

GUIDELINES AND STANDARDS

Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography

Sherif F. Nagueh, MD, Chair,[†] Christopher P. Appleton, MD,[†] Thierry C. Gillebert, MD,*
Paolo N. Marino, MD,* Jae K. Oh, MD,[†] Otto A. Smiseth, MD, PhD,*
Alan D. Waggoner, MHS,[†] Frank A. Flachskampf, MD, Co-Chair,*
Patricia A. Pellikka, MD,[†] and Arturo Evangelista, MD,* *Houston, Texas; Phoenix, Arizona;
Ghent, Belgium; Novara, Italy; Rochester, Minnesota; Oslo, Norway; St. Louis, Missouri; Erlangen, Germany;
Barcelona, Spain*

Keywords: Diastole , Echocardiography, Doppler, Heart failure

Continuing Medical Education Activity for "Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography"

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Target Audience:

This activity is designed for all cardiovascular physicians, cardiac sonographers, cardiovascular anesthesiologists, and cardiology fellows.

Objectives:

Upon completing this activity, participants will be able to: 1. Describe the hemodynamic determinants and clinical application of mitral inflow velocities. 2. Recognize the hemodynamic determinants and clinical application of pulmonary venous flow velocities. 3. Identify the clinical application and limitations of early diastolic flow propagation velocity. 4. Assess the hemodynamic determinants and clinical application of mitral annulus tissue Doppler velocities. 5. Use echocardiographic methods to estimate left ventricular filling pressures in patients with normal and depressed EF, and to grade the severity of diastolic dysfunction.

Author Disclosures:

Thierry C. Gillebert: Research Grant – Participant in comprehensive research agreement between GE Ultrasound, Horten, Norway and Ghent University; Advisory Board – Astra-Zeneca, Merck, Sandoz.

The following stated no disclosures: Sherif F. Nagueh, Frank A. Flachskampf, Arturo Evangelista, Christopher P. Appleton, Thierry C. Gillebert, Paolo N. Marino, Jae K. Oh, Patricia A. Pellikka, Otto A. Smiseth, Alan D. Waggoner.

Conflict of interest: The authors have no conflicts of interest to disclose except as noted above.

Estimated time to complete this activity: 1 hour

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From the Methodist DeBakey Heart and Vascular Center, Houston, TX (S.F.N.); Mayo Clinic Arizona, Phoenix, AZ (C.P.A.); the University of Ghent, Ghent, Belgium (T.C.G.); Eastern Piedmont University, Novara, Italy (P.N.M.); Mayo Clinic, Rochester, MN (J.K.O., P.A.P.); the University of Oslo, Oslo, Norway (O.A.S.); Washington University School of Medicine, St Louis, MO (A.D.W.); the University of Erlangen, Erlangen, Germany (F.A.F.); and Hospital Vall d'Hebron, Barcelona, Spain (A.E.).

Reprint requests: American Society of Echocardiography, 2100 Gateway Centre Boulevard, Suite 310, Morrisville, NC 27560 (E-mail: ase@asecho.org).

* Writing Committee of the European Association of Echocardiography.

[†] Writing Committee of the American Society of Echocardiography.

0894-7317/\$36.00

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doi:10.1016/j.echo.2008.11.023

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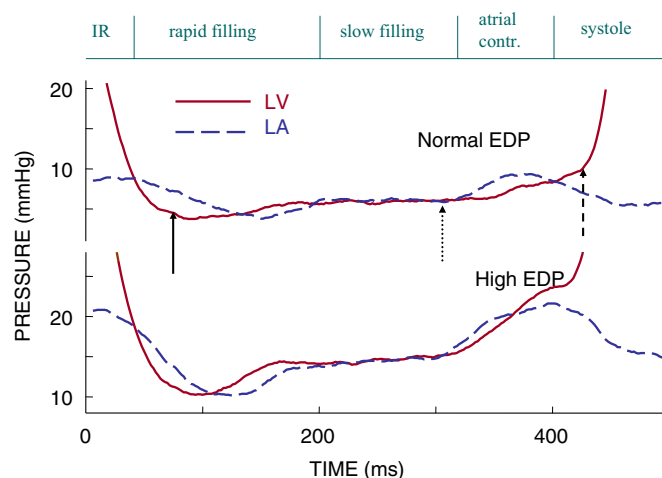


Figure 1 The 4 phases of diastole are marked in relation to high-fidelity pressure recordings from the left atrium (LA) and left ventricle (LV) in anesthetized dogs. The first pressure crossover corresponds to the end of isovolumic relaxation and mitral valve opening. In the first phase, left atrial pressure exceeds left ventricular pressure, accelerating mitral flow. Peak mitral E roughly corresponds to the second crossover. Thereafter, left ventricular pressure exceeds left atrial pressure, decelerating mitral flow. These two phases correspond to rapid filling. This is followed by slow filling, with almost no pressure differences. During atrial contraction, left atrial pressure again exceeds left ventricular pressure. The *solid arrow* points to left ventricular minimal pressure, the *dotted arrow* to left ventricular pre-A pressure, and the *dashed arrow* to left ventricular end-diastolic pressure. The *upper panel* was recorded at a normal end-diastolic pressure of 8 mm Hg. The *lower panel* was recorded after volume loading and an end-diastolic pressure of 24 mm Hg. Note the larger pressure differences in both tracings of the *lower panel*, reflecting decreased operating compliance of the LA and LV. Atrial contraction provokes a sharp rise in left ventricular pressure, and left atrial pressure hardly exceeds this elevated left ventricular pressure. (Courtesy of T. C. Gillebert and A. F. Leite-Moreira.)

PREFACE

The assessment of left ventricular (LV) diastolic function should be an integral part of a routine examination, particularly in patients presenting with dyspnea or heart failure. About half of patients with new diagnoses of heart failure have normal or near normal global ejection fractions (EFs). These patients are diagnosed with “diastolic heart failure” or “heart failure with preserved EF.”¹ The assessment of LV diastolic function and filling pressures is of paramount clinical importance to distinguish this syndrome from other diseases such as pulmonary disease resulting in dyspnea, to assess prognosis, and to identify underlying cardiac disease and its best treatment.

LV filling pressures as measured invasively include mean pulmonary wedge pressure or mean left atrial (LA) pressure (both in the absence of mitral stenosis), LV end-diastolic pressure (LVEDP; the pressure at the onset of the QRS complex or after A-wave pressure), and pre-A LV diastolic pressure (Figure 1). Although these pressures are different in absolute terms, they are closely related, and they change in a predictable progression with myocardial disease, such that LVEDP increases prior to the rise in mean LA pressure.

Echocardiography has played a central role in the evaluation of LV diastolic function over the past two decades. The purposes of this

document is to provide a comprehensive review of the techniques and the significance of diastolic parameters, as well as recommendations for nomenclature and reporting of diastolic data in adults. The recommendations are based on a critical review of the literature and the consensus of a panel of experts.

I. PHYSIOLOGY

The optimal performance of the left ventricle depends on its ability to cycle between two states: (1) a compliant chamber in diastole that allows the left ventricle to fill from low LA pressure and (2) a stiff chamber (rapidly rising pressure) in systole that ejects the stroke volume at arterial pressures. The ventricle has two alternating functions: systolic ejection and diastolic filling. Furthermore, the stroke volume must increase in response to demand, such as exercise, without much increase in LA pressure.² The theoretically optimal LV pressure curve is rectangular, with an instantaneous rise to peak and an instantaneous fall to low diastolic pressures, which allows for the maximum time for LV filling. This theoretically optimal situation is approached by the cyclic interaction of myofilaments and assumes competent mitral and aortic valves. Diastole starts at aortic valve

closure and includes LV pressure fall, rapid filling, diastasis (at slower heart rates), and atrial contraction.²

Elevated filling pressures are the main physiologic consequence of diastolic dysfunction.² Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is >12 mm Hg or when the LVEDP is >16 mm Hg.¹ Filling pressures change minimally with exercise in healthy subjects. Exercise-induced elevation of filling pressures limits exercise capacity and can indicate diastolic dysfunction. LV filling pressures are determined mainly by filling and passive properties of the LV wall but may be further modulated by incomplete myocardial relaxation and variations in diastolic myocardial tone.

At the molecular level, the cyclic interaction of myofilaments leads to a muscular contraction and relaxation cycle. Relaxation is the process whereby the myocardium returns after contraction to its unstressed length and force. In normal hearts, and with normal load, myocardial relaxation is nearly complete at minimal LV pressure. Contraction and relaxation belong to the same molecular processes of transient activation of the myocyte and are closely intertwined.³ Relaxation is subjected to control by load, inactivation, and asynchrony.²

Increased afterload or late systolic load will delay myocardial relaxation, especially when combined with elevated preload, thereby contributing to elevating filling pressures.⁴ Myocardial inactivation relates to the processes underlying calcium extrusion from the cytosol and cross-bridge detachment and is affected by a number of proteins that regulate calcium homeostasis,⁵ cross-bridge cycling,² and energetics.³ Minor regional variation of the timing of regional contraction and relaxation is physiological. However, dyssynchronous relaxation results in a deleterious interaction between early reextension in some segments and postsystolic shortening of other segments and contributes to delayed global LV relaxation and elevated filling pressures.⁶

The rate of global LV myocardial relaxation is reflected by the monoexponential course of LV pressure fall, assuming a good fit ($r > 0.97$) to a monoexponential pressure decay. Tau is a widely accepted invasive measure of the rate of LV relaxation, which will be 97% complete at a time corresponding to 3.5τ after dP/dt_{\min} . Diastolic dysfunction is present when $\tau > 48$ ms.¹ In addition, the rate of relaxation may be evaluated in terms of LV dP/dt_{\min} and indirectly with the isovolumetric relaxation time (IVRT), or the time interval between aortic valve closure and mitral valve opening.

LV filling is determined by the interplay between LV filling pressures and filling properties. These filling properties are described with stiffness ($\Delta P/\Delta V$) or inversely with compliance ($\Delta V/\Delta P$) and commonly refer to end-diastolic properties. Several factors extrinsic and intrinsic to the left ventricle determine these end-diastolic properties. Extrinsic factors are mainly pericardial restraint and ventricular interaction. Intrinsic factors include myocardial stiffness (cardiomyocytes and extracellular matrix), myocardial tone, chamber geometry, and wall thickness.⁵

Chamber stiffness describes the LV diastolic pressure-volume relationship, with a number of measurements that can be derived. The operating stiffness at any point is equal to the slope of a tangent drawn to the curve at that point ($\Delta P/\Delta V$) and can be approximated with only two distinct pressure-volume measurements. Diastolic dysfunction is present when the slope is >0.20 mm Hg/mL.⁷ On the other hand, it is possible to characterize LV chamber stiffness over the duration of diastole by the slope of the exponential fit to the diastolic pressure-volume relation. Such a curve fit can be applied to the diastolic LV pressure-volume relation of a single beat or to the end-diastolic pressure-volume relation constructed by fitting the lower right corner

of multiple pressure-volume loops obtained at various preloads. The latter method has the advantage of being less dependent on ongoing myocardial relaxation. The stiffness modulus, kc , is the slope of the curve and can be used to quantify chamber stiffness. Normal values do not exceed 0.015 (C. Tschöpe, personal communication).

A distinct aspect of diastolic function is related to longitudinal function and torsion. Torrent-Guasp et al⁸ described how the ventricles may to some extent be assimilated to a single myofiber band starting at the right ventricle below the pulmonary valve and forming a double helix extending to the left ventricle, where it attaches to the aorta. This double helicoidal fiber orientation leads to systolic twisting (torsion) and diastolic untwisting (torsional recoil).

Key Points

1. Diastolic function is related to myocardial relaxation and passive LV properties and is modulated by myocardial tone.
2. Myocardial relaxation is determined by load, inactivation, and nonuniformity.
3. Myocardial stiffness is determined by the myocardial cell (eg, titin) and by the interstitial matrix (fibrosis).

II. MORPHOLOGIC AND FUNCTIONAL CORRELATES OF DIASTOLIC DYSFUNCTION

A. LV Hypertrophy

Although diastolic dysfunction is not uncommon in patients with normal wall thickness, LV hypertrophy is among the important reasons for it. In patients with diastolic heart failure, concentric hypertrophy (increased mass and relative wall thickness), or remodeling (normal mass but increased relative wall thickness), can be observed. In contrast, eccentric LV hypertrophy is usually present in patients with depressed EFs. Because of the high prevalence of hypertension, especially in the older population, LV hypertrophy is common, and hypertensive heart disease is the most common abnormality leading to diastolic heart failure.

LV mass may be best, although laboriously, measured using 3-dimensional echocardiography.⁹ Nevertheless, it is possible to measure it in most patients using 2-dimensional (2D) echocardiography, using the recently published guidelines of the American Society of Echocardiography.¹⁰ For clinical purposes, at least LV wall thickness should be measured in trying to arrive at conclusions on LV diastolic function and filling pressures.

In pathologically hypertrophied myocardium, LV relaxation is usually slowed, which reduces early diastolic filling. In the presence of normal LA pressure, this shifts a greater proportion of LV filling to late diastole after atrial contraction. Therefore, the presence of predominant early filling in these patients favors the presence of increased filling pressures.

B. LA Volume

The measurement of LA volume is highly feasible and reliable in most echocardiographic studies, with the most accurate measurements obtained using the apical 4-chamber and 2-chamber views.¹⁰ This assessment is clinically important, because there is a significant relation between LA remodeling and echocardiographic indices of diastolic function.¹¹ However, Doppler velocities and time intervals reflect filling pressures at the time of measurement, whereas LA volume often reflects the cumulative effects of filling pressures over time.

Importantly, observational studies including 6,657 patients without baseline histories of atrial fibrillation and significant valvular heart

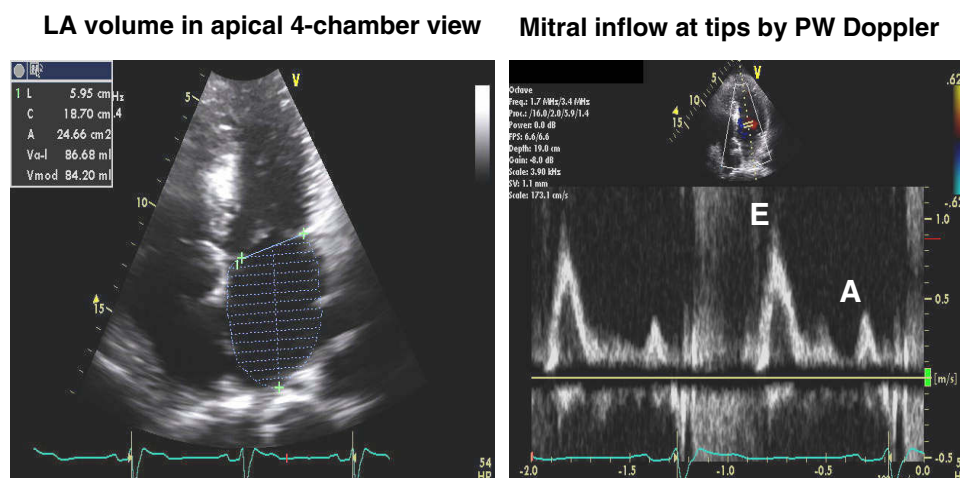


Figure 2 (Left) End-systolic (maximum) LA volume from an elite athlete with a volume index of 33 mL/m². (Right) Normal mitral inflow pattern acquired by PW Doppler from the same subject. Mitral E velocity was 100 cm/s, and A velocity was 38 cm/s. This athlete had trivial MR, which was captured by PW Doppler. Notice the presence of a larger LA volume despite normal function.

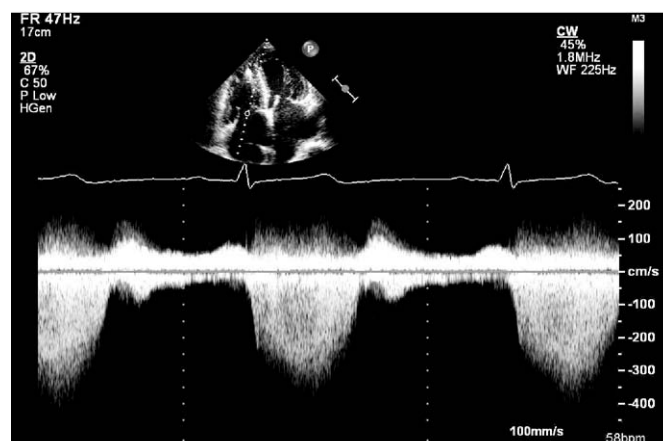
disease have shown that LA volume index ≥ 34 mL/m² is an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.¹² However, one must recognize that dilated left atria may be seen in patients with bradycardia and 4-chamber enlargement, anemia and other high-output states, atrial flutter or fibrillation, and significant mitral valve disease, in the absence of diastolic dysfunction. Likewise, it is often present in elite athletes in the absence of cardiovascular disease (Figure 2). Therefore, it is important to consider LA volume measurements in conjunction with a patient's clinical status, other chambers' volumes, and Doppler parameters of LV relaxation.

C. LA Function

The atrium modulates ventricular filling through its reservoir, conduit, and pump functions.¹³ During ventricular systole and isovolumic relaxation, when the atrioventricular (AV) valves are closed, atrial chambers work as distensible reservoirs accommodating blood flow from the venous circulation (reservoir volume is defined as LA passive emptying volume minus the amount of blood flow reversal in the pulmonary veins with atrial contraction). The atrium is also a pumping chamber, which contributes to maintaining adequate LV end-diastolic volume by actively emptying at end-diastole (LA stroke volume is defined as LA volume at the onset of the electrocardiographic P wave minus LA minimum volume). Finally, the atrium behaves as a conduit that starts with AV valve opening and terminates before atrial contraction and can be defined as LV stroke volume minus the sum of LA passive and active emptying volumes. The reservoir, conduit, and stroke volumes of the left atrium can be computed and expressed as percentages of LV stroke volume.¹³

Impaired LV relaxation is associated with a lower early diastolic AV gradient and a reduction in LA conduit volume, while the reservoir-pump complex is enhanced to maintain optimal LV end-diastolic volume and normal stroke volume. With a more advanced degree of diastolic dysfunction and reduced LA contractility, the LA contribution to LV filling decreases.

Aside from LA stroke volume, LA systolic function can be assessed using a combination of 2D and Doppler measurements^{14,15} as the LA ejection force (preload dependent, calculated as $0.5 \times 1.06 \times \text{mitral annular area} \times [\text{peak A velocity}]^2$) and kinetic energy ($0.5 \times 1.06 \times \text{LA stroke volume} \times [\text{A velocity}]^2$). In addition, recent reports



$$4 (V)^2 \text{ of peak TR velocity} = \text{PAS} - \text{RAP}$$

$$4 (3.6)^2 \text{ or } 52 = \text{PAS} - 20$$

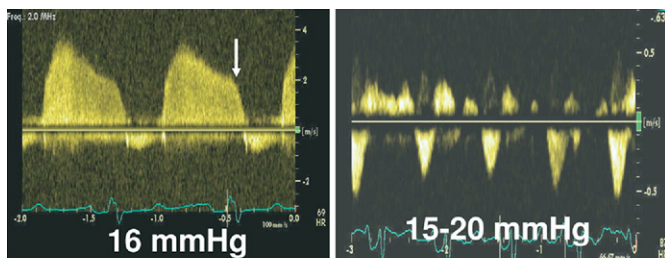
$$\text{PAS} = 52 + 20 = 72 \text{ mmHg}$$

Figure 3 Calculation of PA systolic pressure using the TR jet. In this patient, the peak velocity was 3.6 m/s, and RA pressure was estimated at 20 mm Hg.

have assessed LA strain and strain rate and their clinical associations in patients with atrial fibrillation.^{16,17} Additional studies are needed to better define these clinical applications.

D. Pulmonary Artery Systolic and Diastolic Pressures

Symptomatic patients with diastolic dysfunction usually have increased pulmonary artery (PA) pressures. Therefore, in the absence of pulmonary disease, increased PA pressures may be used to infer the presence of elevated LV filling pressures. Indeed, a significant correlation was noted between PA systolic pressure and noninvasively derived LV filling pressures.¹⁸ The peak velocity of the tricuspid regurgitation (TR) jet by continuous-wave (CW) Doppler together with systolic right atrial (RA) pressure (Figure 3) are used to derive PA systolic pressure.¹⁹ In patients with severe TR and low systolic right ventricular–RA pressure gradients, the accuracy of the PA systolic



$$4 (V)^2 \text{ of end diastolic PR velocity} = \text{PAD} - \text{RAP}$$

$$4 (2)^2 \text{ or } 16 = \text{PAD} - (15 \text{ or } 20)$$

$$\text{PAD} = 16 + (15-20) = 31-36 \text{ mmHg}$$

Figure 4 Calculation of PA diastolic pressure using the PR jet (left) and hepatic venous by PW Doppler (right). In this patient, the PR end-diastolic velocity was 2 m/s (arrow), and RA pressure was estimated at 15 to 20 mm Hg (see Quiñones et al¹⁹ for details on estimating mean RA pressure).

pressure calculation is dependent on the reliable estimation of systolic RA pressure.

Likewise, the end-diastolic velocity of the pulmonary regurgitation (PR) jet (Figure 4) can be applied to derive PA diastolic pressure.¹⁹ Both signals can be enhanced, if necessary, using agitated saline or intravenous contrast agents, with care to avoid overestimation caused by excessive noise in the signal. The estimation of RA pressure is needed for both calculations and can be derived using inferior vena caval diameter and its change with respiration, as well as the ratio of systolic to diastolic flow signals in the hepatic veins.¹⁹

PA diastolic pressure by Doppler echocardiography usually correlates well with invasively measured mean pulmonary wedge pressure and may be used as its surrogate.²⁰ The limitations to this approach are in the lower feasibility rates of adequate PR signals (<60%), particularly in intensive care units and without intravenous contrast agents. In addition, its accuracy depends heavily on the accurate estimation of mean RA pressure, which can be challenging in some cases. The assumption relating PA diastolic pressure to LA pressure has reasonable accuracy in patients without moderate or severe pulmonary hypertension. However, in patients with pulmonary vascular resistance $> 200 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$ or mean PA pressures $> 40 \text{ mm Hg}$, PA diastolic pressure is higher ($>5 \text{ mm Hg}$) than mean wedge pressure.²¹

III. MITRAL INFLOW

A. Acquisition and Feasibility

Pulsed-wave (PW) Doppler is performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling.²² Color flow imaging can be helpful for optimal alignment of the Doppler beam, particularly when the left ventricle is dilated. Performing CW Doppler to assess peak E (early diastolic) and A (late diastolic) velocities should be performed before applying the PW technique to ensure that maximal velocities are obtained. A 1-mm to 3-mm sample volume is then placed between the mitral leaflet tips during diastole to record a crisp velocity profile (Figure 2). Optimizing spectral gain and wall filter settings is important to clearly display the onset and cessation of LV inflow. Excellent-quality mitral inflow waveforms can be recorded in nearly all patients. Spectral mitral velocity recordings should be initially obtained at sweep speeds of 25 to 50 mm/s for the evaluation of respiratory variation of flow velocities, as seen in patients with pulmonary or pericardial disease

(see the following). If variation is not present, the sweep speed is increased to 100 mm/s, at end-expiration, and averaged over 3 consecutive cardiac cycles.

B. Measurements

Primary measurements of mitral inflow include the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time (DT) of early filling velocity, and the IVRT, derived by placing the cursor of CW Doppler in the LV outflow tract to simultaneously display the end of aortic ejection and the onset of mitral inflow. Secondary measurements include mitral A-wave duration (obtained at the level of the mitral annulus), diastolic filling time, the A-wave velocity-time integral, and the total mitral inflow velocity-time integral (and thus the atrial filling fraction) with the sample volume at the level of the mitral annulus.²² Middiastolic flow is an important signal to recognize. Low velocities can occur in normal subjects, but when increased ($\geq 20 \text{ cm/s}$), they often represent markedly delayed LV relaxation and elevated filling pressures.²³

C. Normal Values

Age is a primary consideration when defining normal values of mitral inflow velocities and time intervals. With increasing age, the mitral E velocity and E/A ratio decrease, whereas DT and A velocity increase. Normal values are shown in Table 1.²⁴ A number of variables other than LV diastolic function and filling pressures affect mitral inflow, including heart rate and rhythm, PR interval, cardiac output, mitral annular size, and LA function. Age-related changes in diastolic function parameters may represent a slowing of myocardial relaxation, which predisposes older individuals to the development of diastolic heart failure.

D. Inflow Patterns and Hemodynamics

Mitral inflow patterns are identified by the mitral E/A ratio and DT. They include normal, impaired LV relaxation, pseudonormal LV filling (PNF), and restrictive LV filling. The determination of PNF may be difficult by mitral inflow velocities alone (see the following). Additionally, less typical patterns are sometimes observed, such as the triphasic mitral flow velocity flow pattern. The most abnormal diastolic physiology and LV filling pattern variants are frequently seen in elderly patients with severe and long-standing hypertension or patients with hypertrophic cardiomyopathy.

It is well established that the mitral E-wave velocity primarily reflects the LA-LV pressure gradient (Figure 5) during early diastole and is therefore affected by preload and alterations in LV relaxation.²⁵ The mitral A-wave velocity reflects the LA-LV pressure gradient during late diastole, which is affected by LV compliance and LA contractile function. E-wave DT is influenced by LV relaxation, LV diastolic pressures following mitral valve opening, and LV compliance (ie, the relationship between LV pressure and volume). Alterations in LV end-systolic and/or end-diastolic volumes, LV elastic recoil, and/or LV diastolic pressures directly affect the mitral inflow velocities (ie, E wave) and time intervals (ie, DT and IVRT).

E. Clinical Application to Patients With Depressed and Normal EFs

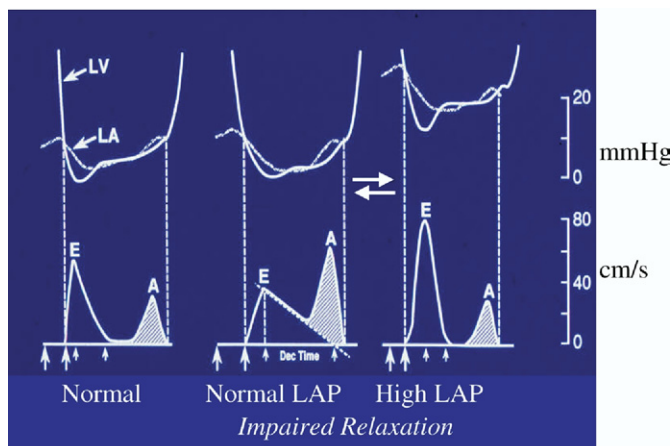
In patients with dilated cardiomyopathies, PW Doppler mitral flow velocity variables and filling patterns correlate better with cardiac filling pressures, functional class, and prognosis than LV EF.²⁶⁻⁴⁷ Patients with impaired LV relaxation filling are the least symptomatic,

Table 1 Normal values for Doppler-derived diastolic measurements

Measurement	Age group (y)			
	16-20	21-40	41-60	>60
IVRT (ms)	50 ± 9 (32-68)	67 ± 8 (51-83)	74 ± 7 (60-88)	87 ± 7 (73-101)
E/A ratio	1.88 ± 0.45 (0.98-2.78)	1.53 ± 0.40 (0.73-2.33)	1.28 ± 0.25 (0.78-1.78)	0.96 ± 0.18 (0.6-1.32)
DT (ms)	142 ± 19 (104-180)	166 ± 14 (138-194)	181 ± 19 (143-219)	200 ± 29 (142-258)
A duration (ms)	113 ± 17 (79-147)	127 ± 13 (101-153)	133 ± 13 (107-159)	138 ± 19 (100-176)
PV S/D ratio	0.82 ± 0.18 (0.46-1.18)	0.98 ± 0.32 (0.34-1.62)	1.21 ± 0.2 (0.81-1.61)	1.39 ± 0.47 (0.45-2.33)
PV Ar (cm/s)	16 ± 10 (1-36)	21 ± 8 (5-37)	23 ± 3 (17-29)	25 ± 9 (11-39)
PV Ar duration (ms)	66 ± 39 (1-144)	96 ± 33 (30-162)	112 ± 15 (82-142)	113 ± 30 (53-173)
Septal e' (cm/s)	14.9 ± 2.4 (10.1-19.7)	15.5 ± 2.7 (10.1-20.9)	12.2 ± 2.3 (7.6-16.8)	10.4 ± 2.1 (6.2-14.6)
Septal e'/a' ratio	2.4*	1.6 ± 0.5 (0.6-2.6)	1.1 ± 0.3 (0.5-1.7)	0.85 ± 0.2 (0.45-1.25)
Lateral e' (cm/s)	20.6 ± 3.8 (13-28.2)	19.8 ± 2.9 (14-25.6)	16.1 ± 2.3 (11.5-20.7)	12.9 ± 3.5 (5.9-19.9)
Lateral e'/a' ratio	3.1*	1.9 ± 0.6 (0.7-3.1)	1.5 ± 0.5 (0.5-2.5)	0.9 ± 0.4 (0.1-1.7)

Data are expressed as mean ± SD (95% confidence interval). Note that for e' velocity in subjects aged 16 to 20 years, values overlap with those for subjects aged 21 to 40 years. This is because e' increases progressively with age in children and adolescents. Therefore, the e' velocity is higher in a normal 20-year-old than in a normal 16-year-old, which results in a somewhat lower average e' value when subjects aged 16 to 20 years are considered.

*Standard deviations are not included because these data were computed, not directly provided in the original articles from which they were derived.

**Figure 5** Schematic diagram of the changes in mitral inflow in response to the transmitral pressure gradient.

while a short IVRT, short mitral DT, and increased E/A velocity ratio characterize advanced diastolic dysfunction, increased LA pressure, and worse functional class. A restrictive filling pattern is associated with a poor prognosis, especially if it persists after preload reduction. Likewise, a pseudonormal or restrictive filling pattern associated with acute myocardial infarction indicates an increased risk for heart failure, unfavorable LV remodeling, and increased cardiovascular mortality, irrespective of EF.

In patients with coronary artery disease⁴⁸ or hypertrophic cardiomyopathy,^{49,50} in whom LV EFs are ≥50%, mitral variables correlate poorly with hemodynamics. This may be related to the marked variation in the extent of delayed LV relaxation seen in these patients, which may produce variable transmitral pressure gradients for similar LA pressures. A restrictive filling pattern and LA enlargement in a patient with a normal EF are associated with a poor prognosis similar to that of a restrictive pattern in dilated cardiomyopathy. This is most commonly seen in restrictive cardiomyopathies, especially amyloidosis,^{51,52} and in heart transplant recipients.⁵³

F. Limitations

LV filling patterns have a U-shaped relation with LV diastolic function, with similar values seen in healthy normal subjects and patients with cardiac disease. Although this distinction is not an issue when reduced LV systolic function is present, the problem of recognizing PNF and diastolic heart failure in patients with normal EFs was the main impetus for developing the multiple ancillary measures to assess diastolic function discussed in subsequent sections. Other factors that make mitral variables more difficult to interpret are sinus tachycardia,⁵⁴ conduction system disease, and arrhythmias.

Sinus tachycardia and first-degree AV block can result in partial or complete fusion of the mitral E and A waves. If mitral flow velocity at the start of atrial contraction is >20 cm/s, mitral A-wave velocity may be increased, which reduces the E/A ratio. With partial E-wave and A-wave fusion, mitral DT may not be measurable, although IVRT should be unaffected. With atrial flutter, LV filling is heavily influenced by the rapid atrial contractions, so that no E velocity, E/A ratio, or DT is available for measurement. If 3:1 or 4:1 AV block is present, multiple atrial filling waves are seen, with diastolic mitral regurgitation (MR) interspersed between nonconducted atrial beats.⁵⁵ In these cases, PA pressures calculated from Doppler TR and PR velocities may be the best indicators of increased LV filling pressures when lung disease is absent.

Key Points

1. PW Doppler is performed in the apical 4-chamber view to obtain mitral inflow velocities to assess LV filling.
2. A 1-mm to 3-mm sample volume is then placed between the mitral leaflet tips during diastole to record a crisp velocity profile.
3. Primary measurements include peak E and A velocities, E/A ratio, DT, and IVRT.
4. Mitral inflow patterns include normal, impaired LV relaxation, PNF, and restrictive LV filling.
5. In patients with dilated cardiomyopathies, filling patterns correlate better with filling pressures, functional class, and prognosis than LV EF.
6. In patients with coronary artery disease and those with hypertrophic cardiomyopathy in whom the LV EFs are ≥50%, mitral velocities correlate poorly with hemodynamics.

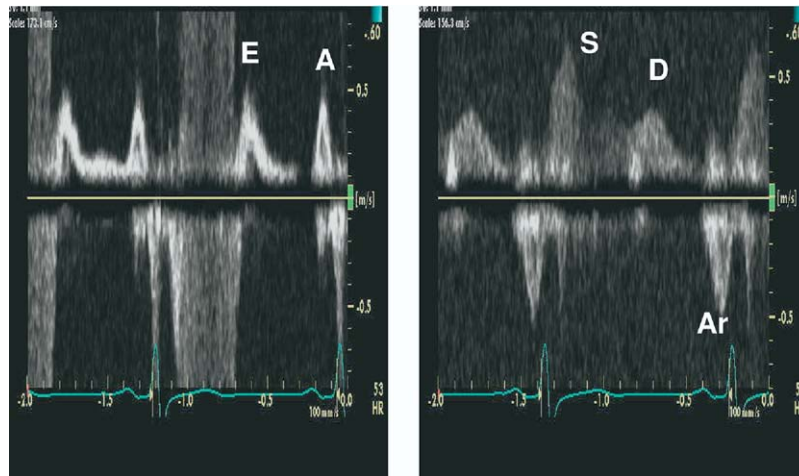


Figure 6 Recording of mitral inflow at the level of the annulus (*left*) and pulmonary venous flow (*right*) from a patient with increased LVEDP. Notice the markedly increased pulmonary venous Ar velocity at 50 cm/s and its prolonged duration at >200 ms in comparison with mitral A (late diastolic) velocity. Mitral A duration is best recorded at the level of the annulus.²²

IV. VALSALVA MANEUVER

A. Performance and Acquisition

The Valsalva maneuver is performed by forceful expiration (about 40 mm Hg) against a closed nose and mouth, producing a complex hemodynamic process involving 4 phases.⁵⁶ LV preload is reduced during the strain phase (phase II), and changes in mitral inflow are observed to distinguish normal from PNF patterns. The patient must generate a sufficient increase in intrathoracic pressure, and the sonographer needs to maintain the correct sample volume location between the mitral leaflet tips during the maneuver. A decrease of 20 cm/s in mitral peak E velocity is usually considered an adequate effort in patients without restrictive filling.

B. Clinical Application

A pseudonormal mitral inflow pattern is caused by a mild to moderate increase in LA pressure in the setting of delayed myocardial relaxation. Because the Valsalva maneuver decreases preload during the strain phase, pseudonormal mitral inflow changes to a pattern of impaired relaxation. Hence, mitral E velocity decreases with a prolongation of DT, whereas the A velocity is unchanged or increases, such that the E/A ratio decreases.⁵⁷ On the other hand, with a normal mitral inflow velocity pattern, both E and A velocities decrease proportionately, with an unchanged E/A ratio. When computing the E/A ratio with Valsalva, the absolute A velocity (peak A minus the height of E at the onset of A) should be used. In cardiac patients, a decrease of $\geq 50\%$ in the E/A ratio is highly specific for increased LV filling pressures,⁵⁷ but a smaller magnitude of change does not always indicate normal diastolic function. Furthermore, the lack of reversibility with Valsalva is imperfect as an indicator that the diastolic filling pattern is irreversible.

C. Limitations

One major limitation of the Valsalva maneuver is that not everyone is able to perform this maneuver adequately, and it is not standardized. Its clinical value in distinguishing normal from pseudonormal mitral inflow has diminished since the introduction of tissue Doppler recordings of the mitral annulus to assess the status of LV relaxation and estimate filling pressures more quantitatively and easily. In a busy clinical laboratory, the Valsalva maneuver can be reserved for patients

in whom diastolic function assessment is not clear after mitral inflow and annular velocity measurements.

Key Points

1. The Valsalva maneuver is performed by forceful expiration (about 40 mm Hg) against a closed nose and mouth, producing a complex hemodynamic process involving 4 phases.
2. In cardiac patients, a decrease of $\geq 50\%$ in the E/A ratio is highly specific for increased LV filling pressures,⁵⁷ but a smaller magnitude of change does not always indicate normal diastolic function.

V. PULMONARY VENOUS FLOW

A. Acquisition and Feasibility

PW Doppler of pulmonary venous flow is performed in the apical 4-chamber view and aids in the assessment of LV diastolic function.²² Color flow imaging is useful for the proper location of the sample volume in the right upper pulmonary vein. In most patients, the best Doppler recordings are obtained by angulating the transducer superiorly such that the aortic valve is seen. A 2-mm to 3-mm sample volume is placed >0.5 cm into the pulmonary vein for optimal recording of the spectral waveforms. Wall filter settings must be low enough to display the onset and cessation of the atrial reversal (Ar) velocity waveform. Pulmonary venous flow can be obtained in >80% of ambulatory patients,⁵⁸ though the feasibility is much lower in the intensive care unit setting. The major technical problem is LA wall motion artifacts, caused by atrial contraction, which interferes with the accurate display of Ar velocity. It is recommended that spectral recordings be obtained at a sweep speed of 50 to 100 mm/s at end-expiration and that measurements include the average of ≥ 3 consecutive cardiac cycles.

B. Measurements

Measurements of pulmonary venous waveforms include peak systolic (S) velocity, peak anterograde diastolic (D) velocity, the S/D ratio, systolic filling fraction ($S_{\text{time-velocity integral}} / [S_{\text{time-velocity integral}} + D_{\text{time-velocity integral}}]$), and the peak Ar velocity in late diastole. Other measurements are the duration of the Ar velocity, the time difference between it and mitral A-wave duration (Ar – A); and D velocity DT. There are two systolic velocities (S1 and S2), mostly

noticeable when there is a prolonged PR interval, because S1 is related to atrial relaxation. S2 should be used to compute the ratio of peak systolic to peak diastolic velocity.

C. Hemodynamic Determinants

S1 velocity is primarily influenced by changes in LA pressure and LA contraction and relaxation,^{59,60} whereas S2 is related to stroke volume and pulse-wave propagation in the PA tree.^{59,60} D velocity is influenced by changes in LV filling and compliance and changes in parallel with mitral E velocity.⁶¹ Pulmonary venous Ar velocity and duration are influenced by LV late diastolic pressures, atrial preload, and LA contractility.⁶² A decrease in LA compliance and an increase in LA pressure decrease the S velocity and increase the D velocity, resulting in an S/D ratio < 1, a systolic filling fraction < 40%,⁶³ and a shortening of the DT of D velocity, usually < 150 ms.⁶⁴

With increased LVEDP, Ar velocity and duration increase (Figure 6), as well as the time difference between Ar duration and mitral A-wave duration.^{48,65,66} Atrial fibrillation results in a blunted S wave and the absence of Ar velocity.

D. Normal Values

Pulmonary venous inflow velocities are influenced by age (Table 1). Normal young subjects aged < 40 years usually have prominent D velocities, reflecting their mitral E waves. With increasing age, the S/D ratio increases. In normal subjects, Ar velocities can increase with age but usually do not exceed 35 cm/s. Higher values suggest increased LVEDP.⁶⁷

E. Clinical Application to Patients With Depressed and Normal EFs

In patients with depressed EFs, a reduced systolic fraction of antero-grade flow (< 40%) is related to decreased LA compliance and increased mean LA pressure. This observation has limited accuracy in patients with EFs > 50%,⁴⁸ atrial fibrillation,⁶⁸ mitral valve disease,⁶⁹ and hypertrophic cardiomyopathy.⁵⁰

On the other hand, the Ar – A duration difference is particularly useful because it is the only age-independent indication of LV A-wave pressure increase⁶⁷ and can separate patients with abnormal LV relaxation into those with normal filling pressures and those with elevated LVEDPs but normal mean LA pressures. This isolated increase in LVEDP is the first hemodynamic abnormality seen with diastolic dysfunction. Other Doppler echocardiographic variables, such as maximal LA size, mitral DT, and pseudonormal filling, all indicate an increase in mean LA pressure and a more advanced stage of diastolic dysfunction. In addition, the Ar – A duration difference remains accurate in patients with normal EFs,⁴⁸ mitral valve disease,⁷⁰ and hypertrophic cardiomyopathy.⁵⁰ In summary, an Ar – A velocity duration > 30 ms indicates an elevated LVEDP. Unlike mitral inflow velocities, few studies have shown the prognostic role of pulmonary venous flow.^{71–73}

F. Limitations

One of the important limitations in interpreting pulmonary venous flow is the difficulty in obtaining high-quality recordings suitable for measurements. This is especially true for Ar velocity, for which atrial contraction can create low-velocity wall motion artifacts that obscure the pulmonary flow velocity signal. Sinus tachycardia and first-degree AV block often result in the start of atrial contraction occurring before diastolic mitral and pulmonary venous flow velocity has declined to the zero baseline. This increases the width of the mitral A-wave

Flow Propagation Velocity: Vp

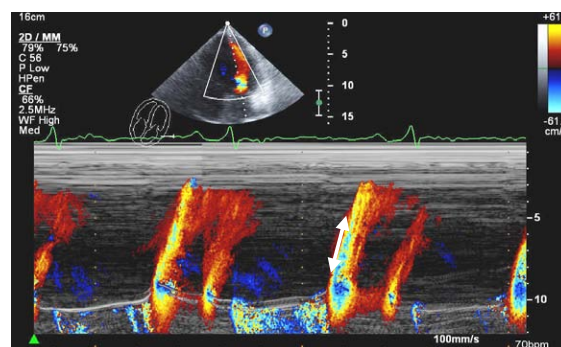


Figure 7 Color M-mode Vp from a patient with depressed EF and impaired LV relaxation. The slope (arrow) was 39 cm/s.

velocity and decreases that of the reversal in the pulmonary vein, making the Ar-A relationship difficult to interpret for assessing LV A-wave pressure increase. With atrial fibrillation, the loss of atrial contraction and relaxation reduces pulmonary venous systolic flow regardless of filling pressures. With a first-degree AV block of ≥ 300 ms, flow into the left atrium with its relaxation (S1) cannot be separated from later systolic flow (S2), or can even occur in diastole.

Key Points

1. PW Doppler of pulmonary venous flow is performed in the apical 4-chamber view and aids in the assessment of LV diastolic function.
2. A 2-mm to 3-mm sample volume is placed > 0.5 cm into the pulmonary vein for optimal recording of the spectral waveforms.
3. Measurements include peak S and D velocities, the S/D ratio, systolic filling fraction, and peak Ar velocity in late diastole. Another measurement is the time difference between Ar duration and mitral A-wave duration (Ar – A).
4. With increased LVEDP, Ar velocity and duration increase, as well as the Ar – A duration.
5. In patients with depressed EFs, reduced systolic filling fractions (< 40%) are related to decreased LA compliance and increased mean LA pressure.

VI. COLOR M-MODE FLOW PROPAGATION VELOCITY

A. Acquisition, Feasibility, and Measurement

The most widely used approach for measuring mitral-to-apical flow propagation is the slope method.^{74,75} The slope method (Figure 7) appears to have the least variability.⁷⁶ Acquisition is performed in the apical 4-chamber view, using color flow imaging with a narrow color sector, and gain is adjusted to avoid noise. The M-mode scan line is placed through the center of the LV inflow blood column from the mitral valve to the apex. Then the color flow baseline is shifted to lower the Nyquist limit so that the central highest velocity jet is blue. Flow propagation velocity (Vp) is measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity.⁷⁵ Alternatively, the slope of the transition from no color to color is measured.⁷⁴ Vp > 50 cm/s is considered normal.^{75,77} It is also possible to estimate the mitral-to-apical pressure gradient noninvasively by color M-mode Doppler by taking into account inertial forces,^{78,79} but this approach is complicated and not yet feasible for routine clinical application.

B. Hemodynamic Determinants

Similar to transmitral filling, normal LV intracavitary filling is dominated by an early wave and an atrial-induced filling wave. Most of the

attention has been on the early diastolic filling wave, because it changes markedly during delayed relaxation with myocardial ischemia and LV failure. In the normal ventricle, the early filling wave propagates rapidly toward the apex and is driven by a pressure gradient between the LV base and the apex.⁸⁰ This gradient represents a suction force and has been attributed to LV restoring forces and LV relaxation. During heart failure and during myocardial ischemia, there is slowing of mitral-to-apical flow propagation, consistent with a reduction of apical suction.^{74,81,82} However, evaluation and interpretation of intraventricular filling in clinical practice is complicated by the multitude of variables that determine intraventricular flow. Not only driving pressure, inertial forces, and viscous friction but geometry, systolic function, and contractile dyssynchrony play major roles.^{83,84} Furthermore, flow occurs in multiple and rapidly changing directions, forming complex vortex patterns. The slow mitral-to-apical flow propagation in a failing ventricle is in part attributed to ring vortices that move slowly toward the apex.⁷⁹ In these settings, the relationship between mitral-to-apical Vp and the intraventricular pressure gradient is more complicated. The complexity of intraventricular flow and the limitations of current imaging techniques make it difficult to relate intraventricular flow patterns to LV myocardial function in a quantitative manner.

C. Clinical Application

There is a well-defined intraventricular flow disturbance that has proved to be a semiquantitative marker of LV diastolic dysfunction, that is, the slowing of mitral-to-apical flow propagation measured by color M-mode Doppler. In addition, it is possible to use Vp in conjunction with mitral E to predict LV filling pressures.

Studies in patients have shown that the ratio of peak E velocity to Vp is directly proportional to LA pressure, and therefore, E/Vp can be used to predict LV filling pressures by itself⁷⁵ and in combination with IVRT.⁸⁵ In most patients with depressed EFs, multiple echocardiographic signs of impaired LV diastolic function are present, and Vp is often redundant as a means to identify diastolic dysfunction. However, in this population, should other Doppler indices appear inconclusive, Vp can provide useful information for the prediction of LV filling pressures, and E/Vp ≥ 2.5 predicts PCWP > 15 mm Hg with reasonable accuracy.⁸⁶

D. Limitations

Caution should be exercised when using the E/Vp ratio for the prediction of LV filling pressures in patients with normal EFs.⁸⁶ In particular, patients with normal LV volumes and EFs but abnormal filling pressures can have a misleadingly normal Vp.^{83,84,86} In addition, there are reports showing a positive influence of preload on Vp in patients with normal EFs⁸⁷ as well as those with depressed EFs.⁸⁸

Key Points

1. Acquisition is performed in the apical 4-chamber view, using color flow imaging.
2. The M-mode scan line is placed through the center of the LV inflow blood column from the mitral valve to the apex, with baseline shift to lower the Nyquist limit so that the central highest velocity jet is blue.
3. Vp is measured as the slope of the first aliasing velocity during early filling, measured from the mitral valve plane to 4 cm distally into the LV cavity, or the slope of the transition from no color to color.
4. Vp > 50 cm/s is considered normal.
5. In most patients with depressed EFs, Vp is reduced, and should other Doppler indices appear inconclusive, an E/Vp ratio ≥ 2.5 predicts PCWP > 15 mm Hg with reasonable accuracy.

6. Patients with normal LV volumes and EFs but elevated filling pressures can have misleadingly normal Vp.

VII. TISSUE DOPPLER ANNULAR EARLY AND LATE DIASTOLIC VELOCITIES

A. Acquisition and Feasibility

PW tissue Doppler imaging (DTI) is performed in the apical views to acquire mitral annular velocities.⁸⁹ Although annular velocities can also be obtained by color-coded DTI, this method is not recommended, because the validation studies were performed using PW Doppler. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5-10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Attention should be directed to Doppler spectral gain settings, because annular velocities have high signal amplitude. Most current ultrasound systems have tissue Doppler presets for the proper velocity scale and Doppler wall filter settings to display the annular velocities. In general, the velocity scale should be set at about 20 cm/s above and below the zero-velocity baseline, though lower settings may be needed when there is severe LV dysfunction and annular velocities are markedly reduced (scale set to 10-15 cm/s). Minimal angulation ($<20^\circ$) should be present between the ultrasound beam and the plane of cardiac motion. DTI waveforms can be obtained in nearly all patients ($>95\%$), regardless of 2D image quality. It is recommended that spectral recordings be obtained at a sweep speed of 50 to 100 mm/s at end-expiration and that measurements should reflect the average of ≥ 3 consecutive cardiac cycles.

B. Measurements

Primary measurements include the systolic (S), early diastolic, and late diastolic velocities.⁹⁰ The early diastolic annular velocity has been expressed as Ea, Em, E', or e', and the late diastolic velocity as Aa, Am, A', or a'. The writing group favors the use of e' and a', because Ea is commonly used to refer to arterial elastance. The measurement of e' acceleration and DT intervals, as well as acceleration and deceleration rates, does not appear to contain incremental information to peak velocity alone⁹¹ and need not be performed routinely. On the other hand, the time interval between the QRS complex and e' onset is prolonged with impaired LV relaxation and can provide incremental information in special patient populations (see the following). For the assessment of global LV diastolic function, it is recommended to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and their average, given the influence of regional function on these velocities and time intervals.^{86,92}

Once mitral flow, annular velocities, and time intervals are acquired, it is possible to compute additional time intervals and ratios. The ratios include annular e'/a' and the mitral inflow E velocity to tissue Doppler e' (E/e') ratio.⁹⁰ The latter ratio plays an important role in the estimation of LV filling pressures. For time intervals, the time interval between the QRS complex and the onset of mitral E velocity is subtracted from the time interval between the QRS complex and e' onset to derive ($T_{E-e'}$), which can provide incremental information to E/e' in special populations, as outlined in the following discussion. Technically, it is important to match the RR intervals for measuring both time intervals (time to E and time to e') and to optimize gain and filter settings, because higher gain and filters can preclude the correct identification of the onset of e' velocity.

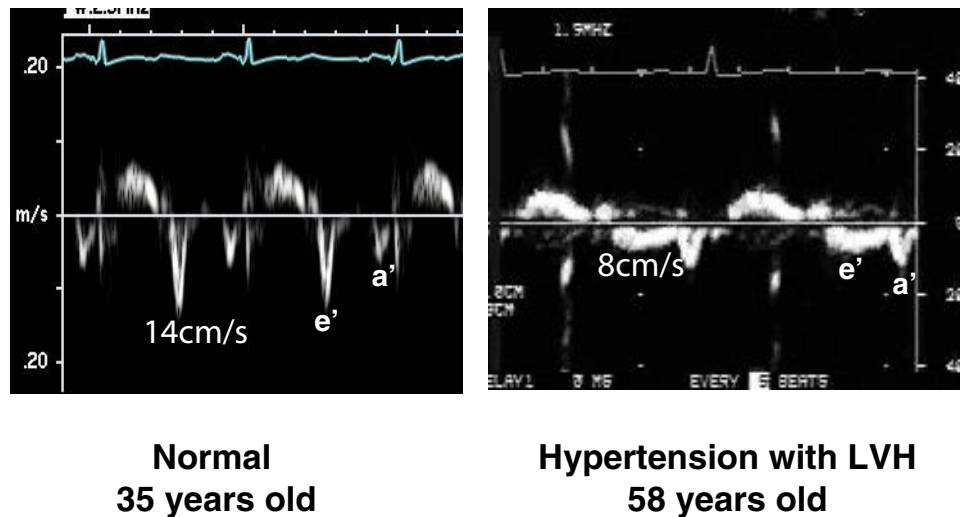


Figure 8 Tissue Doppler (TD) recording from the lateral mitral annulus from a normal subject aged 35 years (*left*) ($e' = 14$ cm/s) and a 58-year-old patient with hypertension, LV hypertrophy, and impaired LV relaxation (*right*) ($e' = 8$ cm/s).

Mitral Inflow and Annulus TD

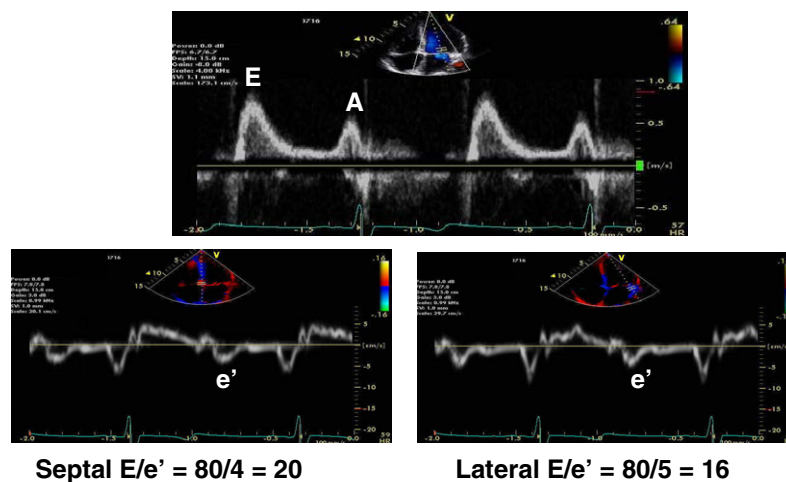


Figure 9 Mitral inflow (*top*), septal (*bottom left*), and lateral (*bottom right*) tissue Doppler signals from a 60-year-old patient with heart failure and normal EF. The E/e' ratio was markedly increased, using e' from either side of the annulus.

C. Hemodynamic Determinants

The hemodynamic determinants of e' velocity include LV relaxation (Figure 8), preload, systolic function, and LV minimal pressure. A significant association between e' and LV relaxation was observed in animal^{93,94} and human⁹⁵⁻⁹⁷ studies. For preload, LV filling pressures have a minimal effect on e' in the presence of impaired LV relaxation.^{87,93,94} On the other hand, with normal or enhanced LV relaxation, preload increases e' .^{93,94,98,99} Therefore, in patients with cardiac disease, e' velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and the E/e' ratio can be applied for the prediction of LV filling pressures (Figure 9). The main hemodynamic determinants of a' include LA systolic function and LVEDP, such that an increase in LA contractility leads to increased a' velocity, whereas an increase in LVEDP leads to a decrease in a' .⁹³

In the presence of impaired LV relaxation and irrespective of LA pressure, the e' velocity is reduced and delayed, such that it occurs at

the LA-LV pressure crossover point.^{94,100} On the other hand, mitral E velocity occurs earlier with PNF or restrictive LV filling. Accordingly, the time interval between the onset of E and e' is prolonged with diastolic dysfunction. Animal^{94,100} and human¹⁰⁰ studies have shown that ($T_{E-e'}$) is strongly dependent on the time constant of LV relaxation and LV minimal pressure.¹⁰⁰

D. Normal Values

Normal values (Table 1) of DTI-derived velocities are influenced by age, similar to other indices of LV diastolic function. With age, e' velocity decreases, whereas a' velocity and the E/e' ratio increase.¹⁰¹

E. Clinical Application

Mitral annular velocities can be used to draw inferences about LV relaxation and along with mitral peak E velocity (E/e' ratio) can be used to predict LV filling pressures.^{86,90,97,102-106} To arrive at reliable

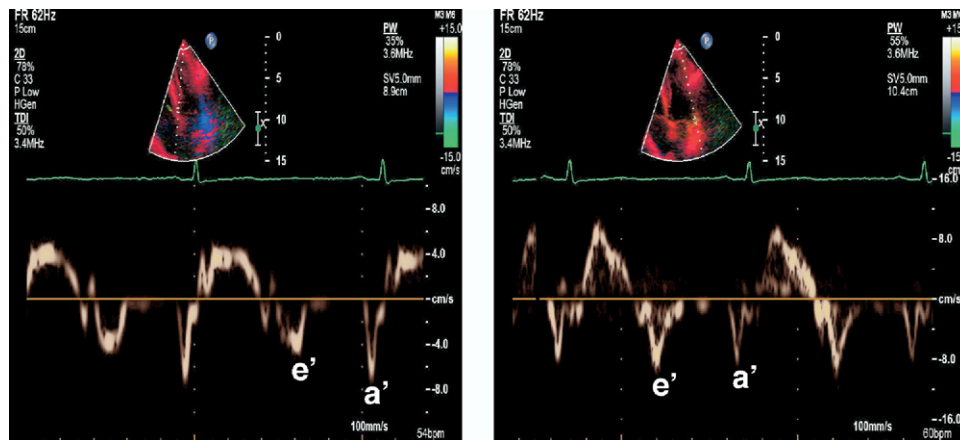


Figure 10 Septal (*left*) and lateral (*right*) tissue Doppler recordings from a patient with an anteroseptal myocardial infarction. Notice the difference between septal e' (5 cm/s) and lateral e' (10 cm/s). It is imperative to use the average of septal and lateral e' velocities in such patients to arrive at more reliable assessments of LV relaxation and filling pressures.

conclusions, it is important to take into consideration the age of a given patient, the presence or absence of cardiovascular disease, and other abnormalities noted in the echocardiogram. Therefore, e' and the E/e' ratio are important variables but should not be used as the sole data in drawing conclusions about LV diastolic function.

It is preferable to use the average e' velocity obtained from the septal and lateral sides of the mitral annulus for the prediction of LV filling pressures. Because septal e' is usually lower than lateral e' velocity, the E/e' ratio using septal signals is usually higher than the ratio derived by lateral e' , and different cutoff values should be applied on the basis of LV EF, as well as e' location. Although single-site measurements are sometimes used in patients with globally normal or abnormal LV systolic function, it is imperative to use the average (septal and lateral) e' velocity (Figure 10) in the presence of regional dysfunction.⁸⁶ Additionally, it is useful to consider the range in which the ratio falls. Using the septal E/e' ratio, a ratio < 8 is usually associated with normal LV filling pressures, whereas a ratio > 15 is associated with increased filling pressures.⁹⁷ When the value is between 8 and 15, other echocardiographic indices should be used. A number of recent studies have noted that in patients with normal EFs, lateral tissue Doppler signals (E/e' and e'/a') have the best correlations with LV filling pressures and invasive indices of LV stiffness.^{86,106} These studies favor the use of lateral tissue Doppler signals in this population.

$T_{E-e'}$ is particularly useful in situations in which the peak e' velocity has its limitations, and the average of 4 annular sites is more accurate than a single site measurement¹⁰⁰ for this time interval. The clinical settings in which it becomes advantageous to use it include subjects with normal cardiac function¹⁰⁰ or those with mitral valve disease⁶⁹ and when the E/e' ratio is 8 to 15.¹⁰⁷ In particular, an $IVRT/T_{E-e'}$ ratio < 2 has reasonable accuracy in identifying patients with increased LV filling pressures.¹⁰⁰

F. Limitations

There are both technical and clinical limitations. For technical limitations, proper attention to the location of the sample size, as well as gain, filter, and minimal angulation with annular motion, is essential for reliable velocity measurements. With experience, these are highly reproducible with low variability. Because time interval measurements are performed from different cardiac cycles, additional vari-

ability is introduced. This limits their application to selective clinical settings in which other Doppler measurements are not reliable.

There are a number of clinical settings in which annular velocity measurements and the E/e' ratio should not be used. In normal subjects, e' velocity is positively related to preload,⁹⁸ and the E/e' ratio may not provide a reliable estimate of filling pressures. These individuals can be recognized by history, normal cardiac structure and function, and the earlier (or simultaneous) onset of annular e' in comparison with mitral E velocity.¹⁰⁰ Additionally, e' velocity is usually reduced in patients with significant annular calcification, surgical rings, mitral stenosis, and prosthetic mitral valves. It is increased in patients with moderate to severe primary MR and normal LV relaxation due to increased flow across the regurgitant valve. In these patients, the E/e' ratio should not be used, but the $IVRT/T_{E-e'}$ ratio can be applied.⁶⁹

Patients with constrictive pericarditis usually have increased septal e' , due largely to preserved LV longitudinal expansion compensating for the limited lateral and anteroposterior diastolic excursion. Lateral e' may be less than septal e' in this condition, and the E/e' ratio was shown to relate inversely to LV filling pressures or annulus paradoxus.¹⁰⁸

Key Points

1. PW DTI is performed in the apical views to acquire mitral annular velocities.
2. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets.
3. It is recommended that spectral recordings be obtained at a sweep speed of 50 to 100 mm/s at end-expiration and that measurements should reflect the average of ≥ 3 consecutive cardiac cycles.
4. Primary measurements include the systolic and early (e') and late (a') diastolic velocities.
5. For the assessment of global LV diastolic function, it is recommended to acquire and measure tissue Doppler signals at least at the septal and lateral sides of the mitral annulus and their average.
6. In patients with cardiac disease, e' can be used to correct for the effect of LV relaxation on mitral E velocity, and the E/e' ratio can be applied for the prediction of LV filling pressures.
7. The E/e' ratio is not accurate as an index of filling pressures in normal subjects or in patients with heavy annular calcification, mitral valve disease, and constrictive pericarditis.

VIII. DEFORMATION MEASUREMENTS

Strain means deformation and can be calculated using different formulas. In clinical cardiology, strain is most often expressed as a percentage or fractional strain (Lagrangian strain). Systolic strain represents percentage shortening when measurements are done in the long axis and percentage radial thickening in the short axis. Systolic strain rate represents the rate or speed of myocardial shortening or thickening, respectively. Myocardial strain and strain rate are excellent parameters for the quantification of regional contractility and may also provide important information in the evaluation of diastolic function.

During the heart cycle, the LV myocardium goes through a complex 3-dimensional deformation that leads to multiple shear strains, when one border is displaced relative to another. However, this comprehensive assessment is not currently possible by echocardiography. By convention, lengthening and thickening strains are assigned positive values and shortening and thinning strains negative values.

Until recently, the only clinical method to measure myocardial strain has been magnetic resonance imaging with tissue tagging, but complexity and cost limit this methodology to research protocols. Tissue Doppler-based myocardial strain has been introduced as a bedside clinical method and has undergone comprehensive evaluation for the assessment of regional systolic function.^{109,110} Strain may also be measured by 2D speckle-tracking echocardiography, an emerging technology that measures strain by tracking speckles in grayscale echocardiographic images.^{111,112} The speckles function as natural acoustic markers that can be tracked from frame to frame, and velocity and strain are obtained by automated measurement of distance between speckles. The methodology is angle independent; therefore, measurements can be obtained simultaneously from multiple regions within an image plane. This is in contrast to tissue Doppler-based strain, which is very sensitive to misalignment between the cardiac axis and the ultrasound beam. Problems with tissue Doppler-based strain include significant signal noise and signal drifting. Speckle-tracking echocardiography is limited by relatively lower frame rates.

A number of studies suggest that myocardial strain and strain rate may provide unique information regarding diastolic function. This includes the quantification of postsystolic myocardial strain as a measure of postejection shortening in ischemic myocardium¹¹³ and regional diastolic strain rate, which can be used to evaluate diastolic stiffness during stunning and infarction.^{114,115} There is evidence in an animal model that segmental early diastolic strain rate correlates with the degree of interstitial fibrosis.¹¹⁵ Similarly, regional differences in the timing of transition from myocardial contraction to relaxation with strain rate imaging can identify ischemic segments.¹¹⁶

Few studies have shown a significant relation between segmental¹¹⁷ and global¹¹⁸ early diastolic strain rate and the time constant of LV relaxation. Furthermore, a recent study that combined global myocardial strain rate during the isovolumetric relaxation period (by speckle tracking) and transmitral flow velocities showed that the mitral E velocity/global myocardial strain rate ratio predicted LV filling pressure in patients in whom the E/e' ratio was inconclusive and was more accurate than E/e' in patients with normal EFs and those with regional dysfunction.¹¹⁸ Therefore, the evaluation of diastolic function by deformation imaging is promising but needs more study of its incremental clinical value. Currently, Doppler flow velocity and myocardial velocity imaging

are the preferred initial echocardiographic methodologies for assessing LV diastolic function.

IX. LEFT VENTRICULAR UNTWISTING

LV twisting motion (torsion) is due to contraction of obliquely oriented fibers in the subepicardium, which course toward the apex in a counterclockwise spiral. The moments of the subepicardial fibers dominate over the subendocardial fibers, which form a spiral in opposite direction. Therefore, when viewed from apex toward the base, the LV apex shows systolic counterclockwise rotation and the LV base shows a net clockwise rotation. Untwisting starts in late systole but mostly occurs during the isovolumetric relaxation period and is largely finished at the time of mitral valve opening.¹¹⁹ Diastolic untwist represents elastic recoil due to the release of restoring forces that have been generated during the preceding systole. The rate of untwisting is often referred to as the recoil rate. LV twist appears to play an important role for normal systolic function, and diastolic untwisting contributes to LV filling through suction generation.^{119,120} It has been assumed that the reduction in LV untwisting with attenuation or loss of diastolic suction contributes to diastolic dysfunction in diseased hearts.¹²⁰⁻¹²³ Diastolic dysfunction associated with normal aging, however, does not appear to be due to a reduction in diastolic untwist.¹²⁴

A. Clinical Application

Because the measurement of LV twist has been possible only with tagged magnetic resonance imaging and other complex methodologies, there is currently limited insight into how the quantification of LV twist, untwist, and rotation can be applied in clinical practice.¹²⁰⁻¹²⁶ With the recent introduction of speckle-tracking echocardiography, it is feasible to quantify LV rotation, twist, untwist clinically.^{127,128} LV twist is calculated as the difference between basal and apical rotation measured in LV short-axis images. To measure basal rotation, the image plane is placed just distal to the mitral annulus and for apical rotation just proximal to the level with luminal closure at end-systole. The clinical value of assessing LV untwisting rate is not defined. When LV twist and untwisting rate were assessed in patients with diastolic dysfunction or diastolic heart failure, both twist and untwisting rate were preserved,^{129,130} and no significant relation was noted with the time constant of LV relaxation.¹²⁹ On the other hand, in patients with depressed EFs, these measurements were abnormally reduced. In an animal model, and in both groups of heart failure, the strongest association was observed with LV end-systolic volume and twist,¹²⁹ suggesting that LV untwisting rate best reflects the link between systolic compression and early diastolic recoil.

In conclusion, measurements of LV twist and untwisting rate, although not currently recommended for routine clinical use and although additional studies are needed to define their potential clinical application, may become an important element of diastolic function evaluation in the future.

B. Limitations

The selection of image plane is a challenge, and further clinical testing of speckle-tracking echocardiography in patients is needed to determine whether reproducible measurements can be obtained from ventricles with different geometries. Speckle tracking can be suboptimal at the LV base, thus introducing significant variability in the measurements.¹²⁸

X. ESTIMATION OF LEFT VENTRICULAR RELAXATION

A. Direct Estimation

1. IVRT. When myocardial relaxation is impaired, LV pressure falls slowly during the isovolumic relaxation period, which results in a longer time before it drops below LA pressure. Therefore, mitral valve opening is delayed, and IVRT is prolonged. IVRT is easily measured by Doppler echocardiography, as discussed in previous sections. However, IVRT by itself has limited accuracy, given the confounding influence of preload on it, which opposes the effect of impaired LV relaxation.

It is possible to combine IVRT with noninvasive estimates of LV end-systolic pressure and LA pressure to derive τ (IVRT/[ln LV end-systolic pressure – ln LA pressure]). This approach has been validated¹³¹ and can be used to provide a quantitative estimate of τ in place of a qualitative assessment of LV relaxation.

2. Aortic regurgitation CW signal. The instantaneous pressure gradient between the aorta and the left ventricle during diastole can be calculated from the CW Doppler aortic regurgitant velocity spectrum. Because the fluctuation of aortic pressure during IVRT is negligibly minor, and because LV minimal pressure is usually low, LV pressure during the IVRT period may be derived from the CW Doppler signal of the aortic regurgitation jet. The following hemodynamic measurements can be derived from the CW signal: mean and LVEDP gradients between the aorta and the left ventricle, dP/dt_{min} ($4V^2 \times 1,000/20$, where V is aortic regurgitation velocity in meters per second at 20 ms after the onset of regurgitation), and τ (the time interval between the onset of aortic regurgitation and the regurgitant velocity corresponding to $[1 - 1/e]^{1/2}$ of the maximal velocity). Tau calculation was validated in an animal study,¹³² but clinical experience is limited to only a few patients.¹³³

3. MR CW signal. Using the modified Bernoulli equation, the maximal and mean pressure gradients between the left ventricle and the left atrium can be determined by CW Doppler in patients with MR, which correlate well with simultaneously measured pressures by catheterization.¹³⁴ The equation to derive $-dP/dt_{min}$ is $-dP/dt_{min}$ (mm Hg/s) = $[4(V_{MR2})^2 - 4(V_{MR1})^2] \times 1,000/20$, where V_{MR1} and V_{MR2} are MR velocities (in meters per second) 20 ms apart. A simplified approach to calculate τ from the MR jet is τ = time interval between the point of $-dP/dt_{min}$ to the point at which the MR velocity = $(1/e)^{1/2}$ of the MR velocity at the time of $-dP/dt_{min}$. Given the presence of more simple methods to assess myocardial relaxation, both the aortic regurgitation and MR methods described above are rarely used in clinical practice.

Aside from the above-described calculations, it is of value to examine the morphology of the jets by CW Doppler. For MR, an early rise followed by a steep descent after peak velocity are consistent with a prominent “v”-wave pressure signal and elevated mean LA pressure. On the other hand, a rounded signal with slow ascent and descent supports the presence of LV systolic dysfunction and impaired relaxation. For aortic regurgitation, in the absence of significant aortic valve disease (in patients with mild aortic regurgitation), a rapid rate of decline of peak velocity and a short pressure half time are usually indicative of a rapid rise in LV diastolic pressure due to increased LV stiffness.

B. Surrogate Measurements

1. Mitral inflow velocities. When myocardial relaxation is markedly delayed, there is a reduction in the E/A ratio (<1) and a

prolongation of DT (>220 ms). In addition, in the presence of bradycardia, a characteristic low middiastolic (after early filling) mitral inflow velocity may be seen, due to a progressive fall in LV diastolic pressure related to slow LV relaxation. However, increased filling pressure can mask these changes in mitral velocities. Therefore, an E/A ratio < 1 and DT > 240 ms have high specificity for abnormal LV relaxation but can be seen with either normal or increased filling pressures, depending on how delayed LV relaxation is. Because impaired relaxation is the earliest abnormality in most cardiac diseases, it is expected in most, if not all, patients with diastolic dysfunction.

2. Tissue Doppler annular signals. Tissue Doppler e' is a more sensitive parameter for abnormal myocardial relaxation than mitral variables. Several studies in animals and humans demonstrated significant correlations between e' and τ (see previous discussion). Most patients with e' (lateral) < 8.5 cm/s or e' (septal) < 8 cm/s have impaired myocardial relaxation. However, for the most reliable conclusions, it is important to determine whether e' is less than the mean minus 2 standard deviations of the age group to which the patient belongs (see Table 1).

In the presence of impaired myocardial relaxation, the time interval $T_{E-e'}$ lengthens and correlates well with τ and LV minimal pressure. However, this approach has more variability than a single velocity measurement and is needed in few select clinical scenarios (see previous discussion).

3. Color M-Mode Vp. Normal Vp is ≥ 50 cm/s and correlates with the rate of myocardial relaxation. However, Vp can be increased in patients with normal LV volumes and EFs, despite impaired relaxation. Therefore, Vp is most reliable as an index of LV relaxation in patients with depressed EFs and dilated left ventricles. In the other patient groups, it is preferable to use other indices.

Key Points

1. IVRT by itself has limited accuracy, given the confounding influence of preload on it, which opposes the effect of impaired LV relaxation.
2. Most patients with e' (lateral) < 8.5 cm/s or e' (septal) < 8 cm/s have impaired myocardial relaxation.
3. Vp is most reliable as an index of LV relaxation in patients with depressed EFs and dilated left ventricles. In the other patient groups, it is preferable to use other indices.
4. For research purposes, mitral and aortic regurgitation signals by CW Doppler can be used to derive τ .

XI. ESTIMATION OF LEFT VENTRICULAR STIFFNESS

A. Direct estimation

Diastolic pressure-volume curves can be derived from simultaneous high-fidelity pressure recordings and mitral Doppler inflow, provided filling rates (multiplying on a point-to-point basis the Doppler curve by the diastolic annular mitral area) are integrated to obtain cumulative filling volumes and normalized to stroke volume by 2D imaging.^{135,136} Using this technique, the LV chamber stiffness constant can be computed. The estimation of end-diastolic compliance (the reciprocal of LV stiffness) from a single coordinate of pressure and volume is also feasible at end-diastole, using echocardiography to measure LV end-diastolic volume and to predict LVEDP, but this method can be misleading in patients with advanced diastolic dysfunction.

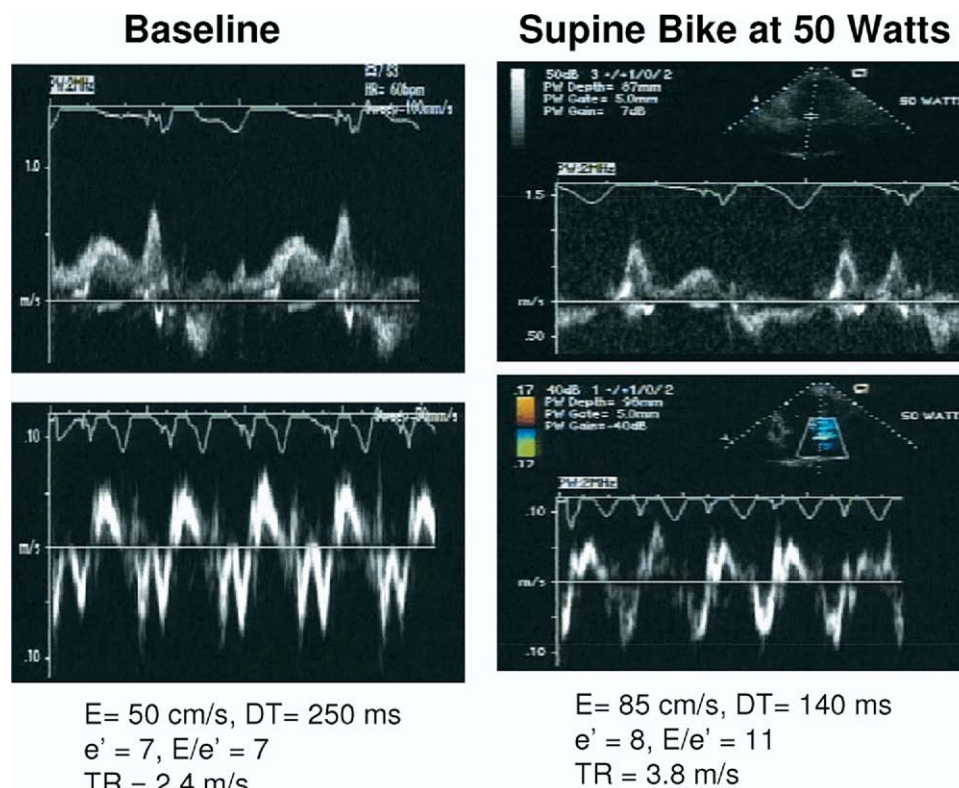


Figure 11 Exercise Doppler recordings from a patient with reduced diastolic reserve. At baseline, mitral inflow shows an impaired relaxation pattern, with an E/e' ratio of 7, and the peak velocity of the TR jet was 2.4 m/s (PA systolic pressure \geq 23 mm Hg). During supine bike exercise, mitral E velocity and the E/A ratio increase with shortening of DT. The E/e' ratio is now 11, and the PA systolic pressure is increased to \geq 58 mm Hg (TR peak velocity = 3.8 m/s).

Table 2 Changes in mitral and tissue Doppler septal velocities with exercise in normal subjects (mean age, 59 \pm 14 years)¹⁴⁵

Variable	Baseline	Exercise
E (cm/s)	73 \pm 19	90 \pm 25
A (cm/s)	69 \pm 17	87 \pm 22
DT (ms)	192 \pm 40	176 \pm 42
e' (cm/s)	12 \pm 4	15 \pm 5
E/e'	6.7 \pm 2.2	6.6 \pm 2.5

2. A-Wave transit time. LA contraction generates a pressure-velocity wave that enters the left ventricle. The wave moves through the inflow tract of the ventricle and reflects off the apex in the direction of the aortic valve. The time taken for the pressure-velocity wave to propagate through the ventricle, referred to as A-wave transit time, may be measured using PW Doppler echocardiography.¹⁴³ This time interval relates well to late diastolic stiffness (and LVEDP) measured by high-fidelity pressure catheters.^{143,144} The limitations to this approach include its dependence on Doppler sampling site, the stiffness of the containing system, and LV geometry.

B. Surrogate Measurements

1. DT of mitral E velocity. Patients with conditions associated with increased LV stiffness have more rapid rates of deceleration of early LV filling and shorter DTs.¹³⁷ Theoretical analysis predicts that with a relatively constant LA pressure during early LV filling, DT is proportional to the inverse square root of LV stiffness.¹³⁸ This assumption is supported by recent studies showing that LA stiffness does not change during the period of deceleration of early LV filling.¹³⁹ Experimental observations and limited data in humans have confirmed the theoretical predictions (stiffness [in millimeters of mercury per milliliter], calculated as $K_{LV} = [70\text{ms}/(\text{DT} - 20\text{ms})]^2$).^{140,141} To achieve greater accuracy, accounting for viscoelasticity and LV relaxation is needed.¹⁴² In summary, mitral DT is an important parameter that should be considered in drawing conclusions about operative LV stiffness, particularly in patients without marked slowing of LV relaxation.

XII. DIASTOLIC STRESS TEST

Many patients with diastolic dysfunction have symptoms, mainly with exertion, because of the rise in filling pressures that is needed to maintain adequate LV filling and stroke volume. Therefore, it is useful to evaluate LV filling pressure with exercise as well, similar to the use of exercise to evaluate patients with coronary artery or mitral valve disease. The E/e' ratio has been applied for that objective (Figure 11). In subjects with normal myocardial relaxation, E and e' velocities increase proportionally (Table 2), and the E/e' ratio remains unchanged or is reduced.¹⁴⁵ However, in patients with impaired myocardial relaxation, the increase in e' with exercise is much less than that of mitral E velocity, such that the E/e' ratio increases.¹⁴⁶ In that regard, E/e' was shown to relate significantly to LV filling pressures during exercise, when Doppler echocardiography was acquired simultaneously with cardiac catheterization.¹⁴⁷ In addition, mitral DT

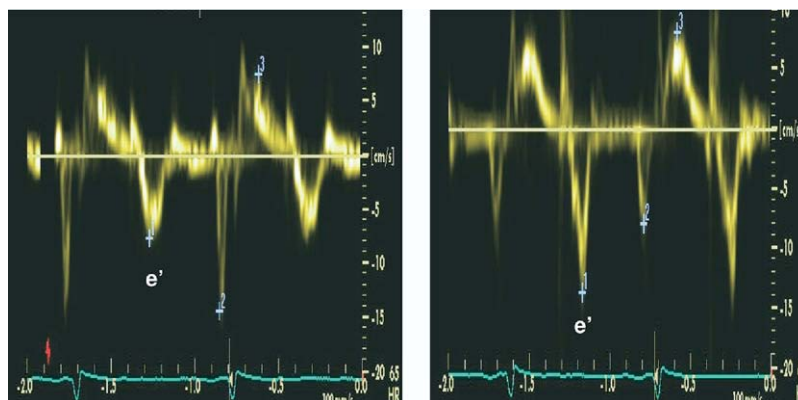


Figure 12 Lateral (*left*) and septal (*right*) TD velocities from a patient with constrictive pericarditis. Notice the higher septal e' at 14 cm/s in comparison with lateral e' at 8 cm/s. 1 = e' , 2 = a' , and 3 = systolic velocity.

decreases slightly in normal individuals with exercise, but shortens > 50 ms in patients with a marked elevation of filling pressures.

In cardiac patients, mitral E velocity increases with exertion and stays increased for a few minutes after the termination of exercise, whereas e' velocity remains reduced at baseline, exercise, and recovery. Therefore, E and e' velocities can be recorded after exercise, after 2D images have been obtained for wall motion analysis. Furthermore, the delayed recording of Doppler velocities avoids the merging of E and A velocities that occurs at faster heart rates. Exercise is usually performed using a supine bicycle protocol, and TR signals by CW Doppler are recorded as well to allow for the estimation of PA systolic pressure at rest and during exercise and recovery. Diastolic stress echocardiography has been also performed with dobutamine infusion, and restrictive filling with dobutamine was shown to provide prognostic information.¹⁴⁸

The test is most useful in patients with unexplained exertional dyspnea who have mild diastolic dysfunction and normal filling pressures at rest. However, the paucity of clinical data and the potential limitations in patients with regional LV dysfunction, mitral valve disease, and atrial fibrillation preclude recommendations for its routine clinical use at this time.

XIII. OTHER REASONS FOR HEART FAILURE SYMPTOMS IN PATIENTS WITH NORMAL EJECTION FRACTIONS

A. Pericardial Diseases

It is important to consider the possibility of constrictive pericarditis when evaluating patients with the clinical diagnosis of heart failure with normal EFs, because it is potentially curable. Because LV filling pressures are elevated in constrictive pericarditis, the mitral inflow velocity pattern resembles that of pseudonormal or restrictive filling, with $E/A > 1$ and short DT, although a subset may have mitral E velocity lower than A, especially during the inspiratory phase. In addition, typically, patients with constrictive pericarditis have respiratory variation in mitral E velocity: a $\geq 25\%$ increase with expiration.¹⁴⁹ However, up to 50% of patients with constrictive pericarditis demonstrate <25% respiratory variation in mitral E velocity. On the other hand, patients in respiratory distress, such as those with asthma, sleep apnea, chronic obstructive lung disease, and obesity, may show exaggerated respiratory variation in mitral E velocity due to increased swings in intrathoracic pressure. Recording hepatic venous flow is essential for the differential diagnosis and in establishing the presence

Table 3 Differentiation of constrictive pericarditis from restrictive cardiomyopathy

Variable	Restriction	Constriction
Septal motion	Normal	Respiratory shift
Mitral E/A ratio	>1.5	>1.5
Mitral DT (ms)	<160	<160
Mitral inflow respiratory variation	Absent	Usually present
Hepatic vein Doppler	Inspiratory diastolic flow reversal	Expiratory diastolic flow reversal
Mitral septal annular e'	Usually <7 cm/s	Usually >7 cm/s
Mitral lateral annular e'	Higher than septal e'	Lower than septal e'
Ventricular septal strain	Reduced	Usually normal

of constrictive pericarditis.¹⁵⁰ The hepatic veins are usually dilated in patients with pericardial constriction and show prominent diastolic flow reversal during expiration. Patients with restrictive cardiomyopathy exhibit diastolic flow reversal during inspiration, whereas patients with pulmonary disease overflow the right heart chambers with inspiration, as seen by large increases in superior vena cava and inferior vena cava velocities. Patients with constrictive pericarditis and atrial fibrillation still have the typical 2D echocardiographic features, and a longer period of Doppler velocity observation is needed to detect velocity variation with respiration.¹⁵¹

Mitral annular velocities by tissue Doppler are important to acquire and analyze. In patients with restrictive cardiomyopathy, myocardial relaxation is impaired, leading to reductions in s' and e' velocities and an increase in the $T_{E-e'}$ time interval.¹⁵²⁻¹⁵⁴ However, in patients with constriction, annular vertical excursion is usually preserved (Figure 12). A septal e' velocity ≥ 7 cm/s is highly accurate in differentiating patients with constrictive pericarditis from those with restrictive cardiomyopathy. The limitations of e' are in patients with significant annular calcification and in those with coexisting myocardial disease, when it is decreased despite the presence of pericardial constriction. More recent reports have shown that in some patients, e' also varies with respiration, but in an opposite direction to that of mitral inflow.¹⁵⁵ In addition, systolic strain is usually reduced in patients with myocardial disease but tends to be preserved in constriction (Table 3), where there are signs of ventricular interdependence.

Key point. Restrictive LV filling, prominent diastolic flow reversal during expiration in the hepatic veins, and normal or increased tissue Doppler annular velocities should raise suspicion of constrictive pericarditis in patients with heart failure and normal EFs, even when the respiratory variation in mitral inflow is absent or not diagnostic.

B. Mitral Stenosis

Typically, patients with mitral stenosis have normal or reduced LV diastolic pressures, except for the rare occurrence of coexisting myocardial disease. The same hemodynamic findings are present in patients with other etiologies of LV inflow obstruction, such as LA tumors, cor triatriatum, and congenital mitral valve stenosis.

The transmitral gradient is influenced by the severity of stenosis, cardiac output, and the diastolic filling period. If atrial fibrillation occurs, LA pressure increases to maintain adequate LV filling. Although the severity of valvular stenosis, patient symptoms, and secondary pulmonary hypertension are the focus of clinical management, a semiquantitative estimation of instantaneous LA pressure can be provided in early and late diastole by Doppler variables. The shorter the IVRT (auscultatory opening snap interval) and the higher peak E-wave velocity (modified Bernoulli equation; $P = 4V^2$), the higher the early diastolic LA pressure. LA pressure is significantly elevated at end-diastole if the mitral velocity remains >1.5 m/s at this point. In addition, the $IVRT/(T_E - T_{E-e'})$ ratio correlates well with mean PCWP and LA pressure (a ratio <4.2 is accurate in identifying patients with filling pressures >15 mm Hg). However, the E/e' ratio is not useful.⁶⁹

Key point. Mitral stenosis renders the assessment of LV diastolic function more challenging, but IVRT, $T_{E-e'}$, and mitral inflow peak velocity at early and late diastole can be of value in the semiquantitative prediction of mean LA pressure.

C. MR

Primary MR leads to LA and LV enlargement and an increase in the compliance of both chambers, which attenuates the increase in LA pressure. If LA compensation is incomplete, mean LA pressure and right-sided pressures increase, which is related not to LV dysfunction but to the regurgitant volume entering the left atrium and pulmonary veins. With LV diastolic dysfunction, a myocardial component of increased filling pressures is added over time. The sequence is opposite to that seen in primary myocardial disease such as dilated cardiomyopathy, which leads to increased filling pressures earlier on and later to functional MR. Therefore, in patients with secondary MR, echocardiographic correlates of increased filling pressures reflect the combination of both myocardial and valvular disorders.

Moderate and severe MR usually lead to an elevation of peak E velocity and reductions in pulmonary venous systolic flow wave and the S/D ratio. In severe MR, systolic pulmonary venous flow reversal can be seen in late systole. Thus, MR per se can induce changes in transmitral and pulmonary venous flow patterns resembling advanced LV dysfunction, with the possible exception of the difference in $Ar - A$ duration.⁷⁰ Aside from PW signals, the MR velocity recording by CW Doppler can provide a highly specific, though not sensitive, sign of increased LA pressure, as discussed previously.

The ability of tissue Doppler parameters (E/e') to predict LV filling pressures in the setting of moderate or severe MR depends on systolic function.^{69,156,157} In patients with depressed EFs, an increased E/e' ratio relates well to filling pressures and predicts hospitalizations and mortality. In patients with normal EFs, these parameters do not correlate with filling pressures. In contrast, IVRT and the ratio of IVRT

Table 4 Assessment of LV filling pressures in special populations

Disease	Echocardiographic measurements and cutoff values
Atrial fibrillation ^{68,104,159}	Peak acceleration rate of mitral E velocity ($\geq 1,900$ cm/s ²), IVRT (≤ 65 ms), DT of pulmonary venous diastolic velocity (≤ 220 ms), E/Vp ratio (≥ 1.4), and septal E/e' ratio (≥ 11)
Sinus tachycardia ^{102,105}	Mitral inflow pattern with predominant early LV filling in patients with EFs $<50\%$, IVRT ≤ 70 ms is specific (79%), systolic filling fraction $\leq 40\%$ is specific (88%), lateral $E/e' > 10$ (a ratio >12 has highest the specificity of 96%)
Hypertrophic cardiomyopathy ⁵⁰	Lateral $E/e' (\geq 10)$, $Ar - A (\geq 30$ ms), PA pressure (>35 mm Hg), and LA volume (≥ 34 mL/m ²)
Restrictive cardiomyopathy ^{51,52,160}	DT (<140 ms), mitral E/A (>2.5), IVRT (<50 ms has high specificity), and septal $E/e' (>15)$
Noncardiac pulmonary hypertension ¹⁶³	Lateral E/e' can be applied to determine whether a cardiac etiology is the underlying reason for the increased PA pressures (cardiac etiology: $E/e' > 10$; noncardiac etiology: $E/e' < 8$)
Mitral stenosis ⁶⁹	IVRT (<60 ms has high specificity), IVRT/ $T_{E-e'} (<4.2)$, mitral A velocity (>1.5 m/s)
MR ^{69,70,157}	$Ar - A (\geq 30$ ms), IVRT (<60 ms has high specificity), and IVRT/ $T_{E-e'} (<3)$ may be applied for the prediction of LV filling pressures in patients with MR and normal EFs, whereas average $E/e' (>15)$ is applicable only in the presence of a depressed EF

A comprehensive approach is recommended in all of the above settings, and conclusions should not be based on single measurements. Specificity comments refer to predicting filling pressures >15 mm Hg.

to $T_{E-e'}$ correlate reasonably well with mean PCWP, regardless of EF.⁶⁹ In particular, an IVRT/ $T_{E-e'}$ ratio <3 appears to readily predict PCWP >15 mm Hg in this patient subgroup.⁶⁹ In patients with atrial fibrillation and MR, it is possible to use matched RR intervals to calculate IVRT/ $T_{E-e'}$, which necessitates the acquisition of a large number of cardiac cycles (≥ 20).

Key point. The time intervals $Ar - A$, IVRT, and IVRT/ $T_{E-e'}$ may be applied for the prediction of LV filling pressures in patients with MR and normal EFs, whereas the E/e' ratio is applicable only in the presence of a depressed EF.

XIV. ESTIMATION OF LEFT VENTRICULAR FILLING PRESSURES IN SPECIAL POPULATIONS (TABLE 4)

A. Atrial Fibrillation

The Doppler estimation of LV filling pressures in atrial fibrillation is limited by the variability in cycle length, the absence of organized atrial activity, and the frequent occurrence of LA enlargement. In general, when LV EF is depressed, mitral DT (≤ 150 ms) has reason-

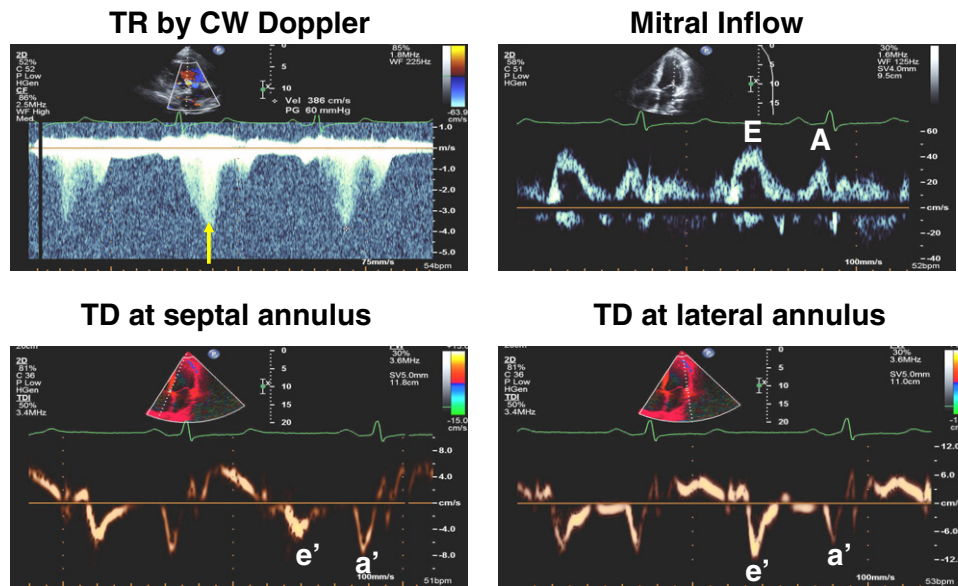


Figure 13 (Top left) Recording of TR jet by CW Doppler (peak velocity marked by yellow arrow) from a patient with primary pulmonary hypertension. The right ventricular–RA systolic pressure gradient is 60 mmHg. (Top right) Mitral inflow at the level of the leaflet tips with mitral E velocity of 50 cm/s. (Bottom left) Recording of septal tissue Doppler velocities with e' of 5.5 cm/s. (Bottom right) Lateral tissue Doppler signals with a normal e' velocity of 11.5 cm/s.

able accuracy for the prediction of increased filling pressures and adverse clinical outcome.^{68,158} Other Doppler measurements that can be applied include the peak acceleration rate of mitral E velocity ($\geq 1,900$ cm/s²), IVRT (≤ 65 ms), DT of pulmonary venous¹⁵⁹ diastolic velocity (≤ 220 ms), the E/Vp ratio (≥ 1.4), and the E/e' ratio (≥ 11). In one study,¹⁰⁴ septal e' < 8 cm/s had reasonable accuracy in identifying patients with $\tau \geq 50$ ms. Likewise, an E/e' ratio ≥ 11 predicted LVEDP ≥ 15 mm Hg. The variability of mitral inflow velocity with the RR cycle length should be examined, because patients with increased filling pressures have less beat-to-beat variation.⁶⁸ Thus, Doppler echocardiography is useful in the estimation of filling pressures in patients with atrial fibrillation. Measurements from 10 cardiac cycles are most accurate, though velocities and time intervals averaged from 3 nonconsecutive beats with cycle lengths within 10% to 20% of the average heart rate and measurements from 1 cardiac cycle with an RR interval corresponding to a heart rate of 70 to 80 beats/min are still useful.⁶⁸

B. Sinus Tachycardia

Conventional mitral and pulmonary venous flow velocity variables are poor indicators of LV filling pressures in sinus tachycardia (>100 beats/min) in patients with normal EFs. However, a ratio of Doppler peak E-wave velocity to lateral mitral annular e' velocity (E/e') > 10 predicts a mean pulmonary wedge pressure > 12 mm Hg with sensitivity of 78% and specificity of 95%. Importantly, this relation remained strong irrespective of mitral inflow pattern and LV EF, as well as in the presence of a single velocity due to complete merging of both mitral and annular E and A.^{102,105}

C. Restrictive Cardiomyopathy

Regardless of whether idiopathic or infiltrative in nature, mitral, pulmonary venous, and tissue Doppler variables are all good indicators of the marked elevation in filling pressures in patients with restrictive cardiomyopathy. A short (<140 ms) mitral DT^{51,52,160} and increases in either PW Doppler mitral E/A ratio (>2.5) or E/e'

ratio (>15) indicate markedly elevated filling pressures. A short LV IVRT of <50 ms also indicates high LA pressure due to an early opening of the mitral valve.¹⁶⁰

D. Hypertrophic Cardiomyopathy

In contrast to restrictive cardiomyopathies, the mitral variables of E/A ratio and DT have weak to no correlations with LV filling pressures in patients with hypertrophic cardiomyopathy.^{49,50} The marked variability in phenotype, muscle mass, amount of myocardial fiber disarray, and obstructive versus nonobstructive physiology results in many different combinations of altered relaxation and compliance and resultant numerous variations of mitral inflow patterns. In one study, the E/e' ratio (≥ 10 , using lateral e') correlated reasonably well with LV pre-A pressure,⁵⁰ whereas in another report, a wide spread was seen in the noninvasive prediction of mean LA pressure.¹⁶¹ Similar to other groups, Ar – A duration (≥ 30 ms) in this population may be used to predict LVEDP.⁵⁰ A comprehensive approach is recommended when predicting LV filling pressures in patients with hypertrophic cardiomyopathy, with consideration of all echocardiographic data, including PA pressures and LA volume (particularly in the absence of significant MR).

E. Pulmonary Hypertension

In patients with pulmonary hypertension, echocardiography plays an essential role in the estimation of PA pressures, the assessment of right ventricular size and function, and the identification of the underlying etiology, whether cardiac or not. If the etiology is related to pulmonary parenchymal or vascular disease, LV filling pressures are usually normal or low, and an impaired relaxation mitral filling pattern is usually observed¹⁶² due to reduced LV filling rather than diastolic dysfunction per se. Typically, these patients have normal lateral annular e' velocities (Figure 13) and lateral E/e' ratios < 8.¹⁶³ Conversely, patients with pulmonary hypertension secondary to diastolic dysfunction have increased E/e' ratios, because the mitral E velocity is increased because of increased LA pressure, and lateral e'

Table 5 Prognostic studies for Doppler diastolic measurements

Study	n	Population	Follow-up	Events	Diastolic measurement	Results
Xie et al ³⁰	100	CHF, EF < 40%	16 ± 8 mo	Death	E/A, DT	Death in res. at 1 y, 19% vs 5%; at 2 y, 51% vs 5%
Rihal et al ³¹	102	DCM	36 mo	Death	E/A, DT	EF < 25% + DT < 130 ms had 35% 2-y survival, EF < 25% + DT > 130 ms had 72% 2-y survival, EF ≥ 25% had 2-y survival ≥ 95% regardless of DT
Giannuzzi et al ³³	508	EF ≤ 35%	29 ± 11 mo	Death + hospital admission	DT	Survival free of events 77% when DT > 125 ms, survival free of events 18% when DT ≤ 125 ms; DT was incremental to age, functional class, third heart sound, EF, and LA area
Pozzoli et al ⁴⁰	173	CHF, EF < 35%	17 ± 9 mo	Cardiac death and urgent heart transplantation	Mitral inflow changes with loading	Event rate 51% in irreversible restrictive pattern, 19% in reversible restrictive, 33% in unstable nonrestrictive, and 6% in stable nonrestrictive filling
Pinamonti et al ⁴¹	110	DCM	41 ± 20 mo	Death + heart transplantation	Mitral inflow changes after 3 mo of treatment	After 1, 2, and 4 y, survival of patients with persistent restrictive (65%, 46%, and 13%) was significantly lower than that of patients with reversible restrictive (100% at 1 and 2 y and 96% at 4 y), and those with nonrestrictive (100% at 1 and 2 y and 97% at 4 y)
Traversi et al ³²	98	ICM + DCM	12 ± 7 mo	Cardiac death and heart transplantation	Mitral inflow changes after 6 mo of treatment	Event rate of 35% with persistent restrictive pattern, 5% with a reversible restrictive pattern, and 4% with persistent nonrestrictive pattern
Temporelli et al ⁴²	144	CHF + DT ≤ 125 ms	26 ± 7 mo	Cardiac death	DT changes after 6 mo of treatment	Event rate: 37% with persistent restrictive pattern vs 11% with reversible restrictive; prolongation of short DT was the single best predictor of survival
Hurrell et al ³⁴	367	Restrictive filling: DT ≤ 130 ms	2.2 y	Death	DT	Survival 42% for sinus rhythm and DT ≤ 130 ms and 39% for atrial fibrillation and DT ≤ 130 ms
Hansen et al ³⁵	311	ICM + DCM	512 ± 314 d	Death + heart transplantation	Mitral inflow pattern	2-y survival rate of 52% with restrictive pattern vs 80% with nonrestrictive pattern; transmitral flow was incremental to peak oxygen consumption

Table 5 Continued

Study	n	Population	Follow-up	Events	Diastolic measurement	Results
Faris et al ³⁶	337	DCM	43 ± 25 mo	Death	Mitral inflow pattern	1, 3, and 5 y survival of patients with restrictive filling (88%, 77%, and 61%) was significantly lower than that of patients with nonrestrictive filling (96%, 92%, and 80%)
Whalley et al ³⁷	115	ICM + DCM	0.87 ± 0.28 y	Death + hospital admission	Mitral inflow pattern	Event rate of 62.9% with restrictive filling vs 26.1% in patients with impaired relaxation
Bella et al ³⁹	3,008	American Indians	3 y	All-cause and cardiac death	E/A	All-cause mortality was higher with E/A < 0.6 or E/A > 1.5 (12% and 13%), as was cardiac mortality (4.5% and 6.5%) vs 6% and 1.6% for normal E/A ratio
Rossi et al ³⁸	106	DCM	524 ± 138 d	Death	Mitral inflow pattern	Survival rate was 38% with restrictive filling vs 90% with nonrestrictive filling, after 600 d of follow-up
Dini et al ⁷²	145	ICM + DCM	15 ± 8 mo	Death + hospital admission	DT + Ar – A	The 24-mo cardiac event-free survival was best (86.3%) for DT > 130 ms + Ar – A < 30 ms; it was intermediate (37.9%) for DT > 130 ms + Ar – A ≥ 30 ms; and worst (22.9%) for DT ≤ 130 ms + Ar – A ≥ 30 ms
Dini et al ⁷³	115	ICM + DCM	12 mo	Cardiac death	S/D peak velocity ratio	Mortality was 23% with S/D < 1 and significantly higher than in those with S/D ≥ 1 (7%)
Yamamoto et al ¹⁶⁸	96	ICM + DCM, EF ≤ 40%	29 ± 10 mo	Cardiac death and hospitalization for CHF	Mitral, PW E/e', a' (posterior wall)	Survival at 40 mo was ~72% with a' > 5 cm/s and ~22% with a' ≤ 5 cm/s; on multiple regression, A' ≤ 5 cm/s, E/e' ≥ 15, and DT < 140 ms were independent predictors of events
Hillis et al ¹⁷⁰	250	Acute MI	13 mo	Death	DT, PW E/e' (septal e')	Mortality of 26% with E/e' > 15 and 5.6% with E/e' ≤ 15; E/e' > 15 was incremental to clinical data, EF, and DT ≤ 140 ms
Wang et al ¹⁷¹	182	Cardiac patients with EFs < 50%	48 mo	Cardiac death	Mitral, color-coded e' (average of septal, lateral, anterior, and inferior), Vp	Cardiac death rate was 32% with e' < 3 cm/s and 12% with e' ≥ 3 cm/s; e' was incremental to DT < 140 ms and E/e' > 15
Wang et al ¹⁷³	252	Hypertension, median EF = 51%	Median 19 mo	Cardiac death	Mitral, color-coded e' (average of septal, lateral, anterior, and inferior), Vp	Cardiac death in 19 patients (7.5%); on multivariate regression, e' (<3.5 cm/s) was the most powerful independent predictor of events

Table 5 Continued

Study	n	Population	Follow-up	Events	Diastolic measurement	Results
Dokainish et al ¹⁷²	110	ICM + DCM	527 ± 47 d	Cardiac death and rehospitalization for CHF	DT, PW E/e' (average of septal and lateral)	Predischarge BNP and E/e' were incremental predictors of events (54/110, or 49% event rate)
Troughton et al ¹⁸⁸	225	ICM + DCM (EF < 35%)	Median 10 mo	Death + heart transplantation + hospitalization for CHF	DT, S/D, Vp, PW E/e' (septal)	Event rate 45% with E/e' > 16 and 13% with E/e' < 16; event rate 37% with E/Vp > 2.7 and 22% with E/Vp < 2.7; event rate 44% with DT < 170 ms and 14% with DT > 170 ms; event rate 45% with S/D < 1 and 10% with S/D > 1; E/e' and S/D ratios independent predictors of outcome
Okura et al ¹⁷⁵	230	Nonvalvular atrial fibrillation	245 ± 200 d	Total mortality, cardiac mortality, incident CHF	Mitral DT, S/D, DT of pulmonary D velocity, PW E/e' (septal)	Total mortality was higher at 16.7% for E/e' > 15, and 4.3% for E/e' ≤ 15; cardiac mortality of 11.1% for E/e' > 15 vs 1.4% for E/e' ≤ 15; CHF occurred more frequently with E/e' > 15 at 17.8% vs 5.7% with E/e' ≤ 15; E/e' and age independent predictors of mortality
Sharma et al ¹⁷⁴	125	End-stage renal disease, EF 66 ± 14%	1.61 ± 0.56 y	Total mortality	Mitral, pulmonary veins, Vp, and PW E/e' (average of septal and lateral)	Total mortality was 9.6% and was significantly higher for E/e' ≥ 15; no difference in mortality between patients with and without restrictive inflow patterns
Bruch et al ¹⁷⁶	370 CHF + MR, in 92 ERO ≥ 0.2 cm ²	ICM + DCM, EF < 50%	790 ± 450 d	Death and rehospitalization for CHF	DT, PW E/e' (average of septal and lateral)	Mortality rate was higher in patients with significant MR vs those without (33% vs 14%); in patients with MR, event-free survival rate was 31% for E/e' > 13.5 and 64% for E/e' ≤ 13.5

BNP, Brain natriuretic peptide; CHF, congestive heart failure; DCM, dilated cardiomyopathy; ERO, effective regurgitant orifice; ICM, idiopathic cardiomyopathy; MI, myocardial infarction.

velocity is reduced because of myocardial disease. The use of septal e' and the E/e' ratio is limited in patients with noncardiac etiologies of pulmonary hypertension because septal e' is reduced because of right ventricular contribution to septal velocity signals.¹⁶³

With successful lowering of pulmonary vascular resistance, cardiac output increases, the LV filling pattern reverts to being more normal, and the lateral E/e' ratio increases.¹⁶³ These changes may be of value in monitoring the response to medical and surgical treatment of pulmonary hypertension.

XV. PROGNOSIS

Diastolic dysfunction develops early in most cardiac diseases and leads to the elevation of LV filling pressures. Therefore, echocardiographic measurements of diastolic function provide important prognostic information (Table 5).

graphic measurements of diastolic function provide important prognostic information (Table 5).

Clinical studies have shown the association of short mitral DT with heart failure and death and hospitalizations in patients presenting with acute myocardial infarctions.³⁰⁻⁴⁶ Diastolic measurements provide incremental information to wall motion score index. A recent meta-analysis of 12 post-acute myocardial infarction studies involving 1,286 patients confirmed these previous observations.⁴⁷ Similar findings were reported in patients with ischemic or dilated cardiomyopathy, including those in atrial fibrillation.³⁴ Pulmonary venous velocities⁷¹⁻⁷³ and Vp^{88,164-166} were less frequently examined but were still predictive of clinical events. Given the variability in measuring DT, Vp, and pulmonary venous flow velocity duration, recent studies have examined the prognostic power of E/e' (Table 5).

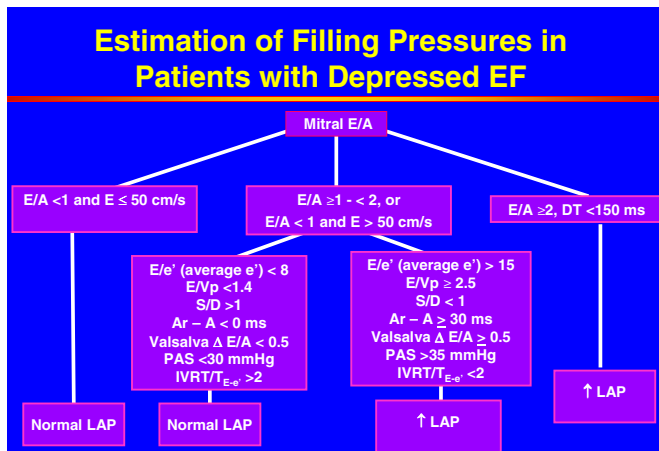


Figure 14 Diagnostic algorithm for the estimation of LV filling pressures in patients with depressed EFs.

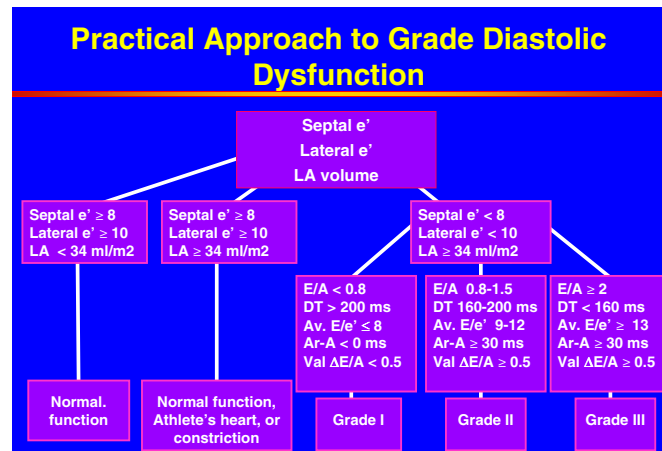


Figure 16 Scheme for grading diastolic dysfunction. Av., Average; LA, left atrium; Val., Valsalva.

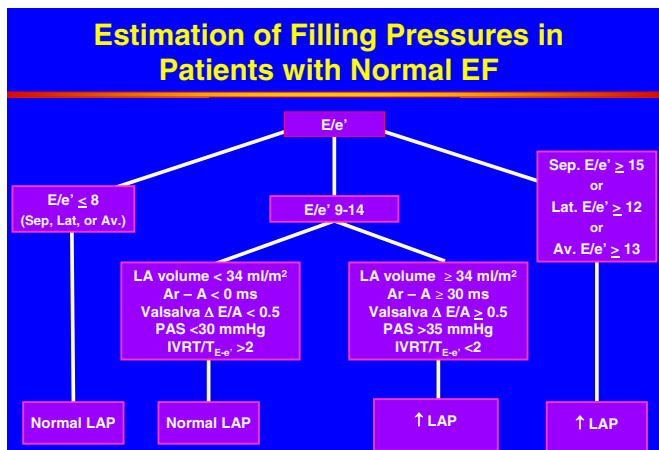


Figure 15 Diagnostic algorithm for the estimation of LV filling pressures in patients with normal EFs.

Several studies^{88,167-178} have shown that E/e' is highly predictive of adverse events after acute myocardial infarction and in hypertensive heart disease, severe secondary MR, end-stage renal disease, atrial fibrillation, and cardiomyopathic disorders.

The E/e' ratio is among the most reproducible echocardiographic parameters to estimate PCWP and is the preferred prognostic parameter in many cardiac conditions.

XVI. RECOMMENDATIONS FOR CLINICAL LABORATORIES

When the technical quality is adequate and the findings are not equivocal, the report should include a conclusion on LV filling pressures and the presence and grade of diastolic dysfunction.

A. Estimation of LV Filling Pressures in Patients With Depressed EFs

The mitral inflow pattern by itself can be used to estimate filling pressures with reasonable accuracy in this population. Furthermore,

the changes in the inflow pattern can be used to track filling pressures in response to medical therapy. In patients with impaired relaxation patterns and peak E velocities < 50 cm/s, LV filling pressures are usually normal. With restrictive filling, mean LA pressure is increased (Figure 14). The use of additional Doppler parameters is recommended in patients with E/A ratios ≥ 1 to < 2. A change in E/A ratio with the Valsalva maneuver of ≥ 0.5 , a systolic peak velocity/diastolic peak velocity ratio in pulmonary venous flow < 1, $Ar - A$ duration ≥ 30 ms, $E/Vp \geq 2.5$, E/e' (using average e') ≥ 15 , $IVRT/T_{E-e'} < 2$, and PA systolic pressure ≥ 35 mm Hg (in the absence of pulmonary disease) can be used to infer the presence of increased filling pressures. Conversely, a change in E/A ratio with the Valsalva maneuver of < 0.5, a systolic peak velocity/diastolic peak velocity ratio in pulmonary venous flow > 1, $Ar - A$ duration < 0 ms, $E/Vp < 1.4$, E/e' (using average e') < 8, $IVRT/T_{E-e'} > 2$, and PA systolic pressure < 30 mm Hg occur with normal filling pressures. In patients with pseudonormal filling, it is preferable to base the conclusions on ≥ 2 Doppler findings, giving more weight to signals with higher technical quality. Some LA dilatation commonly occurs in this population, even when LV filling pressures are normal, and therefore should not be used as the final arbitrator in this setting.

B. Estimation of LV Filling Pressures in Patients With Normal EFs

The estimation of LV filling pressures in patients with normal EFs is more challenging than in patients with depressed EFs. In this patient group, the E/e' ratio should be calculated. An average ratio ≤ 8 identifies patients with normal LV filling pressures, whereas a ratio ≥ 13 indicates an increase in LV filling pressures.⁸⁶ When the ratio is between 9 and 13, other measurements are essential (Figure 15).

An $Ar - A$ duration ≥ 30 ms, a change in E/A ratio with the Valsalva maneuver of ≥ 0.5 , $IVRT/T_{E-e'} < 2$, PA systolic pressure ≥ 35 mm Hg (in the absence of pulmonary disease), and maximal LA volume ≥ 34 mL/m² are all indicative of increased LV filling pressures. The presence of ≥ 2 abnormal measurements increases the confidence in the conclusions. Although $E/Vp > 1.9$ occurs with mean PCWP > 15 mm Hg, a number of patients with diastolic dysfunction and normal EFs and LV volumes can have normal or even increased Vp , resulting in ratios < 1.9, even though filling pressures are increased.

C. Grading Diastolic Dysfunction

The grading scheme is mild or grade I (impaired relaxation pattern), moderate or grade II (PNF), and severe (restrictive filling) or grade III (Figure 16). This scheme was an important predictor of all-cause mortality in a large epidemiologic study.¹⁶⁹ Importantly, even in asymptomatic patients, grade I (see the following) diastolic dysfunction was associated with a 5-fold higher 3-year to 5-year mortality in comparison with subjects with normal diastolic function. Assessment should take into consideration patients' ages and heart rates (mitral E, E/A ratio, and annular e' decrease with increasing heart rate). Specifically, in older individuals without histories of cardiovascular disease, caution should be exercised before concluding that grade I diastolic dysfunction is present. Because the majority of subjects aged >60 years without histories of cardiovascular disease have E/A ratios < 1 and DTs > 200 ms, such values in the absence of further indicators of cardiovascular disease (eg, LV hypertrophy) can be considered normal for age.

In patients with mild diastolic dysfunction, the mitral E/A ratio is <0.8, DT is >200 ms, IVRT is ≥ 100 ms, predominant systolic flow is seen in pulmonary venous flow ($S > D$), annular e' is <8 cm/s, and the E/e' ratio is <8 (septal and lateral). These patients have reduced diastolic reserve that can be uncovered by stress testing. However, a reduced mitral E/A ratio in the presence of normal annular tissue Doppler velocities can be seen in volume-depleted normal subjects, so an E/A ratio < 0.8 should not be universally used to infer the presence of diastolic dysfunction. In most situations, when the E/A ratio is <0.8, mean LA pressure is not elevated, except for some patients with severely impaired myocardial relaxation, as in long-standing hypertension or hypertrophic cardiomyopathy.

In patients with moderate diastolic dysfunction (grade II), the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by $\geq 50\%$ during the Valsalva maneuver, the E/e' (average) ratio is 9 to 12, and e' is <8 cm/s. Other supporting data include an Ar velocity > 30 cm/s and an S/D ratio < 1. In some patients with moderate diastolic dysfunction, LV end-diastolic pressure is the only pressure that is increased (ie, mean LA pressure is normal) and is recognized by Ar – A duration ≥ 30 ms. Grade II diastolic dysfunction represents impaired myocardial relaxation with mild to moderate elevation of LV filling pressures.

With severe diastolic dysfunction (grade III), restrictive LV filling occurs with an E/A ratio ≥ 2 , DT < 160 ms, IVRT ≤ 60 ms, systolic filling fraction $\leq 40\%$, mitral A flow duration shorter than Ar duration, and average E/e' ratio > 13 (or septal E/e' ≥ 15 and lateral E/e' > 12). LV filling may revert to impaired relaxation with successful therapy in some patients (grade IIIa), whereas in others, LV filling remains restrictive (grade IIIb). The latter is an ominous finding and predicts a high risk for cardiac morbidity and mortality. However, grade IIIb dysfunction should not be determined by a single examination and requires serial studies after treatment is optimized. LA volume is increased in grades II and III of diastolic dysfunction, but can be within normal limits in grade I and in patients with preclinical disease.

XVII. RECOMMENDATIONS FOR APPLICATION IN RESEARCH STUDIES AND CLINICAL TRIALS

Myocardial relaxation, LV stiffness, and filling pressures can only be assessed indirectly in the echocardiography laboratory, because the prediction of hemodynamic data with echocardiography often im-

plies simplifying assumptions, which may be valid in a given patient population but are not necessarily applicable to all patients.

Doppler echocardiographic measurements of diastolic function can show individual variability and can vary day to day in the same patient with changes in preload, afterload, and sympathetic tone. Cutoff values for differentiating normal from abnormal subjects should consider the age group from which the study sample is selected. It is also preferable to report Doppler measurements adjusted for sex, body weight, and blood pressure in statistical models, when such relations are noted.

On the basis of a clearly formulated question, one should define the needs: to examine changes in relaxation, stiffness, and/or filling pressures. The main indicators of abnormal relaxation are IVRT and isovolumetric or early diastolic annular motion or LV strain rate. Indicators of reduced operating compliance are DT of mitral E velocity, A-wave transit time, the ratio of LVEDP to LV end-diastolic volume, and surrogates of increased LVEDP, namely, an abbreviated mitral A-wave duration, reduced a', and prolonged Ar duration in pulmonary venous flow. Indicators of early diastolic LV and LA pressures are the E/e' ratio, DT of mitral E velocity in patients with depressed EFs, and to some extent LA enlargement, which reflects chronic rather than acute pressure changes. LV untwisting rate can be useful in studying the effects of suction on LV filling and the link between LV systolic and diastolic function. Each experimental question should be addressed with the most suitable echocardiographic approach that answers the question, as outlined in these recommendations. In addition, care should be exercised when drawing inferences about changes in LV relaxation, because these may occur because of load changes per se rather than an intrinsic improvement in myocardial function.

When selecting from the echocardiographic methods for investigating problems related to diastolic function, it is possible to entertain either a general simple approach with high feasibility and reproducibility or a more tailored and sophisticated one. Although the former approach is suited for clinically oriented trials, the latter approach may be superior for answering mechanistic questions. An example of the former approach is the echocardiographic substudy of the Irbesartan in Heart Failure With Preserved Systolic Function Study, completed in April 2008.¹⁷⁹ This substudy selected LA size, LV size and function, LV mass index, and the E/e' ratio. On the other hand, strain measurements by speckle tracking appear to have good reproducibility and can be applied to study segmental deformation and to address mechanistic issues.

REFERENCES

1. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J* 2007;28:2539-50.
2. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: pathophysiology and therapeutic implications. *J Am Coll Cardiol* 1993;22:318-25.
3. Yip GW, Zhang Y, Tan PY, Wang M, Ho PY, Brodin LA, et al. Left ventricular long-axis changes in early diastole and systole: impact of systolic function on diastole. *Clin Sci (Lond)* 2002;102:515-22.
4. Leite-Moreira AF, Correia-Pinto J, Gillebert TC. Afterload induced changes in myocardial relaxation: a mechanism for diastolic dysfunction. *Cardiovasc Res* 1999;43:344-53.
5. Leite-Moreira AF. Current perspectives in diastolic dysfunction and diastolic heart failure. *Heart* 2006;92:712-8.

6. Gillebert TC, Lew WY. Nonuniformity and volume loading independently influence isovolumic relaxation rates. *Am J Physiol* 1989;257:H1927-35.
7. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. *Circulation* 2008;117:2051-60.
8. Torrent-Guasp F, Ballester M, Buckberg GD, Carreras F, Flotats A, Carrió I, et al. Spatial orientation of the ventricular muscle band: physiologic contribution and surgical implications. *J Thorac Cardiovasc Surg* 2001;122:389-92.
9. Hung J, Lang R, Flachskampf F, Shernan SK, McCulloch ML, Adams DB, et al. 3D echocardiography: a review of the current status and future directions. *J Am Soc Echocardiogr* 2007;20:213-33.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography, European Society of Cardiology recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79-108.
11. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol* 2002;90:1284-9.
12. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol* 2006;47:2357-63.
13. Prioli A, Marino P, Lanzoni L, Zardini P. Increasing degrees of left ventricular filling impairment modulate left atrial function in humans. *Am J Cardiol* 1998;82:756-61.
14. Manning WJ, Silverman DI, Katz SE, Douglas PS. Atrial ejection force: a noninvasive assessment of atrial systolic function. *J Am Coll Cardiol* 1993;22:221-5.
15. Stefanadis C, Dernellis J, Lambrou S, Toutouzas P. Left atrial energy in normal subjects, in patients with symptomatic mitral stenosis, and in patients with advanced heart failure. *Am J Cardiol* 1998;82:1220-3.
16. Inaba Y, Yuda S, Kobayashi N, Hashimoto A, Uno K, Nakata T, et al. Strain rate imaging for noninvasive functional quantification of the left atrium: comparative studies in controls and patients with atrial fibrillation. *J Am Soc Echocardiogr* 2005;18:729-36.
17. Di Salvo G, Caso P, Lo Piccolo R, Fusco A, Martiniello AR, Russo MG, et al. Atrial myocardial deformation properties predict maintenance of sinus rhythm after external cardioversion of recent-onset lone atrial fibrillation. *Circulation* 2005;112:387-95.
18. Bouchard JL, Aurigemma GP, Hill JC, Ennis CA, Tighe DA. Usefulness of the pulmonary arterial systolic pressure to predict pulmonary arterial wedge pressure in patients with normal left ventricular systolic function. *Am J Cardiol* 2008;101:1673-6.
19. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002;15:167-84.
20. Lee RT, Lord CP, Plappert T, Sutton MS. Prospective Doppler echocardiographic evaluation of pulmonary artery diastolic pressure in the medical intensive care unit. *Am J Cardiol* 1989;64:1366-70.
21. Rapp AH, Lange RA, Cigarroa JE, Keeley EC, Hillis LD. Relation of pulmonary arterial diastolic and mean pulmonary arterial wedge pressures in patients with and without pulmonary hypertension. *Am J Cardiol* 2001;88:823-4.
22. Appleton CP, Jensen JL, Hatle LK, Oh JK. Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. *J Am Soc Echocardiogr* 1997;10:271-91.
23. Ha JW, Oh JK, Redfield MM, Ujino K, Seward JB, Tajik AJ. Triphasic mitral inflow velocity with middiastolic filling: clinical implications and associated echocardiographic findings. *J Am Soc Echocardiogr* 2004;17:428-31.
24. Klein AL, Burstow DJ, Tajik AJ, Zachariah PK, Bailey KR, Seward JB. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc* 1994;69:212-24.
25. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426-40.
26. Vanoverschelde JL, Raphael DA, Robert AR, Cosyns JR. Left ventricular filling in dilated cardiomyopathy: relation to functional class and hemodynamics. *J Am Coll Cardiol* 1990;15:1288-95.
27. Pinamonti B, Di Lenarda A, Sinagra G, Camerini F; Heart Muscle Disease Study Group. Restrictive left ventricular filling pattern in dilated cardiomyopathy assessed by Doppler echocardiography: clinical, echocardiographic and hemodynamic correlations and prognostic implications. *J Am Coll Cardiol* 1993;22:808-15.
28. Giannuzzi P, Imparato A, Temporelli PL, de Vito F, Silva PL, Scapellato F, et al. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary wedge pressure in postinfarction patients with left ventricular dysfunction. *J Am Coll Cardiol* 1994;23:1630-7.
29. Pozzoli M, Capomolla S, Pinna G, Cobelli F, Tavazzi L. Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure with and without mitral regurgitation. *J Am Coll Cardiol* 1996;27:883-93.
30. Xie GY, Berk MR, Smith MD, Gurley JC, DeMaria AN. Prognostic value of Doppler transmitral flow patterns in patients with congestive heart failure. *J Am Coll Cardiol* 1994;24:132-9.
31. Rihal CS, Nishimura RA, Hatle LK, Bailey KR, Tajik AJ. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. *Circulation* 1994;90:2772-2779.
32. Traversi E, Pozzoli M, Cioffi G, Capomolla S, Forni G, Sanarico M, et al. Mitral flow velocity changes after 6 months of optimized therapy provide important hemodynamic and prognostic information in patients with chronic heart failure. *Am Heart J* 1996;132:809-19.
33. Giannuzzi P, Temporelli PL, Bosmini E, Silva P, Imparato A, Corrà U, et al. Independent and incremental prognostic value of Doppler-derived mitral deceleration time of early filling in both symptomatic and asymptomatic patients with left ventricular dysfunction. *J Am Coll Cardiol* 1996;28:383-90.
34. Hurrell DG, Oh JK, Mahoney DW, Miller FA Jr, Seward JB. Short deceleration time of mitral inflow E velocity: prognostic implication with atrial fibrillation versus sinus rhythm. *J Am Soc Echocardiogr* 1998;11:450-7.
35. Hansen A, Haass M, Zugck C, Krueger C, Unnebrink K, Zimmermann R, et al. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with congestive heart failure. *J Am Coll Cardiol* 2001;37:1049-55.
36. Faris R, Coats A, Henein M. Echocardiography-derived variables predict outcome in patients with non-ischemic dilated cardiomyopathy with or without a restrictive filling pattern. *Am Heart J* 2002;144:343-50.
37. Whalley GA, Doughty RN, Gamble GD, Wright SP, Walsh HJ, Muncaster SA, et al. Pseudonormal mitral filling pattern predicts hospital re-admission in patients with congestive heart failure. *J Am Coll Cardiol* 2002;39:1787-95.
38. Rossi A, Ciccoira M, Golia G, Zanolta L, Franceschini L, Marino P, et al. Amino-terminal propeptide of type III procollagen is associated with restrictive mitral filling pattern in patients with dilated cardiomyopathy: a possible link between diastolic dysfunction and prognosis. *Heart* 2004;90:650-4.
39. Bella JN, Palmieri V, Roman MJ, Liu JE, Welty TK, Lee ET, et al. Mitral ratio of peak early to late diastolic filling velocity as a predictor of mortality in middle-aged and elderly adults: the Strong Heart Study. *Circulation* 2002;105:1928-33.
40. Pozzoli M, Traversi E, Cioffi G, Stenner R, Sanarico M, Tavazzi L. Loading manipulations improve the prognostic value of Doppler evaluation of mitral flow in patients with chronic heart failure. *Circulation* 1997;95:1222-30.

41. Pinamonti B, Zecchin M, Di Lenarda A, Gregori D, Sinagra G, Camerini F. Persistence of restrictive left ventricular filling pattern in dilated cardiomyopathy: an ominous prognostic sign. *J Am Coll Cardiol* 1997; 29:604-12.
42. Temporelli PL, Corra U, Imparato A, Bosimini E, Scapellato F, Giannuzzi P. Reversible restrictive left ventricular diastolic filling with optimized oral therapy predicts a more favorable prognosis in patients with chronic heart failure. *J Am Coll Cardiol* 1998;31:1591-7.
43. Oh JK, Ding ZP, Gersh BJ, Bailey KR, Tajik AJ. Restrictive left ventricular diastolic filling identifies patients with heart failure after acute myocardial infarction. *J Am Soc Echocardiogr* 1992;5:497-503.
44. Pozzoli M, Capomolla S, Sanarico M, Pinna G, Cobelli F, Tavazzi L. Doppler evaluations of left ventricular diastolic filling and pulmonary wedge pressure provide similar prognostic information in patients with systolic dysfunction after myocardial infarction. *Am Heart J* 1995;129: 716-25.
45. Nijland F, Kamp O, Karreman AJ, van Eenige MJ, Visser CA. Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. *J Am Coll Cardiol* 1997;30:1618-24.
46. Sakata K, Kashiwa S, Hirata S, Yanagisawa A, Ishikawa K. Prognostic value of Doppler transmitral flow velocity patterns in acute myocardial infarction. *Am J Cardiol* 1997;79:1165-9.
47. Somaratne JB, Whalley GA, Gamble GD, Doughty RN. Restrictive filling pattern is a powerful predictor of heart failure events post acute myocardial infarction and in established heart failure: a literature-based meta-analysis. *J Card Fail* 2007;13:346-52.
48. Yamamoto K, Nishimura RA, Chaliki HP, Appleton CP, Holmes DR Jr, Redfield MM. Determination of left ventricular filling pressure by Doppler echocardiography in patients with coronary artery disease: critical role of left ventricular systolic function. *J Am Coll Cardiol* 1997;30:1819-26.
49. Nishimura RA, Appleton CP, Redfield MM, Ilstrup DM, Holmes DR Jr, Tajik AJ. Noninvasive Doppler echocardiographic evaluation of left ventricular filling pressures in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. *J Am Coll Cardiol* 1996;28:1226-33.
50. Nagueh SF, Lakkis NM, Middleton KJ, Spencer WH III, Zoghbi WA, Quinones MA. Doppler estimation of left ventricular filling pressures in patients with hypertrophic cardiomyopathy. *Circulation* 1999;99: 254-61.
51. Klein AL, Hatle LK, Taliencio CP, Taylor CL, Kyle RA, Bailey KR, et al. Serial Doppler echocardiographic follow-up of left ventricular diastolic function in cardiac amyloidosis. *J Am Coll Cardiol* 1990;16:1135-41.
52. Klein AL, Hatle LK, Taliencio CP, Oh JK, Kyle RA, Gertz MA, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiography study. *Circulation* 1991;83:808-16.
53. Valantine HA, Appleton CP, Hatle LK, Hunt SA, Billingham ME, Shumway NE, et al. A hemodynamic and Doppler echocardiographic study of ventricular function in long-term cardiac allograft recipients. Etiology and prognosis of restrictive-constrictive physiology. *Circulation* 1989;79:66-75.
54. Appleton CP. Influence of incremental changes in heart rate on mitral flow velocity: assessment in lightly sedated, conscious dogs. *J Am Coll Cardiol* 1991;17:227-36.
55. Schnittger I, Appleton CP, Hatle LK, Popp RL. Diastolic mitral and tricuspid regurgitation by Doppler echocardiography in patients with atrioventricular block: new insight into the mechanism of atrioventricular valve closure. *J Am Coll Cardiol* 1988;11:83-8.
56. Nishimura RA, Tajik AJ. The Valsalva maneuver—3 centuries later. *Mayo Clin Proc* 2004;79:577-8.
57. Hurrell D, Nishimura RA, Ilstrup DM, Appleton CP. Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol* 1997;30:459-67.
58. Jensen JL, Williams FE, Beilby BJ, Johnson BL, Miller LK, Ginter TL, et al. Feasibility of obtaining pulmonary venous flow velocity in cardiac patients using transthoracic pulsed wave Doppler technique. *J Am Soc Echocardiogr* 1997;10:60-6.
59. Appleton CP. Hemodynamic determinants of Doppler pulmonary venous flow velocity components: new insights from studies in lightly sedated normal dogs. *J Am Coll Cardiol* 1997;30:1562-74.
60. Smiseth OA, Thompson CR, Lohavanichbutr K, Ling H, Abel JG, Miyagishima RT, et al. The pulmonary venous systolic flow pulse—its origin and relationship to left atrial pressure. *J Am Coll Cardiol* 1999; 34:802-9.
61. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography. Effect of different loading conditions. *Circulation* 1990;81:1488-97.
62. Keren G, Bier A, Sherez J, Miura D, Keefe D, Lejemtel T. Atrial contraction is an important determinant of pulmonary venous flow. *J Am Coll Cardiol* 1986;7:693-5.
63. Kuecherer HF, Muhiudeen IA, Kusumoto FM, Lee E, Moulinier LE, Cahalan MK, et al. Estimation of mean left atrial pressure from transesophageal pulsed Doppler echocardiography of pulmonary venous flow. *Circulation* 1990;82:1127-39.
64. Yamamuro A, Yoshida K, Hozumi T, Akasaka T, Takagi T, Kaji S, et al. Noninvasive evaluation of pulmonary capillary wedge pressure in patients with acute myocardial infarction by deceleration time of pulmonary venous flow velocity in diastole. *J Am Coll Cardiol* 1999;34:90-4.
65. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol* 1993;21:1687-96.
66. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. *J Am Coll Cardiol* 1993;22:1972-82.
67. Klein AL, Tajik AJ. Doppler assessment of pulmonary venous flow in healthy subjects and in patients with heart disease. *J Am Soc Echocardiogr* 1991;4:379-92.
68. Nagueh SF, Kopelen HA, Quinones MA. Assessment of left ventricular filling pressures by Doppler in the presence of atrial fibrillation. *Circulation* 1996;94:2138-45.
69. Diwan A, McCulloch M, Lawrie GM, Reardon MJ, Nagueh SF. Doppler estimation of left ventricular filling pressures in patients with mitral valve disease. *Circulation* 2005;111:3281-9.
70. Rossi A, Cicoira M, Golia G, Anselmi M, Zardini P. Mitral regurgitation and left ventricular diastolic dysfunction similarly affect mitral and pulmonary vein flow Doppler parameters: the advantage of end-diastolic markers. *J Am Soc Echocardiogr* 2001;14:562-8.
71. Poulsen SH, Jensen SE, Gotzsche O, Egstrup K. Evaluation and prognostic significance of left ventricular diastolic function assessed by Doppler echocardiography in the early phase of a first acute myocardial infarction. *Eur Heart J* 1997;18:1882-9.
72. Dini F, Michelassi C, Micheli G, Rovai D. Prognostic value of pulmonary venous flow Doppler signal in left ventricular dysfunction: contribution of the difference in duration of pulmonary venous and mitral flow at atrial contraction. *J Am Coll Cardiol* 2000;36:1295-302.
73. Dini FL, Dell'Anna R, Micheli A, Michaelassi C, Rovai D. Impact of blunted pulmonary venous flow on the outcome of patients with left ventricular systolic dysfunction secondary to either ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2000;85:1455-60.
74. Brun P, Tribouilloy C, Duval AM, Iserin L, Meguir A, Pelle G, et al. Left ventricular flow propagation during early filling is related to wall relaxation: a color M-mode Doppler analysis. *J Am Coll Cardiol* 1992;20: 420-32.
75. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD. An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. *J Am Coll Cardiol* 1997;29:448-54.

76. Sessoms MW, Lissauskas J, Kovács SJ. The left ventricular color M-mode Doppler flow propagation velocity $V(p)$: in vivo comparison of alternative methods including physiologic implications. *J Am Soc Echocardiogr* 2002;15:339-48.
77. Takatsuji H, Mikami T, Urasawa K, Teranishi J, Onozuka H, Takagi C, et al. A new approach for evaluation of left ventricular diastolic function: spatial and temporal analysis of left ventricular filling flow propagation by color M-mode Doppler echocardiography. *J Am Coll Cardiol* 1996; 27:365-71.
78. Greenberg NL, Vandervoort PM, Firstenberg MS, Garcia MJ, Thomas JD. Estimation of diastolic intraventricular pressure gradients by Doppler M-mode echocardiography. *Am J Physiol Heart Circ Physiol* 2001;280: H2507-15.
79. Yotti R, Bermejo J, Antoranz JC, Desco MM, Cortina C, Rojo-Alvarez JL, et al. A noninvasive method for assessing impaired diastolic suction in patients with dilated cardiomyopathy. *Circulation* 2005;112:2921-9.
80. Courtois M, Kovacs SJ Jr, Ludbrook PA. Physiological early diastolic intraventricular pressure gradient is lost during acute myocardial ischemia. *Circulation* 1990;81:1688-96.
81. Stugaard M, Smiseth OA, Risoe C, Ihlen H. Intraventricular early diastolic filling during acute myocardial ischemia. Assessment by multi-gated color M-mode Doppler echocardiography. *Circulation* 1993;88: 2705-13.
82. Steine K, Stugaard M, Smiseth OA. Mechanisms of retarded apical filling in acute ischemic left ventricular failure. *Circulation* 1999;99:2048-54.
83. Ohte N, Narita H, Akita S, Kurokawa K, Hayano J, Kimura G. Striking effect of left ventricular systolic performance on propagation velocity of left ventricular early diastolic filling flow. *J Am Soc Echocardiogr* 2001; 14:1070-4.
84. Rovner A, de las Fuentes L, Waggoner AD, Memon N, Chohan R, Dávila-Román VG. Characterization of left ventricular diastolic function in hypertension by use of Doppler tissue imaging and color M-mode techniques. *J Am Soc Echocardiogr* 2006;19:872-9.
85. Gonzalez-Vilchez F, Ares M, Ayuela J, Alonso L. Combined use of pulsed and color M-mode Doppler echocardiography for the estimation of pulmonary capillary wedge pressure: an empirical approach based on an analytical relation. *J Am Coll Cardiol* 1999;34:515-23.
86. Rivas-Gotz C, Manolios M, Thohan V, Nagueh SF. Impact of left ventricular ejection fraction on estimation of left ventricular filling pressures using tissue Doppler and flow propagation velocity. *Am J Cardiol* 2003;91:780-4.
87. Graham RJ, Gelman JS, Donelan L, Mottram PM, Peverill RE. Effect of preload reduction by haemodialysis on new indices of diastolic function. *Clin Sci (Lond)* 2003;105:499-506.
88. Troughton RW, Prior DL, Frampton CM, Nash PJ, Pereira JJ, Martin M, et al. Usefulness of tissue Doppler and color M-mode indexes of left ventricular diastolic function in predicting outcomes in systolic left ventricular heart failure (from the ADEPT study). *Am J Cardiol* 2005; 96:257-62.
89. Waggoner AD, Bierig SM. Tissue Doppler imaging: a useful echocardiographic method for the cardiac sonographer to assess systolic and diastolic left ventricular function. *J Am Soc Echocardiogr* 2001;14:1143-52.
90. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a non-invasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527-33.
91. Ruan Q, Rao L, Middleton KJ, Khoury DS, Nagueh SF. Assessment of left ventricular diastolic function by early diastolic mitral annulus peak acceleration rate: experimental studies and clinical application. *J Appl Physiol* 2006;100:679-84.
92. Nagueh SF, Rao L, Soto J, Middleton KJ, Khoury DS. Haemodynamic insights into the effects of ischaemia and cycle length on tissue Doppler-derived mitral annulus diastolic velocities. *Clin Sci (Lond)* 2004;106: 147-54.
93. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS. Hemodynamic determinants of mitral annulus diastolic velocities by tissue Doppler. *J Am Coll Cardiol* 2001;37:278-85.
94. Hasegawa H, Little WC, Ohno M, Brucks S, Morimoto A, Cheng HJ, et al. Diastolic mitral annular velocity during the development of heart failure. *J Am Coll Cardiol* 2003;41:1590-7.
95. Oki T, Tabata T, Yamada H, Wakatsuki T, Shinohara H, Nishikado A, et al. Clinical application of pulsed tissue Doppler imaging for assessing abnormal left ventricular relaxation. *Am J Cardiol* 1997;79:921-8.
96. Sohn D, Chai I, Lee D, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;30:474-80.
97. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000;102:1788-94.
98. Firstenberg MS, Levine BD, Garcia MJ, Greenberg NL, Cardon L, Morehead AJ, et al. Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. *J Am Coll Cardiol* 2000;36:1664-9.
99. Caiani EG, Weinert L, Takeuchi M, Veronesi F, Sugeng L, Corsi C, et al. Evaluation of alterations on mitral annulus velocities, strain, and strain rates due to abrupt changes in preload elicited by parabolic flight. *J Appl Physiol* 2007;103:80-7.
100. Rivas-Gotz C, Khoury DS, Manolios M, Rao L, Kopelen HA, Nagueh SF. Time interval between onset of mitral inflow and onset of early diastolic velocity by tissue Doppler: a novel index of left ventricular relaxation: experimental studies and clinical application. *J Am Coll Cardiol* 2003; 42:1463-70.
101. De Sutter J, De Backer J, Van de Veire N, Velghe A, De Buyzere M, Gillebert TC. Effects of age, gender, and left ventricular mass on septal mitral annulus velocity (E') and the ratio of transmitral early peak velocity to E' (E'/E'). *Am J Cardiol* 2005;95:1020-3.
102. Nagueh SF, Mikati I, Kopelen HA, Middleton KJ, Quinones MA, Zoghbi WA. Doppler estimation of left ventricular filling pressure in sinus tachycardia. A new application of tissue Doppler imaging. *Circulation* 1998;98:1644-50.
103. Kim YJ, Sohn DW. Mitral annulus velocity in the estimation of left ventricular filling pressure: prospective study in 200 patients. *J Am Soc Echocardiogr* 2000;13:980-5.
104. Sohn DW, Song JM, Zo JH, Chai IH, Kim HS, Chun HG, et al. Mitral annulus velocity in the evaluation of left ventricular diastolic function in atrial fibrillation. *J Am Soc Echocardiogr* 1999;12:927-31.
105. Sohn DW, Kim YJ, Kim HC, Chun HG, Park YB, Choi YS. Evaluation of left ventricular diastolic function when mitral E and A waves are completely fused: role of assessing mitral annulus velocity. *J Am Soc Echocardiogr* 1999;12:203-8.
106. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, 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;116:637-47.
107. Min PK, Ha JW, Jung JH, Choi EY, Choi D, Rim SJ, et al. Incremental value of measuring the time difference between onset of mitral inflow and onset of early diastolic mitral annulus velocity for the evaluation of left ventricular diastolic pressures in patients with normal systolic function and an indeterminate E'/E' . *Am J Cardiol* 2007;100:326-30.
108. Ha JW, Oh JK, Ling LH, Nishimura RA, Seward JB, Tajik AJ. Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. *Circulation* 2001;104:976-8.
109. Heimdal A, Stoylen A, Torp H, Skjaerpe T. Real-time strain rate imaging of the left ventricle by ultrasound. *J Am Soc Echocardiogr* 1998;11: 1013-9.
110. Urheim S, Edvardsen T, Torp H, Angelsen B, Smiseth OA. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation* 2000;102:1158-64.
111. Langeland S, D'hooge J, Wouters PF, Leather HA, Claus P, Bijmens B, et al. Experimental validation of a new ultrasound method for the simul-

- taneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. *Circulation* 2005;112:2157-62.
112. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol* 2006;47:789-93.
 113. Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U, et al. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. *Circulation* 2003;107:2120-6.
 114. Pislaru C, Bruce CJ, Anagnostopoulos PC, Allen JL, Seward JB, Pellikka PA, et al. Ultrasound strain imaging of altered myocardial stiffness: stunned versus infarcted reperfused myocardium. *Circulation* 2004;109:2905-10.
 115. Park TH, Nagueh SF, Khoury DS, Kopelen HA, Akrivakis S, Nasser K, et al. Impact of myocardial structure and function postinfarction on diastolic strain measurements: implications for assessment of myocardial viability. *Am J Physiol Heart Circ Physiol* 2006;290:H724-31.
 116. Abraham TP, Belohlavek M, Thomson HL, Pislaru C, Khandheria B, Seward JB, et al. Time to onset of regional relaxation: feasibility, variability and utility of a novel index of regional myocardial function by strain rate imaging. *J Am Coll Cardiol* 2002;39:1531-7.
 117. Kato T, Noda A, Izawa H, Nishizawa T, Somura F, Yamada A, et al. Myocardial velocity gradient as a noninvasively determined index of left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;42:278-85.
 118. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF. Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. *Circulation* 2007;115:1376-83.
 119. Rademakers FE, Buchalter MB, Rogers WJ, Zerhouni EA, Weisfeldt ML, Weiss JL, et al. Dissociation between left ventricular untwisting and filling. Accentuation by catecholamines. *Circulation* 1992;85:1572-81.
 120. Bell SP, Nyland L, Tischler MD, McNabb M, Granzier H, LeWinter MM. Alterations in the determinants of diastolic suction during pacing tachycardia. *Circ Res* 2000;87:235-40.
 121. DeAnda A Jr, Komeda M, Nikolic SD, Daughters GT II, Ingels NB, Miller DC. Left ventricular function, twist, and recoil after mitral valve replacement. *Circulation* 1995;92(suppl):II58-66.
 122. Gibbons Kroeker CA, Tyberg JV, Beyar R. Effects of ischemia on left ventricular apex rotation: an experimental study in anesthetized dogs. *Circulation* 1995;92:130-41.
 123. Fuchs E, Muller MF, Oswald H, Thony H, Mohacsi P, Hess OM. Cardiac rotation and relaxation in patients with chronic heart failure. *Eur J Heart Fail* 2004;6:715-22.
 124. Hees PS, Fleg JL, Dong SJ, Shapiro EP. MRI and echocardiographic assessment of the diastolic dysfunction of normal aging: altered LV pressure decline or load? *Am J Physiol Heart Circ Physiol* 2004;286:H782-8.
 125. Notomi Y, Martin-Miklovic MG, Oryszak SJ, Shiota T, Deserranno D, Popovic ZB, et al. Enhanced ventricular untwisting during exercise: a mechanistic manifestation of elastic recoil described by Doppler tissue imaging. *Circulation* 2006;113:2524-33.
 126. Dong SJ, Hees PS, Siu CO, Weiss JL, Shapiro EP. MRI assessment of LV relaxation by untwisting rate: a new isovolumic phase measure of tau. *Am J Physiol Heart Circ Physiol* 2001;281:H2002-9.
 127. Notomi Y, Lysyansky P, Setser RM, Shiota T, Popovic ZB, Martin-Miklovic MG, et al. Measurement of ventricular torsion by two-dimensional ultrasound speckle tracking imaging. *J Am Coll Cardiol* 2005;45:2034-41.
 128. Helle-Valle T, Crosby J, Edvardsen T, Lyseggen E, Amundsen BH, Smith HJ, et al. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation* 2005;112:3149-56.
 129. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF. Left ventricular untwisting rate by speckle tracking echocardiography. *Circulation* 2007;116:2580-6.
 130. Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. Left ventricular torsion by two-dimensional speckle tracking echocardiography in patients with diastolic dysfunction and normal ejection fraction. *J Am Soc Echocardiogr* 2008;21:1129-37.
 131. Scalia GM, Greenberg NL, McCarthy PM, Thomas JD, Vandervoort PM. Noninvasive assessment of the ventricular relaxation time constant (tau) in humans by Doppler echocardiography. *Circulation* 1997;95:151-5.
 132. Yamamoto K, Masuyama T, Doi Y, Naito J, Mano T, Kondo H, et al. Noninvasive assessment of LV relaxation using continuous wave Doppler aortic regurgitant velocity curve: its comparative value to the mitral regurgitation method. *Circulation* 1995;91:192-200.
 133. Honda Y, Yokota Y, Yokoyama M. Evaluation of left ventricular relaxation using the continuous-wave Doppler velocity profile of aortic regurgitation: noninvasive measurement of left ventricular negative dP/dt and time constant. *Clin Cardiol* 1996;19:709-15.
 134. Nishimura RA, Schwartz RS, Tajik AJ, Holmes DR Jr. Noninvasive measurement of rate of left ventricular relaxation by Doppler echocardiography: validation with simultaneous cardiac catheterization. *Circulation* 1993;88:146-55.
 135. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004;350:1953-9.
 136. Gorcsan J III, Gasior TA, Mandarino WA, Deneault LG, Hattler BG, Pinsky MR. Assessment of the immediate effects of cardiopulmonary bypass on left ventricular performance by on-line pressure-area relations. *Circulation* 1994;89:180-90.
 137. Ohno M, Cheng CP, Little WC. Mechanism of altered patterns of left ventricular filling during the development of congestive heart failure. *Circulation* 1994;89:2241-50.
 138. Little WC, Ohno M, Kitzman DW, Thomas JD, Cheng CP. Determination of left ventricular chamber stiffness from the time for deceleration of early left ventricular filling. *Circulation* 1995;92:1933-9.
 139. Marino P, Faggian G, Bertolini P, Mazzucco A, Little WC. Early mitral deceleration and left atrial stiffness. *Am J Physiol Heart Circ Physiol* 2004;287:H1172-8.
 140. Garcia MJ, Firstenberg MS, Greenberg NL, Smedira N, Rodriguez L, Prior D, et al. Estimation of left ventricular operating stiffness from Doppler early filling deceleration time in humans. *Am J Physiol Heart Circ Physiol* 2001;280:H554-61.
 141. Marino P, Little WC, Rossi A, Barbieri E, Anselmi M, Destro G, et al. Can left ventricular diastolic stiffness be measured noninvasively? *J Am Soc Echocardiogr* 2002;15:935-43.
 142. Shmuylovich L, Kovacs SJ. E-wave deceleration time may not provide an accurate determination of LV chamber stiffness if LV relaxation/viscoelasticity is unknown. *Am J Physiol Heart Circ Physiol* 2007;292:H2712-20.
 143. Pai RG, Suzuki M, Heywood T, Ferry DR, Shah PM. Mitral A velocity wave transit time to the outflow tract as a measure of left ventricular diastolic stiffness. Hemodynamic correlations in patients with coronary artery disease. *Circulation* 1994;89:553-7.
 144. Pai RG, Varadarajan P. Relative duration of transmitted mitral A wave as a measure of left ventricular end-diastolic pressure and stiffness. *Echocardiography* 2004;21:27-31.
 145. Ha JW, Lulic F, Bailey KR, Pellikka PA, Seward JB, Tajik AJ, et al. Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. *Am J Cardiol* 2003;91:114-5.
 146. Ha JW, Oh JK, Pellikka PA, Ommen SR, Stussy VL, Bailey KR, et al. Diastolic stress echocardiography: a novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. *J Am Soc Echocardiogr* 2005;18:63-8.
 147. Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;47:1891-900.
 148. Duncan AM, Lim E, Gibson DG, Henein MY. Effect of dobutamine stress on left ventricular filling in ischemic dilated cardiomyopathy: pathophysiology and prognostic implications. *J Am Coll Cardiol* 2005;46:488-96.

149. Hatle L, Appleton CP, Popp R. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989;79:357-70.
150. Oh JK, Hatle L, Seward JB, Danielson GK, Schaff HV, Reeder GS, et al. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol* 1994;23:154-62.
151. Tabata T, Kabbani SS, Murray RD, Thomas JD, Abdalla I, Klein AL. Difference in the respiratory variation between pulmonary venous and mitral inflow Doppler velocities in patients with constrictive pericarditis with and without atrial fibrillation. *J Am Coll Cardiol* 2001;37:1936-42.
152. Garcia M, Rodriguez L, Ares M, Griffin BP, Thomas JD, Klein AL. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. *J Am Coll Cardiol* 1996;27:108-14.
153. Ha J, Ommen SR, Tajik AJ, Barnes ME, Ammass NM, Gertz MA, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy using mitral annular velocity by tissue Doppler echocardiography. *Am J Cardiol* 2004;94:316-9.
154. Choi EY, Ha JW, Kim JM, Ahn JA, Seo HS, Lee JH, et al. Incremental value of combining systolic mitral annular velocity and time difference between mitral inflow and diastolic mitral annular velocity to early diastolic annular velocity for differentiating constrictive pericarditis from restrictive cardiomyopathy. *J Am Soc Echocardiogr* 2007;20:738-43.
155. Sohn DW, Kim Y, Kim HS, Kim KB, Park YB, Choi YS. Unique features of early diastolic mitral annulus velocity in constrictive pericarditis. *J Am Soc Echocardiogr* 2004;17:222-6.
156. Olson JJ, Costa SP, Young CE, Palac RT. Early mitral filling/diastolic mitral annular velocity ratio is not a reliable predictor of left ventricular filling pressure in the setting of severe mitral regurgitation. *J Am Soc Echocardiogr* 2006;19:83-7.
157. Bruch C, Stypmann J, Gradaus R, Breithardt G, Wichter T. Usefulness of tissue Doppler imaging for estimation of filling pressures in patients with primary or secondary pure mitral regurgitation. *Am J Cardiol* 2004;93:324-8.
158. Temporelli PL, Scapellato F, Corrà U, Eleuteri E, Imparato A, Giannuzzi P. Estimation of pulmonary wedge pressure by transmitral Doppler in patients with chronic heart failure and atrial fibrillation. *Am J Cardiol* 1999;83:724-7.
159. Chirillo F, Brunazzi MC, Barbiero M, Giavarina D, Pasqualini M, Franceschini-Grisolia E, et al. Estimating mean pulmonary wedge pressure in patients with chronic atrial fibrillation from transthoracic Doppler indexes of mitral and pulmonary venous flow velocity. *J Am Coll Cardiol* 1997;30:19-26.
160. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:757-68.
161. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. *Circulation* 2007;116:2702-8.
162. Menzel T, Wagner S, Kramm T, Mohr-Kahaly S, Mayer E, Braeuninger S, et al. Pathophysiology of impaired right and left ventricular function in chronic embolic pulmonary hypertension: changes after pulmonary thromboendarterectomy. *Chest* 2000;118:897-903.
163. Ruan Q, Nagueh SF. Clinical application of tissue Doppler imaging in patients with idiopathic pulmonary hypertension. *Chest* 2007;131:395-401.
164. Moller JE, Sondergaard E, Seward JB, Appleton CP, Egstrup K. Ratio of left ventricular peak E-wave velocity to flow propagation velocity assessed by color M-mode Doppler echocardiography in first myocardial infarction: prognostic and clinical implications. *J Am Coll Cardiol* 2000;35:363-70.
165. Moller JE, Sondergaard E, Poulsen SH, Egstrup K. Pseudonormal and restrictive filling patterns predict left ventricular dilation and cardiac death after a first myocardial infarction: a serial color M-mode Doppler echocardiographic study. *J Am Coll Cardiol* 2000;36:1841-6.
166. Moller JE, Sondergaard E, Poulsen SH, Seward JB, Appleton CP, Egstrup K. Color M-mode and pulsed wave tissue Doppler echocardiography: powerful predictors of cardiac events after first myocardial infarction. *J Am Soc Echocardiogr* 2001;14:757-63.
167. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. *J Am Coll Cardiol* 2003;41:820-6.
168. Yamamoto T, Oki T, Yamada H, Tanaka H, Ishimoto T, Wakatsuki T, et al. Prognostic value of the atrial systolic mitral annular motion velocity in patients with left ventricular systolic dysfunction. *J Am Soc Echocardiogr* 2003;16:333-9.
169. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003;289:194-202.
170. Hillis GS, Moller JE, Pellikka PA, Gersh BJ, Wright RS, Ommen SR, et al. Noninvasive estimation of left ventricular filling pressure by E/E' is a powerful predictor of survival after acute myocardial infarction. *J Am Coll Cardiol* 2004;43:360-7.
171. Wang M, Yip G, Yu CM, Zhang Q, Zhang Y, Tse D, et al. Independent and incremental prognostic value of early mitral annulus velocity in patients with impaired left ventricular systolic function. *J Am Coll Cardiol* 2005;45:272-7.
172. Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol* 2005;45:1223-6.
173. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricular hypertrophy. *J Hypertens* 2005;23:183-91.
174. Sharma R, Pellerin D, Gaze DC, Mehta RL, Gregson H, Streather CP, et al. Mitral peak Doppler E-wave to peak mitral annulus velocity ratio is an accurate estimate of left ventricular filling pressure and predicts mortality in end-stage renal disease. *J Am Soc Echocardiogr* 2006;19:266-73.
175. Okura H, Takada Y, Kubo T, Iwata K, Mizoguchi S, Taguchi H, et al. Tissue Doppler-derived index of left ventricular filling pressure, E/E', predicts survival of patients with non-valvular atrial fibrillation. *Heart* 2006;92:1248-52.
176. Bruch C, Klem I, Breithardt G, Wichter T, Gradaus R. Diagnostic usefulness and prognostic implications of the mitral E/E' ratio in patients with heart failure and severe secondary mitral regurgitation. *Am J Cardiol* 2007;100:860-5.
177. McMahon CJ, Nagueh SF, Pignatelli RH, Denfield SW, Dreyer WJ, Price JF, et al. Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. *Circulation* 2004;109:1756-62.
178. McMahon CJ, Nagueh SF, Eapen RS, Dreyer WJ, Finkelstyn I, Cao X, et al. Echocardiographic predictors of adverse clinical events in children with dilated cardiomyopathy: a prospective clinical study. *Heart* 2004;90:908-15.
179. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, et al; for the I-PRESERVE Investigators. The Irbesartan in Heart Failure With Preserved Systolic Function (I-PRESERVE) trial: rationale and design. *J Card Fail* 2005;11:576-85.