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# Comprehensive Echocardiographic Assessment of Diastolic Function

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It is now recognized that 30% to 50% of patients who have symptomatic congestive heart failure have preserved left ventricular (LV) ejection fraction [1,2]. Abnormalities in diastolic function not only assume a fundamental role in these but also relate to the severity of symptoms and prognosis in all heart failure patients, regardless of the cause [3,4].

Two-dimensional (2D) and Doppler echocardiography are the most important clinical tools available for the diagnosis of diastolic dysfunction [5]. Echocardiography is widely available, portable, and biologically safe and is also capable of excluding other important causes of heart failure, such as valvular disease. The recent integration of new Doppler modalities in many cases can establish the specific pathophysiologic abnormalities involved and can provide reasonably accurate quantification. In most cases, a comprehensive integration of clinical data, 2D structural information, and Doppler physiologic data is required to provide a complete evaluation.

Diastolic dysfunction may be defined as the inability of the heart to maintain an adequate cardiac output under normal filling pressure [6]. This inability may manifest early as impaired exercise tolerance or as overt left- and right-sided heart failure at rest. There are numerous physiologic parameters that can affect LV diastolic function. These parameters interact to maintain LV filling under relatively low atrial pressure. Of these parameters, the most important intrinsic parameters are the rate of LV relaxation, the stiffness of the LV chamber, and the contractility of the left atrium (LA) (Box 1). Preload and afterload are also critical extrinsic parameters that will contribute to determining the LV filling pressures and cardiac output.

## Left ventricular relaxation

LV relaxation is the most important determinant of the initial phase of diastole. LV relaxation is an energy-dependent process that starts with the reuptake of $Ca^{2+}$ by the sarcoplasmic reticulum, which in turn inactivates the troponin–tropomyosin complex [7], allowing the myocardial fiber to stretch. Rapid relaxation of the LV myocytes generates a force that rapidly decreases the LV intracavitary pressure during early diastole and generates a pressure gradient across the mitral valve, drawing blood from the LA. The onset of LV relaxation is asynchronous, starting earlier in the most apical myocardial segments, leading to the development of a negative intracavitary pressure gradient [8]. In ischemic and dilated cardiomyopathies these gradients are markedly reduced [9]. Increased cardiac mass and conduction abnormalities can also reduce the rate of LV relaxation by slowing the transmission of the depolarizing current. Using high-fidelity pressure recordings, LV relaxation can be estimated from the rate of intracavitary pressure decay during isovolumic relaxation, the period between aortic valve closure and mitral opening. The time constant of isovolumic relaxation ($\tau$) is consid-

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**Box 1. Evaluation of diastolic function parameters using combined Doppler indices**

*Impaired relaxation*

E < A
E > A + low $v_P$ or $E_M$

*Increased LV stiffness*

Short DT

*Decreased LA contractility*

Low A + AR

*Elevated Filling pressures*

Short DT (if LV dilated, low EF)
Increased E/$v_P$
Increased E/$E_M$

*Abbreviations:* A, left ventricular filling pulsed Doppler atrial contraction velocity; AR, pulmonary venous atrial contraction reversed flow velocity; DT, left ventricular early filling pulsed Doppler deceleration time; E, left ventricular early filling pulsed Doppler velocity, $E_M$, early diastolic myocardial tissue Doppler velocity; $v_P$, color M-mode Doppler early diastolic left ventricular propagation velocity.

ered the gold standard that defines LV relaxation. The fall in intraventricular pressure follows an exponential curve and is used to determine $\tau$, assuming either zero ($p_0 e^{-t/\tau}$) or nonzero ($p_0 e^{-t/\tau} + p_b$) asymptote [10,11]. A small value of $\tau$ indicates rapid relaxation and is related directly to the duration of isovolumic relaxation (*IVRT*), whereas it is related inversely to the magnitude of the difference between LV pressure at aortic closure ($P_0$) and LV pressure at mitral opening ($P_{MV}$), as shown in Eq. 1:

$$\tau = IVRT/(\ln P_0 - \ln P_{MV}) \quad (1)$$

Because of its high temporal resolution, M-mode echocardiography can provide precise timing of cardiac events, such as the relationship between the onset of LV contraction and relaxation and the opening and closure of the cardiac valves. M-mode studies may demonstrate changes that occur in LV geometry during isovolumic contraction and relaxation. The velocities of circumferential and longitudinal fiber shortening, as determined from digitized M-mode tracings, are reduced in patients who have cardiomyopathy and hypertensive heart disease with slow LV relaxation [12,13].

2D echocardiography can establish the presence of global and regional LV systolic function abnormalities, increased LV mass, and LA size that are often present in patients who have abnormal LV relaxation. In many patients, regional variability in the magnitude and time of onset of early diastolic endocardial motion may be demonstrated using acoustic quantification for automated boundary detection and color-encoded phase analysis of endocardial motion (color-kinesis) [14,15].

Doppler velocities of LV filling are affected by abnormalities of LV relaxation and preload. Doppler velocities relate to pressure gradients as determined by the Bernoulli flow equation. This equation has three basic components, of which the spectral Doppler component permits obtaining only the convective component (Eq. 2):

$$\left[1/2\rho \times \left(v_V{}^2 - v_A{}^2\right)\right] \quad (2)$$

Thus, spectral Doppler velocities alone cannot provide a quantitative assessment of the pressure gradients across a nonstenotic mitral valve. Nevertheless, there is a direct relationship between the convective and the total pressure gradient that permits obtaining a *qualitative* relationship. This qualitative relationship is fundamental for explaining the clinical observations that relate LV Doppler filling velocities to normal and abnormal diastolic functions. As the ventricular myocardium relaxes during early diastole, the LV cavity pressure ($P_v$) falls below LA pressure ($P_a$). The magnitude of the atrioventricular pressure gradient ($P_a - P_v$) during early LV filling is variable. Rapid relaxation (short $\tau$) generates a low LV minimal pressure, increasing the magnitude of this gradient. On the other hand, an elevated $p_a$ in patients who have heart failure and volume overload has a similar effect. The early atrioventricular pressure gradient accelerates the blood across the mitral valve, generating the early filling (Doppler E) wave. In general, the larger the filling volume during early diastole, the smaller will be the contribution of atrial contraction (Doppler A). During early diastole, the mitral valve opens partially, emptying the LA. Simul-

taneously, the LA volume is replaced by new blood entering from the pulmonary veins (Doppler D). Reduced E velocity, D velocity, and the E/A ratio may indicate either slow LV relaxation or low preload (Fig. 1). For this reason, these indices alone cannot be used reliably to determine LV relaxation. $\tau$ may be estimated from the IVRT, systolic blood pressure ($p_s$), and capillary wedge pressure ($p_w$) [16] as shown in Eq. 3:

$$\tau = \{IVRT/\ln(p_s) - \ln(p_w)\} \quad (3)$$

Although this method requires an invasive assessment of LA pressure, it may have a practical value in patients admitted to the intensive care unit who are undergoing hemodynamic monitoring.

As described elsewhere, standard pulsed-wave Doppler echocardiography provides the temporal distribution of blood flow velocities in a single spatial location. In contrast, color M-mode Doppler echocardiography provides the spatiotemporal distribution of these velocities across a scan line. The information displayed in a color M-mode recording of the LV inflow can be compared with that given by multiple simultaneous pulsed Doppler tracings obtained at different levels from the mitral orifice to the LV apex. The onset of flow at the mitral valve level occurs earlier than at the apical regions. The velocity at which the flow propagates within the ventricle ($v_p$) is given by the slope of the color wavefront. Studies have shown a negative correlation between $v_p$ and $\tau$ in various groups of patients who have coronary disease and cardiomyopathy [17]; and in experimental models, $v_p$ has been shown to decrease during ischemia and increase during catecholamine administration [18,19]. In comparison to standard Doppler filling indices, $v_p$ is relatively insensitive to alterations in preload [20,21]. Thus, pulsed Doppler indices are more similar in patients who have normal diastolic function (normal LV relaxation and normal preload) than in those with advanced diastolic dysfunction (abnormal relaxation and elevated preload). In contrast, color M-mode Doppler $v_p$ is significantly reduced in the latter and correlates better with $\tau$. Young, healthy subjects have a color M-mode $v_p$ >55 cm/s. Older patients or those who have left ventricular hypertrophy, normal systolic function, and delayed relaxation have lower $v_p$ and low-pulsed Doppler E velocity and an E/A ratio of <1. Patients who have advanced diastolic dysfunction have low $v_p$ but higher pulsed Doppler E and an E/A ratio of >1. Numerical velocity values can be obtained in addition to spatial and temporal information, allowing a *quantitative* estimate of true pressure gradients using the complete Bernoulli's equation,

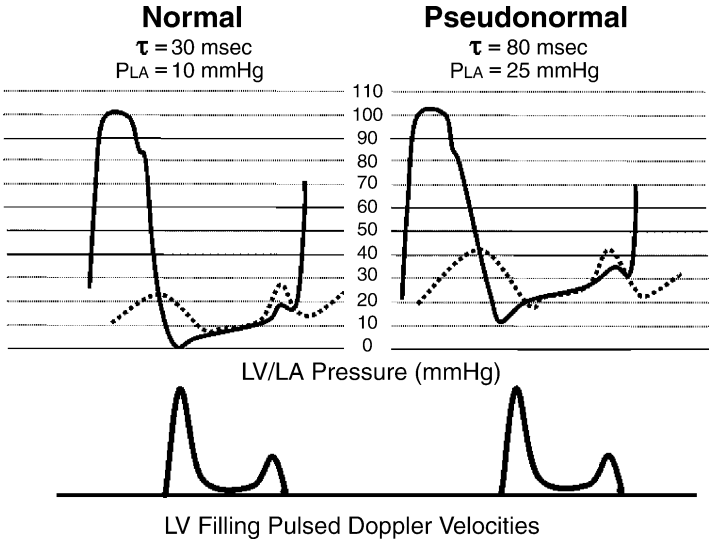


Fig. 1. Influence of preload and relaxation in LV filling pulsed Doppler indices. The normal pattern (*bottom left*) is obtained in the presence of normal relaxation ($\tau = 30$ ms) and normal LA pressure ($P_{LA} = 10$ mm Hg). The pseudonormal pattern (*bottom right*) is obtained in the presence of slow LV relaxation ($\tau = 80$ ms) and elevated LA pressure ($P_{LA} = 25$ mm Hg). Simultaneous LV pressure (*solid lines*) and LA pressure (*dash lines*) are shown at the top.

including its inertial term [22] (Eq. 4) or the simplified Euler equation [23] (Eq. 5):

$$\rho \int_{A}^{V} \frac{d\vec{v}}{dt} \cdot d\vec{s} \tag{4}$$

$$-\frac{\partial p}{\partial s} = \rho\left[\frac{\partial v}{\partial t} + v\frac{\partial v}{\partial s}\right] \tag{5}$$

This physical relationship explains empirical observations that relate color M-mode indices with LV relaxation, given the association previously described between the generation of intraventricular pressure gradients (IVPG), suction, and relaxation (Fig. 2).

Tissue Doppler echocardiography (TDE) bypasses the high-pass filter and uses low-gain amplification to display the velocities of the myocardium and to eliminate the weaker intensity blood flow signals. TDE velocities may be displayed either in spectral pulsed or color-encoded M-mode or by 2D maps superimposed over structural images [24]. The technical principles and limitations of these modalities are similar to those encountered with standard Doppler flow systems. TDE may provide myocardial velocities at multiple locations of the myocardium using different echocardiographic acoustic windows. Following a positive wave represents ventricular systole ($S_M$); two waves corresponding to early filling ($E_M$) and atrial contraction ($A_M$) appear as a mirror image of the mitral inflow early (E) and atrial (A) filling velocities (Fig. 3). In healthy subjects, the peak of $E_M$ is detected earlier than the peak of LV filling E velocity, suggesting that the rapid relaxation of the myocardium generates a suction force that draws blood into the ventricle. TDE velocities may be affected by translation and rotation of the heart; this is particularly problematic when imaging from the parasternal window. To overcome this limitation, the motion of the LV myocardium can instead be measured in the longitudinal axial plane from the apical acoustic window [25]. Off-line analysis of color M-mode TDE may be used to separate velocity components caused by intrinsic myocardial contraction and relaxation from the translational motion of the heart. One method plots the velocity of each adjacent scan line as the distance from epicardium to endocardium. From a parasternal color M-mode image, the rates of circumferential fiber shortening and lengthening are proportional to the slope of the velocity divided by distance of the regression line. The value of this slope has been referred to as myocardial velocity gradient (MVG). Diastolic MVG have been shown to differentiate myocardial hypertrophy seen in athletes from hypertrophic cardiomyopathy [26]. Another approach obtains the velocity of myocardial segmental systolic thickening and lengthening, or "strain rate," by dividing the difference in velocity ($v_2 - v_1$) between two points by their spatial separation ($s_2 - s_1$). This method can be applied to evaluate the kinetic response of longitudinal or circumferential fibers of the myocardium from the apical or parasternal acoustic imaging views. In healthy subjects, the velocities of the myocardium during diastole are a mirror image of pulsed Doppler

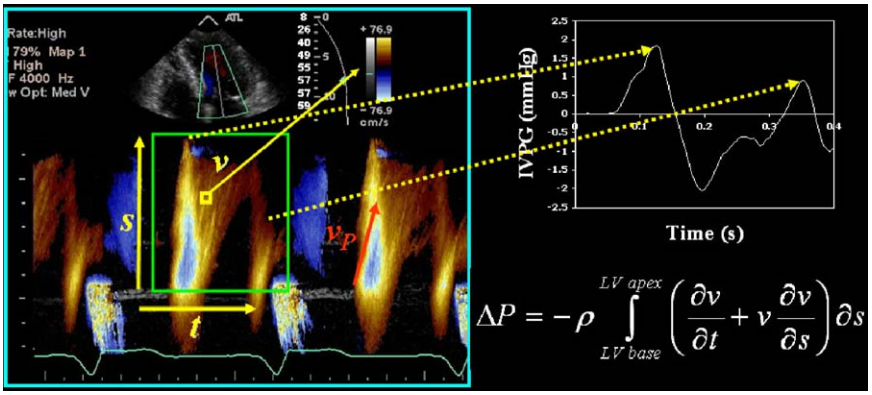


Fig. 2. Color M-mode Doppler assessment of left ventricular filling. $v_P$ represents the slope of the early filling propagation wavefront, measured from the tip of the mitral leaflets to 4 cm distally toward the apex at the first aliasing velocity transition (*red–blue*). The IVPG (*top right*) are determined from computational analysis of velocity (v), space (s) and time (t) using Euler's hydrodynamic equation (*bottom right*). The first positive component corresponds to early diastolic suction. Solid arrows indicate spatial and temporal coordinates. Velocity (v) information is obtained from color table. Dashed arrows point to calculated peak IVPGs during early filling and atrial contraction.

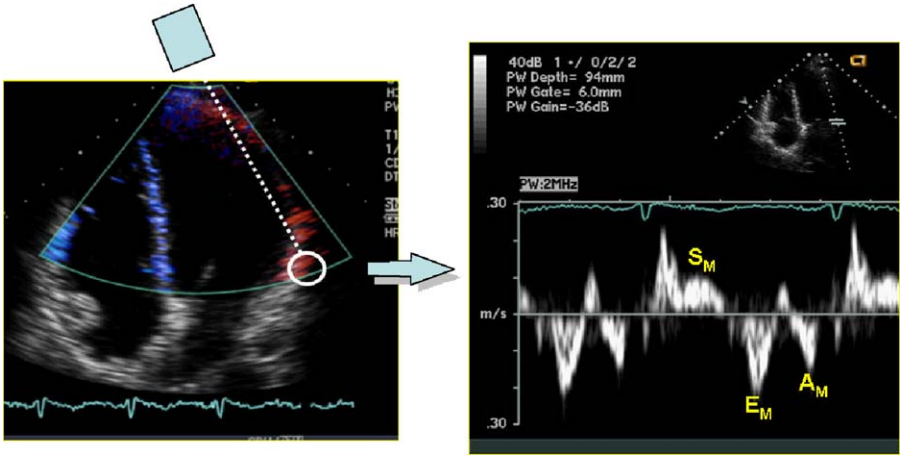


Fig. 3. Tissue Doppler velocities. Color-encoded tissue Doppler velocities obtained in the apical four-chamber view are shown on the left panel. Spectral pulsed Doppler systolic ($S_M$), early diastolic ($E_M$), and atrial contraction ($A_M$) myocardial velocities obtained at the base of the lateral wall are shown on the right image.

transmitral LV filling velocities. Studies have shown an inverse relationship between $E_M$ and LV relaxation ($\tau$) [27,28], both in patients who have normal and those who have elevated preload. Tissue Doppler $E_M$ also appears to be less affected by preload than standard Doppler LV filling indices [27], particularly in the presence of slow ventricular relaxation [29]. Clinical studies suggest that $E_M$ is a better discriminator between patients who have diastolic dysfunction and normal patients, when compared with any other single or combined index of transmitral filling and pulmonary venous Doppler flows [30].

## Left ventricular stiffness

When a myocardial fiber is subjected to a given load (stress), it responds by stretching to a given length (strain). The distensibility (strain–stress relationship) of a muscle fiber is typically nonlinear; that is, the force required to stretch a muscle fiber increases geometrically as the fiber is stretched [31]. This property determines a curvilinear relationship between volume and pressure in the ventricle. As the volume of the LV increases during diastole, the intracavitary pressure also increases. The magnitude of pressure change (dP) over a given change in volume (dV) defines the operating stiffness of the LV ($S_{LV}$). Therefore, with increasing LV filling volume (preload) there is a proportionately larger increase in LV pressure and $S_{LV}$. Paradoxically, a slow LV relaxation rate decreases the apparent $S_{LV}$ during early filling, because myocardium continues to relax during this period [32], which tends to decrease LV cavity pressure. LV relaxation usually does not affect $S_{LV}$ during late diastole, when it is determined mostly by passive properties. The curvilinear slope of the ventricular pressure volume curve can vary according to myocardial fiber distensibility, elasticity of the connective tissue, LV cavity diameter and wall thickness, the duration of active relaxation, and the effect of pericardial constraint. This slope may be represented as the relative dP/dV ratio for a given LV pressure (P), defining the LV diastolic stiffness constant ($K_{LV}$) (Fig. 4). A higher proportion of collagen to elastic fibers, as seen with aging, hypertensive heart disease, cardiomyopathies, and after myocardial infarction, results in an increased $K_{LV}$ [33–35]. The external constraining effect of the pericardium increases $K_{LV}$, a phenomenon that becomes clinically relevant in constrictive pericarditis.

Standard pulsed Doppler velocities of LV filling and pulmonary venous flow may be used to estimate LV stiffness parameters. As the volume of blood enters the LV cavity, LV pressure ($P_v$) increases and LA pressure ($P_a$) decreases until the gradient disappears or reverses, causing a deceleration of E. The deceleration time of E (DT) has been shown to be related to the operating stiffness of the LV in clinical studies [36]. In vitro studies have shown that the rate of early transmitral flow deceleration through a restrictive orifice is proportional to net atrioventricular stiffness ($S_{NET}$) [37,38]. Experiments in an animal model of dilated cardiomyopathy have also

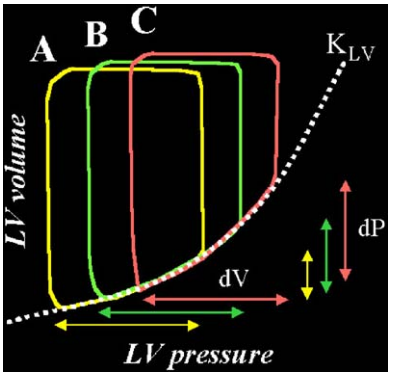


Fig. 4. Calculation of LV stiffness parameters. The LV operating stiffness ($S_{LV}$) is determined by LV pressure-volume relationship (d) over a cardiac cycle ($S_{LV} = \Delta P/\Delta V$). The $\Delta P/\Delta V$ relationship is load-dependent; at higher LV end-diastolic pressure (from A to B and C) (*horizontal and vertical arrows*), $\Delta P$ increases for an equivalent $\Delta V$. The relationship between $S_{LV}$ and end-diastolic volume is determined by the value of the exponential LV stiffness constant ($K_{LV}$), which may be significantly elevated in patients who have hypertrophic and restrictive cardiomyopathies.

validated an analytical expression applicable to non-restrictive orifices relating $S_{LV}$ to 1/DT [39,40]. In humans with cardiac disease, Garcia and colleagues [41] demonstrated recently that DT could be applied clinically to provide a quantitative estimate of LV operating stiffness ($S_{LV} = 70/DT^2$). Following LA systole, some amount of blood is propelled backward into the valveless pulmonary veins. The relative duration of the LV filling A wave and pulmonary venous atrial reversal (AR) wave is inversely related to LV end-diastolic stiffness [42].

## Left atrium contractility

The left atrium has three important functions. It acts as a reservoir of blood, a passive conduit during early LV filling, and an active pump at end diastole [43]. In young, healthy subjects, its role as a pump is insignificant, contributing to <20% of the total filling volume. In the presence of impaired LV relaxation, the atrial contribution to LV filling increases significantly, at times to over 50%. This is an adaptive mechanism governed by the Frank–Starling law, which states that as the volume and pressure in the LA before its contraction increases, LA contractility also increases. In these patients, LV end-diastolic pressure is elevated, but the mean atrial pressure remains relatively normal at rest. Symptoms are usually absent or minimal unless atrial fibrillation occurs. With worsening LV diastolic function and elevation of LV filling pressure, the LA size increases, losing eventually its mechanical efficiency in advanced stages. Left atrial mechanical function also may be decreased after cardioversion of atrial fibrillation [44].

Following a period of diastasis, the LA contracts, increasing $P_a$ and $P_a - P_v$, accelerating flow across the mitral valve (A wave). The magnitude of the A wave is proportional to the stroke volume and contractility of the LA. The magnitude of the AR flow is also related directly to LA systolic stroke volume, and combining both A and AR, a quantitative estimate of LA

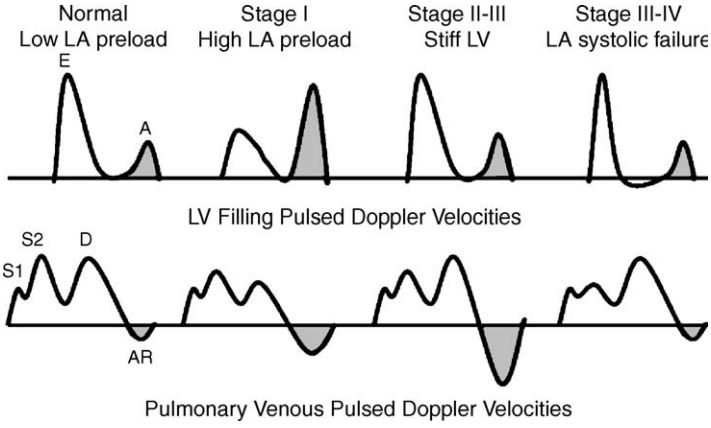


Fig. 5. Evaluation of atrial contractility from LV filling and pulmonary venous pulsed Doppler velocities. The sum of the LV filling atrial (A) area and the pulmonary venous LA reversed flow (AR) area are related directly to the LA contraction stroke volume. A, atrial contraction; D, diastolic; E, early diastolic; S1, first systolic component; S2, second systolic component.

contractility can be obtained (LA dP/dt = 0.1 $A_{AC}$ + 1.8 AR − 4.1 mm Hg) (Fig. 5) [45].

## Left ventricular filling pressure

Several investigators have studied the value of Doppler echocardiography for the assessment of LV filling pressures [46–49]. Most of these studies have demonstrated a relationship among mean LA pressure and the pulmonary venous S/D and mitral E/A ratios and IVRT and DT. A difference in the pulmonary venous inflow AR and mitral inflow A wave duration exceeding 30 ms has been shown to be useful in predicting an LV end-diastolic pressure >15 mm Hg [42]. All these previously proposed methods are accurate when applied to groups of patients who have homogeneously impaired LV relaxation, because the methods assume that the reduction in IVRT, atrial filling fraction, pulmonary venous S/D ratio, and DT will occur solely as a consequence of elevated LA pressure. However, when these methods are applied to younger patients and those who have minimal structural heart disease with a normal EF [50,51], the results overestimate actual LV filling pressure, because the methods cannot separate the effect of LV relaxation and preload as confounding variables. Color M-mode and tissue Doppler velocities used as an index of LV relaxation may be combined with standard Doppler flow indices to separate these confounding effects. As discussed previously, LA pressure and LV relaxation are the main determinants of pulsed Doppler E velocity. A positive linear relation between E and LA pressure and a negative but still linear inverse relationship between E and $\tau$ have been shown in animal experiments. Because there is a strong (negative) linear correlation between $v_p$ and $\tau$, pulsed and color M-mode Doppler data can be combined to predict LApressure, LAP = 5.27 × ($E/v_p$) + 4.6 mm Hg ($r = 0.80$, $P < .001$, Standard Error of the Estimate [SEE] = 3.1 mm Hg). This equation has been developed and validated in relatively heterogeneous groups of patients admitted to coronary, medical, and surgical intensive care units. A normal subject who has rapid relaxation under normal preload conditions will have both increased E and $v_p$. A subject who has impaired relaxation and normal preload will have both reduced E and $v_p$. In contrast, a patient who has impaired relaxation but elevated preload will exhibit a prominent E but a reduced $v_p$. Based on the same principles, the combination of standard pulsed Doppler and diastolic myocardial velocities measured by TDE has also been shown to provide an accurate estimation of LV filling pressure [52].

## Diastolic function patterns

The general clinical and echocardiographic evaluation of diastolic function recognizes four distinct stages, evolving from normal to advanced disease. These patterns are not unique to a specific disease but represent a spectrum of conditions, which is determined by changing hemodynamic variables.

The normal filling pattern is seen in patients who have normal LV relaxation rate, compliance, and filling pressures. The atrial contribution to LV filling is minimal. Thus, standard Doppler indices of LV filling and pulmunoary venous (PV) flow are characterized by high E, a E/A ratio of <1, IVRT<100 ms, and DT< 220 ms. In healthy, young adults, a rapid relaxation rate results in near-complete LV filling during early diastole, causing a relatively short IVRT and a prominent E. The LA behaves primarily as a reservoir and conduit, and D is prominent because it follows transmitral E. Because the LA volume before atrial contraction is minimal, LA contractility is reduced, resulting in low ejection volume, A and AR velocities, reduced LA relaxation force, and consequently low pulmonary venous systolic relaxation (S1) velocity. As the atrial contribution to LV filling increases with age, A and S become more prominent and the S/D ratio becomes >1. Color M-mode $v_p$ is fast, usually >55 cm/s in younger and >45 cm/s in older adults [53]. Tissue Doppler $E_m$ velocities are >10 and >8 cm/s, respectively.

The delayed relaxation (stage I) pattern of diastolic dysfunction is seen in patients who have a reduced LV relaxation rate but relatively normal compliance and filling pressures. Patients are minimally symptomatic (New York Heart Association [NYHA] class I) or may have mild dyspnea during exercise. Atrial size and its contribution to LV filling are increased, frequently >30% of the stroke volume. The delayed relaxation pattern is characterized by an E/A ratio <1, and IVRT (>100 ms). Ongoing relaxation acts by lowering LV cavity pressure during early LV filling, thus reducing early operating stiffness ($S_{LV}$). This results in a prolongation of DT (>220 ms). Pulmonary venous flows show S >D, and the AR may be normal or increased depending on the LV end diastolic pressure. Color M-mode $v_p$ is reduced (<45 cm/s), as is $E_m$ (<8 cm/s).

The pseudonormal (stage II) pattern is often the most difficult to recognize because, as its name implies, Doppler filling indices resemble those found in normal subjects. LV relaxation rate is reduced but filling pressure is now increased as a compensatory or over-compensatory mechanism to maintain cardiac output. Patients have mild-to-moderate symptoms

(NYHA class II) of pulmonary vascular congestion and various degrees of LA enlargement, depending on the chronicity of disease. Other echocardiographic evidence of structural heart disease, such as increased LA and LV volumes and mass and reduced ejection fraction, is commonly present. The elevated LA pressure results in an earlier opening of the mitral valve and thus shorter IVRT. Increased $S_{LV}$ causes a rapid increase in LV pressure with cessation of LV filling and a low normal DT (range 150–220 ms). The atrial contribution to LV filling is relatively reduced because of the increased end-diastolic LV stiffness, resulting in reduced mitral inflow A wave, and the pulmonary venous S/D ratio may be normal or <1, depending on the mean LAP. An important diagnostic clue is that the pulmonary venous AR is >35 cm/s, unless atrial mechanical failure is present. Because LV relaxation is impaired, color M-mode $v_p$ remains reduced, <45 cm/s, as does $E_m$ (<8 cm/s).

The restrictive (NYHA stage III–IV) filling pattern is seen in the presence of severely increased $S_{LV}$ and markedly increased filling pressure. LV relaxation is reduced. Patients have overt heart failure (NYHA class III-IV) and moderate-to-severe LA enlargement depending on the chronicity of disease. Echocardiographic features of advanced structural heart disease are invariably present, and LV systolic function is almost always impaired. Standard Doppler filling indices are characterized by an increased E/A ratio (>2), a short DT (<150 ms), and IVRT (<60 ms). Pulmonary venous flow usually shows markedly blunted S. The AR is usually prominent, similar to the pseudonormal stage, unless there is atrial mechanical failure [54]. Color M-mode $v_p$ and $E_m$ are very low, except in patients who have constrictive pericarditis in whom LV relaxation is normal. Reversibility with a Valsalva or other preload-reducing maneuvers differentiates the reversible (stage III) from the irreversible (stage IV) restrictive pattern, which carries a worse prognosis.

## Diastolic function assessment in specific cardiac diseases

Most patients who have clinical diastolic dysfunction have hypertensive heart disease. Long-standing arterial hypertension augments LV systolic stress, inducing myocardial fiber hypertrophy and increasing LV wall thickness [55,56]. Genetic and hormonal factors, including circulating angiotensin and insulin levels, may also play a role in the development of cardiac hypertrophy. This physiologic adaptation eventually leads to increased LV chamber stiffness. Ventricular relaxation is also prolonged because of the increased proportion of collagen fibers and because of the slow sequence of electrical repolarization that leads to nonuniform relaxation. Pulsed Doppler filling patterns evolve from a pattern of delayed relaxation to pseudonormal and restrictive filling, with the development of heart failure symptoms [57,58]. Hypertensive cardiomyopathy is responsible for approximately one third of patients who have heart failure who require hospitalization [57,58]. Serial echocardiographic studies are useful for monitoring the effect of antihypertensive therapy causing regression of hypertrophy [59,60].

Ischemia affects relaxation by limiting the availability of energy substrates in the form of ATP. The reabsorption of $Ca^{2+}$ ions by the sarcoplasmic reticulum is an energy-dependent process, which is required for the deactivation of the troponin–tropomyosin complex. In the presence of normal systolic function at baseline, ischemia is manifested by a change to a pattern of impaired LV relaxation. Chronically ischemic or scarred myocardium may become stiffer because of the development of interstitial fibrosis [61,62]. Doppler LV filling patterns will vary according to the extent, duration, and severity of ischemia. These patterns have been shown to carry important prognostic information after an acute myocardial infarction [63] and in chronic ischemic heart disease [50].

The restrictive cardiomyopathies are a group of primary and secondary myocardial diseases characterized by small LV cavity size, abnormal LV relaxation, and increased LV stiffness. These hemodynamic abnormalities lead to chronic elevation of LV filling pressures, decreased cardiac output, and left and right heart failure [64]. Commonly, in restrictive cardiomyopathies, the LV wall thickness is normal or increased because of infiltration or fibrosis, and unlike hypertensive heart disease, cardiomyopathies usually present with low QRS voltage or a pseudoinfarction pattern in the electrocardiogram. The systolic function may be normal or abnormal in advanced stages of the disease. Atrial enlargement is present because of chronic pressure overload. Pulsed Doppler LV filling patterns vary according to the severity of the disease. Initially, a pattern of delayed relaxation is seen, progressing to pseudonormal and finally to restrictive filling patterns in advanced disease. Clinical studies have shown that patients who have amyloidosis and presenting with a restrictive filling pattern have a 50% 1-year mortality rate compared with 10% for those presenting with a pattern of delayed relaxation or pseudonormalization [65]. Pulmonary venous flow demonstrates initially

S > D, progressing later to S < D and a prominent AR. Hepatic vein flow demonstrates similar changes according to the stage, corresponding to a prominent *x*-axis or *y*-axis descent or both (“M” pattern) on the central venous pressure tracings. In the advanced stages, the reversed flow (AR and VR) will be increased with inspiration. In cardiac amyloidosis, 2D echocardiography may demonstrate a “sparkling granular” appearance of the myocardium, although this finding is neither highly sensitive nor specific and may be overestimated by the use of tissue harmonic imaging. Increased pericardial thickness and brightness and small pericardial effusions are more specific findings. Abnormal thickening of the cardiac valves and the interatrial septum is often found, as well as mild to moderate valvular regurgitation. The degree of increased LV wall thickness (early, 12–15 mm; advanced, ≥15 mm) may provide important prognostic information in these patients [66].

Hypertrophic cardiomyopathy (HCM) is characterized by a prominent increase in global or segmental LV wall thickness and histologically by myocardial fiber disarray [67]. Diastolic function is characterized by increased LV chamber stiffness and decreased relaxation of variable severity resulting from the asynchronous deactivation of the muscle fibers [68,69]. Patients who have HCM can have symptoms even in the absence of LV outflow tract (LVOT) systolic obstruction, although recent studies suggest that relief of the LVOT gradient after alcohol embolization may be accompanied by an improvement in LV relaxation [70,71]. 2D echocardiography can demonstrate the extension and localization of the hypertrophied myocardium, which frequently has an impaired contractility. Atrial enlargement is common. Pulsed Doppler LV filling usually shows impaired relaxation or pseudonormal patterns and, rarely, the restrictive patterns because of the markedly increased wall thickness and impaired relaxation. Color M-mode Doppler may demonstrate intracavitary flow during isovolumic relaxation because of the asynchronous relaxation. Tissue Doppler echocardiography can identify abnormal regional strain, predominantly in areas of localized hypertrophy (Fig. 6) [72]. These abnormalities can often been found in asymptomatic carriers of hypertrophic cardiomyopathy genetic mutations, even in the absence of phenotypic expression [73].

Left ventricular filling patterns correlate well with functional class and have been shown to carry important and independent prognostic implications in patients who have dilated cardiomyopathy [74]. Diastolic dysfunction is invariably present in these

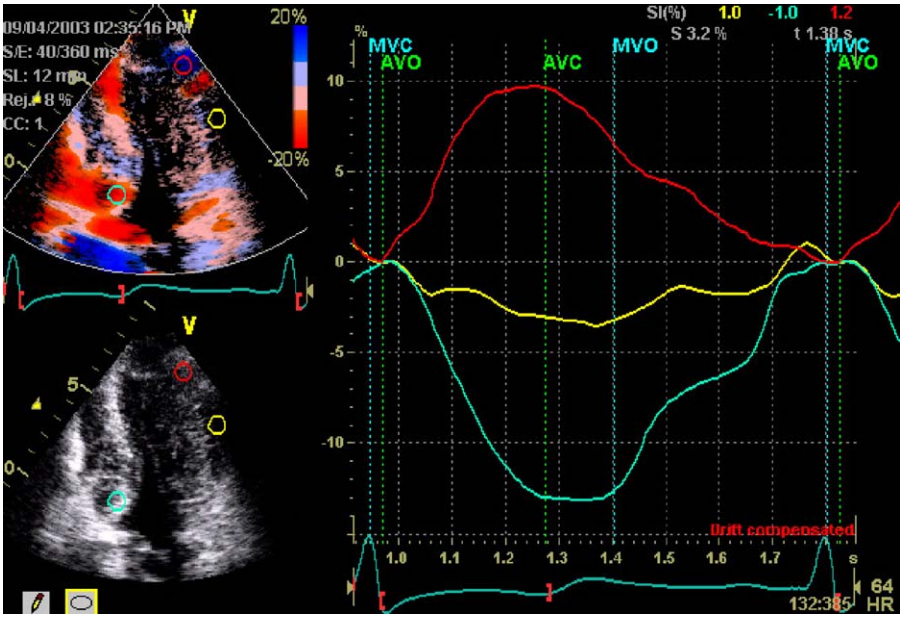


Fig. 6. Regional myocardial systolic strain measured at the anteroapical (*red line*), mid-anterior (*yellow line*) and basal inferior (*blue line*) left ventricular regions obtained from a patient who has apical hypertrophic cardiomyopathy. The basal-inferior systolic strain is within normal range (−13%). The mid-anterior systolic strain is reduced (−3%), whereas the apical-anterior strain is dyskinetic (systolic strain, +10%). Open circles indicate sample volume location.

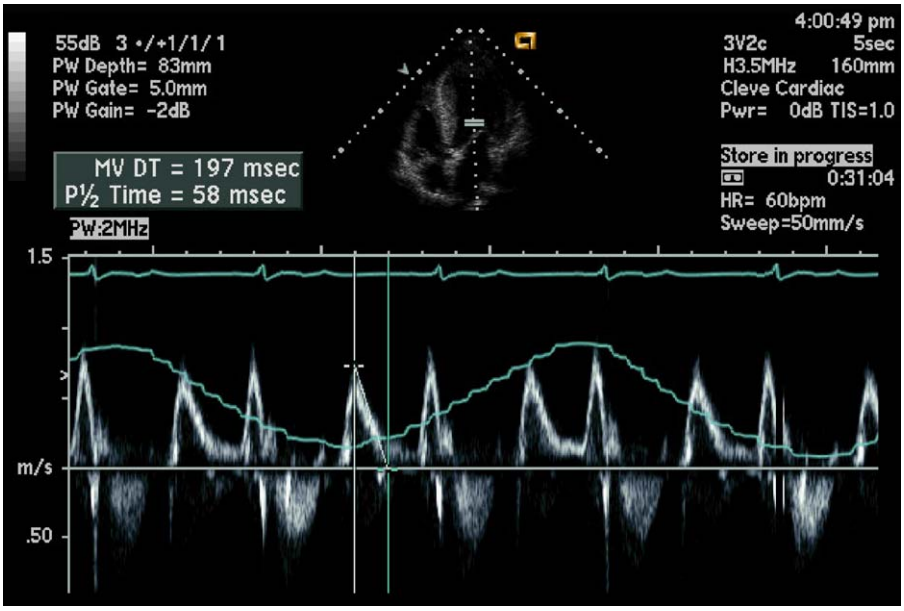


Fig. 7. Measurement of early left ventricular filling pulsed Doppler deceleration time (DT) in a patient who has dilated cardiomyopathy. DT = 197 ms, indicating normal left ventricular operating stiffness.

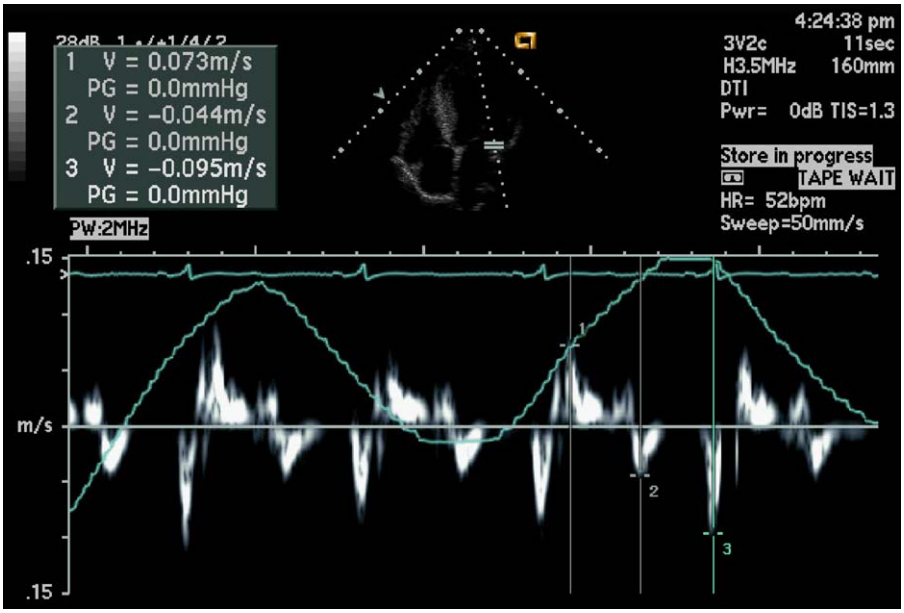


Fig. 8. Measurement of tissue Doppler basal lateral myocardial velocities in a patient who has dilated cardiomyopathy: Early diastolic velocity ($E_M$) = 4.4 cm/s, indicating abnormal LV relaxation. Combining this index with early left ventricular filling pulsed Doppler velocity (E = 80 cm/s) shown in Fig. 7 yields a $E/E_M$ ratio of 18, equivalent to an estimated mean left atrial pressure of 24 mm Hg.

patients. Because relaxation is invariably impaired, changes in LV filling and pulmonary venous Doppler flow parameters predominantly reflect changes in preload. A high E/A ratio, a low S/D ratio, short IVRT, or short DT indicates elevated LV filling pressures (Figs. 7–9). The role of echocardiography in the follow-up of heart transplant patients has not yet been defined clearly. Echocardiography in acute transplant rejection may demonstrate an increase in LV wall thickness, pericardial effusion, and a decrease in ejection fraction. Alterations in LV filling pattern are seen in up to 80% of the cases of severe rejection, including a reduction in DT and IVRT [75]. It is important to consider that Doppler filling patterns may vary according to the age of the donor heart or the duration of transplantation. Abnormal filling patterns are commonly seen immediately after transplantation. These patterns may lag for up to several weeks and have been associated with the duration of circulatory arrest [76]. Therefore, it is important to analyze serial studies in these patients to interpret anomalies in Doppler filling patterns. Transplant patients who have chronic rejection or coronary artery disease may also exhibit abnormal filling patterns. It has been proposed that serial echocardiographic studies may help in reducing the frequency of surveillance biopsies to detect rejection. Preliminary data suggest that diastolic myocardial velocities measured by TDE are very sensitive for detecting rejection in heart transplant patients [77,78]. Transplant rejection is associated with lymphocytic infiltration and edema, resulting in increased myocardial stiffness and abnormal relaxation. In a recent study, 121 heart transplant recipients underwent pulsed-wave TDE examination at the time of their surveillance endomyocardial biopsies. Peak TDE $E_m$ in 98 nonrejecting allograft recipients was 0.21 ± 0.01 m/s. In 16 patients who had moderate rejection, $E_m$ decreased to 0.14 ± 0.01 m/s and subsequently increased to 0.23 ± 0.01 m/s after successful treatment. No differences, however, were detected in TDE systolic velocities. Using a cutoff value of 0.16 m/s, the authors reported sensitivity, specificity, and negative predictive values of 76%, 88%, and 92%, respectively. One caution that must be taken, however, when interpreting these results, is that factors other than rejection may affect LV relaxation and $E_m$ in these patients, such as the age of the donor heart and the time after transplantation. Thus, lower velocities may not imply rejection if the organ belonged to an older donor or if these velocities are obtained several years after transplantation. One way to circumvent this problem would be to compare the results of serial studies obtained in the same patient.

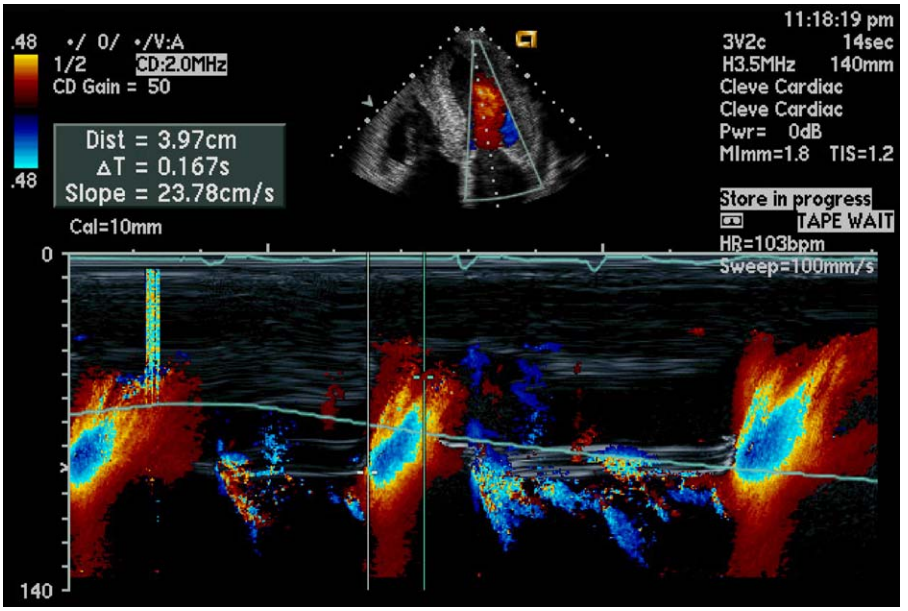


Fig. 9. Measurement of color M-mode early diastolic left ventricular filling propagation velocity ($v_P$) in a patient with dilated cardiomyopathy. $v_P = 24$ cm/s, indicating abnormal LV relaxation. Combining this index with early left ventricular filling pulsed Doppler velocity (E = 80 cm/s) shown in Fig. 8 yields a E/$v_P$ ratio of 3.3, equivalent to an estimated mean left atrial pressure of 22 mm Hg.

In most circumstances, however, the diagnosis of rejection requires the integration of clinical data with the detection of several echocardiographic markers such as pericardial effusions, increased wall thickness, and diastolic abnormalities.

Diastolic dysfunction in constrictive pericarditis results from increased pericardial constraint on the LV that is related to the thickness and rigidity of the pericardium. Patients present predominantly with signs and symptoms of right-sided heart failure, including edema, ascites, pleural effusions, and low cardiac output [79]. Echocardiographic studies demonstrate increased pericardial thickness, dilation of hepatic and caval veins, and a prominent interventricular septal bounce. The septal bounce is an abrupt displacement of the interventricular septum toward the LV during inspiration because the onset of RV filling occurs earlier and the expansion the RV free wall is limited by the pericardial constraint. The Doppler LV filling pattern presents a restrictive filling pattern because of the increased $S_{LV}$, unless the patient is volume-depleted. This pattern corresponds to the ''square root sign'' in the LV filling pressure tracing and a steep *y*-axis descent in the central venous pressure. The right ventricular filling pattern shows an increase in E and DT during inspiration because of the decrease in intrathoracic pressure, causing a decrease in pulmonary venous return to the left and augmented venous return to the right heart [80]. During inspiration, intrathoracic pressure decreases. Normally, this change is transmitted to the intrapericardial space and the cardiac chambers, maintaining a relatively constant pressure gradient between the central and pulmonary veins and the atria. In constrictive pericarditis, the rigid pericardium prevents the transmission of this pressure change to the cardiac chambers. The decrease in intrathoracic pressure lowers the pressure in the pulmonary veins, decreasing the pulmonary venous-left atrial pressure gradient and reducing venous return to the left heart, thus lowering the LV inflow E wave velocity. Because of interventricular dependence and limited pericardial space, the right-sided venous return increases with inspiration. During inspiration, Doppler LV filling demonstrates >30% reduction in E and >50% reduction in IVRT [81]. Simultaneously, RV inflow E increases >40%. These changes are observed with the first cardiac cycle after inspiration. The inferior vena cava will be plethoric, the D flow velocities may not increase because of limited filling, and there may be increased reversals during expiration. Superior vena caval (SVC) flow may decrease during inspiration because the SVC is influenced by intrathoracic pressure. This is equivalent to Kussmaul's sign. Pulmonary venous flow decreases during inspiration, predominantly D flow. It is important to consider that the respiratory variability of flows depend on the depth of the inspiratory effort. Under normal conditions, respiratory variability in healthy subjects is <10%. Acute respiratory illnesses can increase intrathoracic pressure swings, also increasing respiratory flow variability, but usually after the first cardiac cycle after inspiration. Excessive preload attenuates the effect of intrathoracic pressure swings and decreases respiratory variability. It may be useful under these conditions to reexamine the patient in a sitting position or after he or she undergoes diuresis. Very low preload can decrease the constraining effect of the pericardium, also masking the characteristic Doppler signs of constriction. The infusion of 1 to 2 L of saline may be useful in these cases [82]. In an important percentage of cases of constriction, respiratory variability may be absent. Tissue Doppler myocardial velocities may be used to differentiate restrictive cardiomyopathy from constrictive pericarditis. These conditions are often difficult to distinguish in the clinical setting using 2D or standard Doppler echocardiography alone. In restrictive cardiomyopathy patients, both relaxation and stiffness are abnormal. On the other hand, relaxation is preserved in purely constrictive pericarditis. Patients who have constrictive pericarditis and normal systolic function have normal or elevated $E_M$ velocities (>8 cm/s), probably reflecting their preserved ventricular relaxation [25,83].

## Diastolic dysfunction and exercise intolerance

Several factors are known to determine exercise aerobic capacity, including skeletal muscle fitness, cardiovascular state, pulmonary mechanics, and neuroendocrine factors. In most normal individuals, however, the limiting factors that influence $VO_2$ max are the skeletal muscle mass and the capacity of the cardiovascular system [84]. During peak exercise, the duration of diastasis is greatly diminished to account for the increase in heart rate. Yet, for the heart to increase the cardiac output, the diastolic mechanics must adjust to the decrease in time to fill [85]. The ability to accommodate high-volume loads has been demonstrated in athletes [86]. This accommodation is carried out at low filling pressures; rather, the early relaxation is increased to provide for a ''suction'' force and high LV compliance. However, patients who have heart failure may not be able to achieve this necessary increase in diastolic relaxation to accommodate the preload increase [87–89]. Rovner and

colleagues [71] recently investigated the relationship between diastolic intraventricular pressure gradients (IVPG) and exercise tolerance in patients who had heart failure using color M-mode Doppler. Echocardiograms were performed before and after metabolic treadmill stress testing in 31 patients who had heart failure and 15 normal subjects. In this study, resting diastolic function indices, including tissue Doppler $E_M$ and color M-mode Doppler $v_p$, correlated well with metabolic aerobic activity ($VO_2$ max). A statistically significant increase was observed in $v_p$ and IVPG in both groups after exercise, but the change in IVPG was higher in normal subjects compared with patients who had heart failure ($2.6 \pm 0.8$ versus $1.1 \pm 0.8$ mm Hg, respectively; $P<.05$). An increase in IVPG correlated with peak $VO_2$ max ($r = 0.8$, $P< .001$) and was the strongest predictor of exercise capacity. This study also demonstrated that in patients who have heart failure, the decreased ability to augment the diastolic relaxation is responsible for the inability to accommodate the increase in estimated preload during exercise, resulting in higher filling pressures.

## Summary

The analysis of diastolic function is not only relevant to the evaluation of symptoms in patients who have heart failure and normal ejection fraction it also carries prognostic and therapeutic implications in patients who have systolic heart failure. Echocardiographic indices can establish the diagnosis, severity, and specific mechanism of diastolic heart failure in most patients. Accordingly, it is important for both the clinician and the echocardiographer to acquire in-depth knowledge of conventional and newer echocardiographic indices of diastolic function and to apply these indices in clinical practice.

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