hypertrophy, $A_R - A$ dur > 30 msec, prominent L waves, and reduced global longitudinal strain (GLS; see below).

The algorithm in Figure 15 suggests several parameters to estimate mean LAP in patients with known diastolic dysfunction. The utility of using the E/A, E/e' and PV S/D ratios has already been discussed. Increased LA volume is another useful parameter because it closely reflects chronic elevations of LAP.⁶⁰ It has in fact been said that



Figure 9 (A) Transmitral Doppler recording of an L wave. (B) Transmitral L wave in a patient with AF. (C) Mitral annular tissue Doppler recording of an L' wave.



Figure 10 (A) IVRT is measured from the end of the LV outflow tract PW Doppler signal to the onset of the mitral E wave. (B) IVRT increases (red arrow) when LV relaxation is delayed (red curve). (C) Increased LAP (green curve) causes earlier mitral valve opening (MVO), which shortens the IVRT. Note that IVRT varies directly with τ and inversely with LAP.



Figure 11 (A) M-mode recording of mitral annular motion. A, systolic descent of the annulus (ventricular systole); B, early diastolic annular ascent; C, diastasis; D, late diastolic annular ascent (atrial systole). (B) Mitral annular tissue Doppler recording. (C) Illustration of simultaneous M-mode and tissue Doppler recordings of the mitral annulus. *IVCP*, Isovolumic contraction period; *IVRP*, isovolumic relaxation period; *MAPSE*, mitral annular plane systolic excursion.

"LA volume is the hemoglobin A_{1c} of LAP". Increased pulmonary artery systolic pressure (tricuspid regurgitation [TR] velocity) is a similarly sensitive marker of LAP that also demonstrates a stepwise increase with worsening LV filling grade.⁶¹

The first step in applying the algorithm in Figure 15 is to determine the mitral E/A ratio. An E/A ratio > 2 suggests the presence of increased LAP (grade 3 filling), although this may not hold true in young, healthy individuals, as discussed previously. An E/A ratio \leq 0.8 with a peak E-wave velocity \leq 50 cm/sec suggests that normal LAP (grade 1 filling) is present. To establish whether patients between these two extremes have normal or increased LAP, one must determine how many of the following criteria for LA hypertension are met: (1) E/e' > 14, (2) indexed LA volume > 34 mL/m², and (3) peak TR velocity > 2.8 m/sec (a surrogate for increased pulmonary artery systolic pressure). Of note, in patients >40 years of age with reduced LVEFs, a PV S/D ratio < 1 may be used if any of the aforementioned measurements are either technically suboptimal or clinically inapplicable. When two or more criteria are met, grade 2 filling and increased mean LAP is present. On the other hand, when two or more criteria are not met, grade 1 filling and normal mean LAP is present. Last, when just two criteria are available for analysis and they are discordant, mean LAP cannot be determined.5

It is important to note that the guidelines caution against using of the algorithm in Figure 15 to estimate mean LAP in certain circumstances. These include more than moderate MR (effective regurgitant orifice area $\geq 0.30 \text{ cm}^2$), mitral stenosis of any severity, prosthetic mitral valves and annuloplasty rings, moderate to severe MAC, HCM, pericardial constriction, AF and atrial flutter, left bundle branch block, right ventricular or biventricular pacing, and LV assist devices.⁵⁸ Alternative approaches for estimating LVFP in a number of these disorders are discussed in greater detail below.

It is important to emphasize that the presence of a structurally normal left ventricle with a normal LVEF does not preclude the presence of diastolic dysfunction.⁶² In this circumstance, the 2016 guide-lines (Figure 16) suggest that the presence or absence of diastolic dysfunction can be ascertained using the following four criteria: (1) averaged E/e' ratio > 14, (2) septal e' < 7 cm/sec or lateral e' < 10 cm/sec, (3) TR velocity > 2.8 m/sec, and (4) LA volume index > 34 mL/m². The guidelines suggest that patients who satisfy three or more criteria are likely to have diastolic dysfunction. Moreover, such patients' LV filling grades can be determined by using the algorithm in Figure 15. In patients who meet one or no criteria, diastolic dysfunction is unlikely. Among those in whom two criteria are met, the presence of diastolic dysfunction is considered indeterminate.

Caveats in Applying the 2016 Guidelines

A number of caveats pertain when using the 2016 guidelines' algorithms to estimate mean LAP. First, care should be taken when adjudicating LV filling grades in patients with heart rates >90 to 100 beats/min as well as in those with first-degree atrioventricular block. In both, diastasis shortens such that the mitral E and A waves overlap. When the velocity "shared" by the two waveforms, the so-called E-at-A velocity, exceeds 20 cm/sec, peak A-wave velocity increases, thus decreasing the transmitral E/A ratio (Figure 18).⁶³ Increased A-wave velocity is caused by the larger



Figure 12 PV Doppler recording demonstrating A_R , S1, S2, and D waves. This recording is obtained by placing a PW sample volume into the right upper pulmonary vein (RUPV), as is shown in the *insert*.

load imposed on the atrium as a result of atrial systole interrupting rapid filling.⁶⁴ The fortuitous appearance of a premature beat makes accurate measurement of the E/A ratio possible because the individual waveforms become separated (Figure 18). In addition, LA enlargement should not be used as a criterion for increased LAP in athletes or in the presence of mitral valve disease, AF and flutter, high output states (anemia, hyperthyroidism, etc.), and bradycardia.⁵⁸

TR velocity > 2.8 m/sec caused by pulmonary parenchymal or vascular disease (pulmonary arterial hypertension) should also not be used as a criterion to support the presence of increased mean LAP. Increased TR velocity must instead reflect PV hypertension due to increased LAP (grade 2 or 3 filling). Hence, a high TR velocity in a patient with normal mean LAP (grade 1 filling) suggests that pulmonary arterial hypertension is present.⁶⁵

LVFP in Patients With Mitral Valve Disease, AF, and HCM

The algorithms in Figures 15 and 16 should not be used in the presence of certain mitral valve disorders, AF, or HCM. LVFP can nonetheless be estimated in these disorders, although certain caveats, discussed below, must be taken into consideration.

Mitral Valve Disease. The algorithms in Figures 15 and 16 should not be used in patients with mitral stenosis of any severity.⁵⁸ IVRT/ $T_{E-e'} < 4$ has, however, been shown to predict PCWP > 15 mm Hg in these patients.³³

Use of the 2016 guidelines' algorithms should also be avoided in the presence of more than moderate MR (effective regurgitant orifice area $\geq 0.3~{\rm cm}^2).^{58}$ In such cases, parameters that do not reflect increased early diastolic flow resulting from MR are preferred. These include $A_R - A~{\rm dur} > 30~{\rm msec}$ (increased LVEDP), 50 IVRT $< 60~{\rm msec}$ (increased mean LAP), 33 and IVRT/ $T_{E-e'} < 3$ (increased PCWP). 33 Of note, all of the foregoing reliably predict increased LVFP regardless of LVEF.

The 2016 guidelines' algorithms should also not be applied in the presence of moderate to severe MAC, defined as calcification involving more than one third of the circumference of the mitral annulus or calcium encroachment into the mitral orifice.⁶⁶ To estimate LAP in patients with moderate to severe MAC, an



Figure 13 (A) PV and transmitral PW Doppler recordings from a patient with increased LVEDP. Note that A_{R} dur exceeds A dur. **(B)** Figure depicting relative durations of A_{R} dur and A dur when LVEDP is normal *(left)* and when it is elevated *(right)*. Reproduced with permission from Appleton *et al.*²⁴

algorithm combining the mitral E/A ratio and IVRT has recently been proposed (Figure 19). As with the conventional algorithm (Figure 15), the E/A ratio remains a valid indicator of LAP at its extremes. Hence, a ratio < 0.8 indicates normal mean LAP, and a ratio > 1.8 suggests mean LAP is elevated. Intermediate values (0.8–1.8) require measurement of IVRT for further adjudication, with a value of 80 msec used to separate normal from increased mean LAP.⁶⁶

Atrial Fibrillation. The presence of AF precludes use of the algorithms in Figures 15 and 16 to estimate LAP because of the loss of

atrial activity (transmitral A wave). In this respect it should be noted that restoration of sinus rhythm with electrical cardioversion may continue to blunt mitral A-wave velocities for up to several days.⁶⁷

E/septal e' ≥ 11 suggests that mean LAP is increased in patients with AF.⁶⁸ Because of RR variability, however, this measurement requires that 10 consecutive mitral E and annular e' velocities be averaged. Alternatively, three nonconsecutive E and e' velocities may be averaged as long as they are within 10% to 20% of the mean heart rate. An additional clue suggesting the presence of elevated mean LAP in AF is lack of variability in peak E-wave velocity despite varying RR intervals.⁵³ Of note, IVRT < 60 msec, regardless of LVEF,⁵⁸



Figure 14 Findings consistent with increased LVEDP. **(A)** Transmitral PW Doppler recording showing diastolic MR *(arrow)* in a patient with a type 3 filling pattern. **(B)** M-mode recording of the anterior mitral valve leaflet demonstrating a B bump.

suggests the presence of elevated mean LAP. Last, an E-wave DT \leq 160 msec suggests increased mean LAP, but only in patients with reduced LVEFs.⁵³

Hypertrophic Cardiomyopathy. Studies have shown that transmitral filling patterns do not accurately reflect mean LAP in patients with HCM. Indeed, the otherwise predictable rise in mean LAP that is seen with progression from one filling pattern to the next may be absent in patients with HCM.⁶⁹ This is thought to reflect the variable extent to which relaxation and compliance abnormalities each contribute to the various LV filling patterns. This in turn is thought to reflect the similarly variable amounts of fibrosis, myofiber disarray, ischemia, and regional heterogeneity (the substrates of abnormal relaxation and compliance) found among patients with HCM.⁶⁹ Although individual Doppler parameters (e.g., E/A ratio⁶⁹ and E/e' ratio⁷⁰) have been shown

to have modest predictive value for increased mean LAP in patients with HCM, concordance of multiple parameters improves their predictive value.⁵⁸ An algorithm for estimating mean LAP in patients with HCM based on the 2016 guidelines is shown in Figure 17.⁵⁸ In applying the algorithm, it is important to note that when more than moderate MR is present, the only parameters that can be used to determine LV filling grade are $A_R - A$ dur and peak TR velocity > 2.8 m/sec.

NOVEL INDICES OF LV DIASTOLIC FUNCTION

Recent studies using speckle-tracking echocardiography (deformation imaging) have contributed to our understanding of the pathogenesis of LV diastolic dysfunction. Moreover, a number of novel deformation indices, discussed below, have been shown to have clinical, he-modynamic and prognostic significance.

Left Atrial Global Longitudinal Strain

Atrial fibrosis is thought to play an important role in the pathogenesis of LV diastolic dysfunction. Interestingly, atrial fibrosis is present in a number of comorbidities associated with HFpEF, including diabetes mellitus, obesity, CAD, and hypertension, where it is thought to represent the effects of an abnormal hormonal, inflammatory, or oxidative milieu.⁷¹ In addition, chronic LA afterload mismatch, seen with more advanced grades of LV diastolic dysfunction, is also thought to cause atrial fibrosis.⁷¹ Regardless of the cause, atrial scarring is thought to represent the anatomic substrate responsible for the reduced LA reservoir, booster pump, and conduit function seen with LV diastolic dysfunction, all of which lend themselves to study using LA deformation imaging.

During systole (when the mitral valve is closed), the atrium acts a reservoir. Normally, the rise in pressure that occurs as the left atrium fills is blunted by the increase in compliance that results from atrial relaxation and mitral annular descent (see above). However, with the onset of fibrotic scarring, the atrium becomes stiff, such that it fills at higher pressures. These hemodynamic perturbations are associated with a decrease in reservoir strain (peak LA strain; Figure 20), which has, interestingly, been shown to correlate (inversely) with LVFP, New York Heart Association functional class, and LV filling grade.⁷¹ In addition, reduced reservoir, conduit, and booster pump strains have been shown to have prognostic significance in patients with HFpEF, predicting an increased likelihood of cardiovascular hospitalization (including heart failure hospitalizations) and death.⁷²

Left Ventricular Global Longitudinal Strain and Global Longitudinal Strain Rate

Fibrotic disruption of LV subendocardial longitudinal fibers is thought to represent the anatomic substrate responsible for the reduction in LV GLS found in patients with HFpEF⁷¹ (Figure 20). Although decreased LV GLS is a marker of systolic dysfunction, it may nonetheless be associated with impaired diastolic function, attesting to the importance of long-axis fiber integrity in maintaining normal LV systolic, as well as diastolic function. Speckle-tracking studies have in fact demonstrated that reduced (absolute) peak GLS accurately predicts increased LVFP in patients with HFpEF.⁷³

Estimating LAP in Patients with Diastolic Dysfunction



*PV S/D ratio < 1 applicable to conlcude increased LAP if LVEF is depressed

Figure 15 Algorithm for determining LV filling grade and mean LAP in patients with reduced LVEF, LV myocardial disease, or clinical evidence of diastolic dysfunction. See text. Reproduced with permission from Nagueh *et al.*⁵⁸



Figure 16 Algorithm for determining if LV diastolic dysfunction is present in patients with normal LVEFs and no evidence of myocardial disease. See text. Reproduced with permission from Nagueh *et al.*⁵⁸



Hypertrophic Cardiomyopathy

Figure 17 Algorithm for determining LV filling grades in patients with HCM. This algorithm may be applied whether or not LV outflow tract obstruction is present. If more than moderate MR is present, only TR velocity and $A_R - A$ dur may be used to determine LV filling grade.



Figure 18 (A) Superimposition of E and A waves causes a marked rise in peak A-wave velocity. (B) Otherwise fused mitral E and A waves become separated by the fortuitous appearance of a premature atrial contraction (PAC).

Decreased GLS rate measured during isovolumic relaxation (ϵ_{IVR}) and during early diastole (ϵ_E ; Figure 20) have also been found useful in assessing LV diastolic function. Indeed, ϵ_{IVR} , similar to e', has been shown to vary (inversely) with τ .⁷⁴ Similar to E/e', the ratio of E/ ϵ_{IVR} is also useful in predicting LVFP.⁷² Although ϵ_E also reflects LV relaxation, the correlation of E/ ϵ_E with LVFP is not as close as that of E/ ϵ_{IVR} .⁷⁴

Additional research will be needed to determine whether incorporation of the aforementioned LA and LV deformation indices into current algorithms for grading diastolic dysfunction will further increase their diagnostic accuracy; the added time and expertise required to measure them remains a potential barrier to their widespread use.

CONCLUSION

Echocardiography remains the cornerstone of noninvasive assessment of LV diastolic function. Continued technological advancements are likely to increase the simplicity and accuracy of estimating LVFPs noninvasively, which should improve patient outcomes.

Additional topics related to this article can be found in the online Appendix. These topics include (1) diastolic stress testing, (2) clinical correlates of diastolic dysfunction, and (3) the effect of increased aortic stiffness on LV relaxation.



*Transmitral gradient must be < 4 mmHg

Figure 19 Algorithm for determining LAP in patients with moderate to severe MAC. The algorithm should not be applied when the transmitral gradient is \geq 4 mm Hg. Reproduced with permission from Abudiab *et al.*⁶⁶



Figure 20 (A) LA strain tracing showing reservoir, conduit, and booster pump strains. (B) LV GLS tracing. (C) LV GLS rate tracing. ε_{IVR} and ε_{E} indicate peak longitudinal strain rate during isovolumic relaxation and early diastole, respectively. Reproduced with permission from Kasner M, Gaub R, Sinning D, Westermann D, Steendijk P, Hoffmann W, *et al.* Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure-volume loop analysis. Eur J Echocardiogr 2010;11:743–751.

SUPPLEMENTARY DATA

Supplementary material for this article can be found at https://dx.doi. org/10.1016/j.echo.2018.11.011.

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APPENDIX

Diastolic Stress Testing

The increased venous return that accompanies exercise imposes a large volume load on the left ventricle that must be accommodated during an abbreviated diastolic filling period. If not for a number of adaptive responses, the increased load might otherwise increase LVFPs. Among the adaptations to exercise is a sympathetically mediated increase in the rate of LV relaxation (shortening of τ). The resulting drop in LVmin creates an adequate LA-LV gradient to sustain LV filling through suction, such that LAP does not rise. Furthermore, the increased contractility that accompanies tachycardia (treppe phenomenon) decreases LV end-systolic volume, further augmenting suction through enhanced elastic recoil (restoring forces).¹ Finally, early mitral valve opening, caused by rapid LV relaxation, increases LV filling by prolonging the RFP.

Impaired active relaxation in older patients is thought, at least in part, to be caused by reduced SERCA activity resulting from decreased responsiveness to sympathetic stimulation.² Myocardial ischemia due to CAD also reduces the activity of the highly energy dependent SERCA pump.³ Regardless of the mechanism(s) involved, impaired relaxation leads to an increase in LAP,¹ which in turn increases PV pressure resulting in effort intolerance and dyspnea. Last, shortening of diastole due to tachycardia leaves insufficient time for the slowly relaxing left ventricle to achieve complete relaxation. The resultant increase in so-called resting tone decreases LV compliance, which further contributes to increased LAP.⁴

Diastolic stress testing has been shown to be useful in determining whether dyspnea, particularly upon exertion, is due to reduced diastolic reserve. The most appropriate patients for diastolic stress testing are those with grade 1 filling (normal mean LAP) at rest. There is little utility in performing the test in patients who have normal results on resting two-dimensional studies and normal annular e' velocities, as there is little likelihood they will have exercise-induced diastolic dysfunction. Last, there is little to be gained by performing a diastolic stress test in patients with Doppler findings consistent with increased LAP already evident at rest.⁵

The 2016 guidelines suggest that diastolic stress testing should be performed by measuring mitral E-wave, medial annular e', and peak TR velocities at rest and again following exercise. In patients with normal diastolic reserve, increased transmitral flow (E-wave velocity) resulting from exercise is accompanied by an adaptive increase in e'⁶ such that E/average e' (or septal e') remains <10 and TR velocity remains ≤ 2.8 m/sec.⁵ A positive diastolic stress test consists of the following three elements: (1) E/average e' > 14 (or E/septal e' > 15), (2) medial e' to <7 cm/sec (or septal e' < 10 cm/sec), and (3) peak TR velocity > 2.8 m/sec. ⁵

Clinical Correlates of Diastolic Dysfunction

Hypertension, diabetes mellitus,⁷ and increased body mass index, particularly when associated with central adiposity,⁸ are all associated with echocardiographic evidence of diastolic dysfunction. It has therefore been suggested that diastolic dysfunction be regarded as a manifestation of the metabolic syndrome. Indeed, the biochemical milieu associated with metabolic syndrome appears to a have a number of adverse effects on cardiac myocytes and extracellular matrix that play a role in the pathogenesis of diastolic dysfunction. Of particular interest are the stimulation of hypertrophy by insulin, the accu-

mulation of so-called advanced glycation end-products, which increase ventricular and aortic stiffness, and increased levels of cytokines which promote collagen deposition. 9

Myocardial ischemia due to CAD has also been shown to cause diastolic dysfunction, in part because of impairment of the highly energy-dependent process of active relaxation.³ In this respect, it is important to appreciate that the echocardiographic detection of diastolic dysfunction may indicate the presence of CAD.

Increased age is an important determinant of LV diastolic dysfunction. Studies have in fact shown that LV compliance¹⁰ decreases with age. Abnormal relaxation, although prevalent in the elderly,¹¹ appears to be more often related to comorbidities¹² commonly found among these individuals (e.g., hypertension, CAD).¹³ LV remodeling associated with aging results in increased interstitial collagen content and myocardial hypertrophy. At a cellular level, myocardial aging is associated with reduced titin elasticity and decreased SERCA-mediated Ca⁺⁺ reuptake.⁹

Patients with obstructive sleep apnea have also been shown to develop echocardiographic evidence of diastolic dysfunction, but common comorbidities, particularly obesity, hypertension, and CAD may play a contributory role.¹⁴ Last, echocardiographic evidence of LV diastolic dysfunction has been described in patients with hypothyroidism.¹⁵

Increased Aortic Stiffness and LV Diastolic Dysfunction

It has recently been shown that patients with asymptomatic diastolic dysfunction are more likely to develop HFpEF when aortic stiffness is increased.¹⁶ Increased aortic stiffness is thought to influence diastolic function through its effect on reflected waves within the aorta. Blood in the aorta normally reflects backward when it comes into contact with arterial branch points (e.g., the aortic bifurcation). When the aorta is stiff, these waves travel faster such that they reach the left ventricle at a time (first two thirds of the systolic ejection period)¹⁷ when the added load they impose is still capable of recruiting actin-myosin cross-bridges.¹⁸ It has been suggested that increased cross-bridge formation resulting from such loads raises LV pressure and prolongs systole, which in turn cause delayed onset and slowing of the rate of LV relaxation (Supplemental Figure 1).¹⁹ Studies in humans have in fact shown that these abnormalities are associated with increased E/e', τ and LVEDP.²⁰



Supplemental Figure 1 A normal LV pressure tracing is depicted in *blue*. When reflected waves reach the left ventricle early during the systolic ejection period *(arrow)*, peak LV pressure increases and systole lengthens, causing LV relaxation to begin later and to become prolonged *(purple* LV pressure tracing).

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