

REVIEW ARTICLE

Evaluation of Diastolic Filling of Left Ventricle in Health and Disease: Doppler Echocardiography Is the Clinician's Rosetta Stone

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Abnormalities of diastolic function have a major role in producing the signs and symptoms of heart failure. However, diastolic function of the heart is a complex sequence of multiple interrelated events, and it has been difficult to understand, diagnose and treat the various abnormalities of diastolic filling that occur in patients with heart disease. Recently, Doppler echocardiography has been used to examine the different diastolic filling patterns of the left ventricle in health and disease, but confusion about diagnosis and treatment options has arisen because of the misinterpretation of these flow velocity curves. This review presents a simplified approach to under-

standing the process of diastolic filling of the left ventricle and interpreting the Doppler flow velocity curves as they relate to this process. It has been hypothesized that transmitral flow velocity curves show a progression over time with diseases involving the myocardium. This concept can be applied clinically to estimate left ventricular filling pressures and to predict prognosis in selected groups of patients. Specific therapy for diastolic dysfunction based on Doppler flow velocity curves is discussed.

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Heart failure is the diagnosis made most commonly among inpatients in the United States and accounts for 720,000 hospital admissions annually (1). Previously, investigators focused on the abnormalities of systolic function to explain the signs and symptoms of heart failure. The inability of the left ventricle to increase cardiac output commensurate with exertion leads to increased anaerobic metabolism in skeletal muscle, accumulation of lactate and subjective symptoms of fatigue (2,3). Therapy directed at the treatment of these abnormalities (i.e., inotropic agents, diuretic drugs and afterload reducers) is well established for patients with systolic dysfunction presenting with heart failure.

However, it has become increasingly clear that abnormalities of diastolic function have a major role in producing signs and symptoms in patients presenting with heart failure (4-7). As many as one-third of patients with the diagnosis of heart failure have normal systolic function, which implicates diastolic dysfunction as a major pathophysiologic abnormality in these patients (8,9). Even in patients with chronic heart failure that is a result of systolic dysfunction, it is the increase in left ventricular filling pressure that correlates most closely with the degree of exercise limitation, independently of the severity of systolic dysfunction (4,10-12). The incidence of diastolic dysfunction is age related, and heart failure due to diastolic dysfunction rises dramatically with age (13-15).

The term "diastology" is currently used to refer to the science and art of characterizing left ventricular relaxation and filling dynamics and their integration into clinical practice. At

the bedside, diastolic dysfunction is difficult to diagnose and to differentiate from systolic dysfunction on the basis of medical history, physical examination, electrocardiography and chest radiography. The S_1 intensity is usually normal in isolated diastolic heart failure but is usually diminished in systolic dysfunction. However, cardiac catheterization is the standard technique for direct measurement of filling pressures and rate of left ventricular relaxation but is not practical for widespread application or serial longitudinal follow-up examinations. Two-dimensional echocardiography is excellent for diagnosing systolic dysfunction, and Doppler echocardiography has become well accepted as a reliable, reproducible and practical noninvasive method for diagnosis and longitudinal follow-up of patients with diastolic dysfunction. In the past decade, several advances in the application of Doppler echocardiography for assessment of diastology have occurred so that clinical cardiologists can now comprehend, interpret and prognosticate and treat their patients based on Doppler flow velocity curves. Therefore, Doppler echocardiography can be considered akin to the Rosetta Stone* for clinicians for not only deciphering but simplifying the complex "mystery" of diastology.

*Until two centuries ago, the ancient Egyptian language was a mystery to the world. In 1779, Napoleon's expedition to Egypt came upon a large stone in the village of Rosetta bearing inscriptions carved circa 196 BC. The top script was in Egyptian hieroglyphics; the middle inscription was in a cursive form of hieroglyphics known as "Demotic"; and the bottom inscription was in Greek. Thomas Young, a well renowned British scientist, mathematician, physicist, philosopher, physician and Egyptologist, was among the first to decipher the hieroglyphics. The Rosetta Stone has come to be regarded as the key that unlocked the mysteries of ancient Egyptian civilization. Among many innovative contributions, Thomas Young published the mathematical model of determining compliance in the formula that carries his name (Young's modulus of chamber compliance) and is occasionally used for assessment of diastolic function. He also independently described the relation among pressure, force and tension across curved surfaces referred to as the "Young-Laplace law," which is highly relevant to the practice of cardiology.

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Physiology of Diastole

Diastolic function of the heart is a complex sequence of many interrelated events (5–7,16–21). Numerous factors determine how the ventricle fills with blood during diastole. Each of these factors—including ventricular relaxation, diastolic suction, erectile coronary effect, viscoelastic forces of the myocardium, pericardial restraint, ventricular interaction and atrial contribution—is interrelated to the others in a complex sequence of events. Much of the analysis of diastolic function of the left ventricle has been limited to animal models and has required intricate measurements of left ventricular pressures with high fidelity manometer-tipped catheters, instantaneous left ventricular volume, wall thickness and intrapericardial and intramyocardial pressures (5–7,17,19).

Although diastolic function of the left ventricle is a complex interplay of numerous components, a simplistic conceptual framework can provide practical insight for the diagnosis and treatment of diastolic dysfunction. The classic approach has been to divide diastole into four discrete segments: isovolumetric relaxation, rapid filling, slow filling and atrial contraction (19). However, because of the complex interactions among numerous interrelated events, including the influence of the preceding systolic contraction, it has been difficult to apply this approach clinically. A proposed approach that can be used clinically is to consider the cardiac cycle in terms of systolic contraction, relaxation and diastolic filling (Fig. 1), a modification of the model proposed by Brutsaert et al. (16,22–24). Contraction encompasses isovolumetric contraction and the first half of ejection with a transition into relaxation, which consists of a large portion of the second half of ejection, isovolumetric relaxation and the rapid filling phase. Diastolic filling is the period in which the ventricle fills with blood from the left atrium (from the onset of mitral valve opening to mitral valve closure). The early phase of diastolic filling coincides with and is dependent on continued ventricular relaxation.

The two major determinants of left ventricular filling are 1) ventricular relaxation, and 2) effective chamber compliance. Ventricular relaxation is a complex energy-dependent process during which the contractile elements are deactivated and the myofibrils return to their original (precontraction) length. In a normal heart, ventricular relaxation begins during midsystole and continues throughout the first third of diastolic filling. There is a triple control of relaxation in the intact heart consisting of inactivation, the load on the left ventricle and the nonuniformity of relaxation (16,22–24). Simplistically, ventricular relaxation can be thought of as the rate and duration of the decrease in left ventricular pressure after systolic contraction. In the catheterization laboratory, relaxation abnormalities are measured from left ventricular pressures obtained with high fidelity manometer-tipped catheters (19–21). Peak negative change in left ventricular pressure over time (dP/dt) and the time constant of relaxation, or tau, are accepted indexes of the rate of relaxation, although both have limitations (20,21). In disease states, relaxation abnormalities occur early, often preceding dysfunction of the contraction phase. Delayed inactivation, diminished load dependence and increased

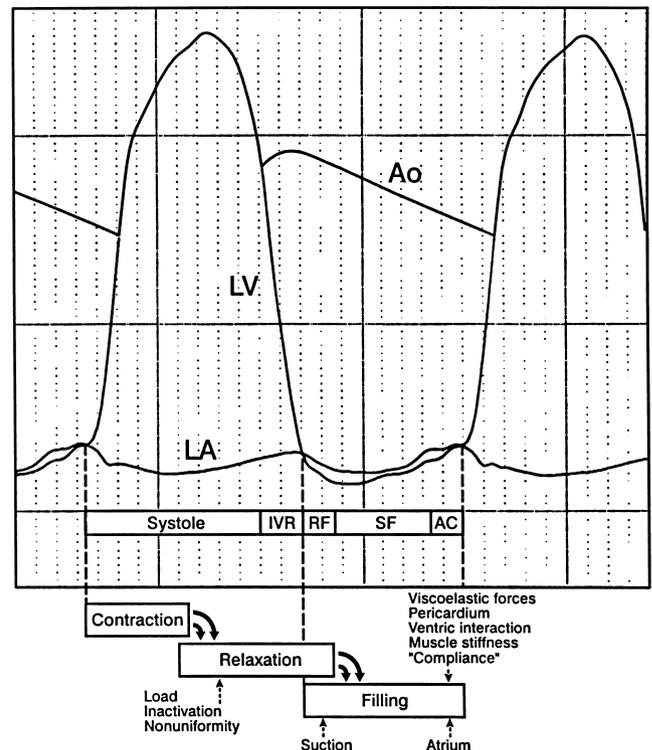


Figure 1. Diastolic filling of the left ventricle in a patient with hypertrophic cardiomyopathy. The high fidelity left ventricular (LV) and left atrial (LA) pressures are shown with a schematic representation of ascending aortic pressure (Ao). In the classic system, the cardiac cycle is divided into systole and four phases of diastole: isovolumetric relaxation (IVR), rapid filling (RF), slow filling (SF) and atrial contraction (AC). In a more practical and simplified system, the cardiac cycle is divided into contraction, relaxation and diastolic filling. Each of the three phases is dependent on effects of the preceding phase (see text).

nonuniformity impair relaxation and diminish the mechanical efficiency of the heart (22–24). This results in a decrease in the ability of the left ventricle to fill with blood in early diastole, that is, the rapid filling phase. There usually is a compensatory increase in filling with atrial contraction. Depression of systolic performance affects relaxation from diminished loads due to less deformation at end-systole (24).

The “effective operating chamber compliance” describes the passive properties of the left ventricle during blood flow across the mitral valve from the left atrium into the left ventricle (5,6,18,19,25–27). Several complex interactions occur during this period, including the continued effect of ventricular relaxation, diastolic suction, passive filling, pericardial restraint, ventricular interaction and viscoelastic forces of the myocardium. The relation of instantaneous wall stress and wall strain has been used to measure myocardial stiffness, but these complex measurements are impractical for clinical application. “Effective operating chamber compliance” (25–27), defined as the change in volume over the change in pressure during diastolic filling, is used in the following discussion to provide a clinical assessment of these passive left ventricular properties. Because of the exponential shape of the diastolic pressure–

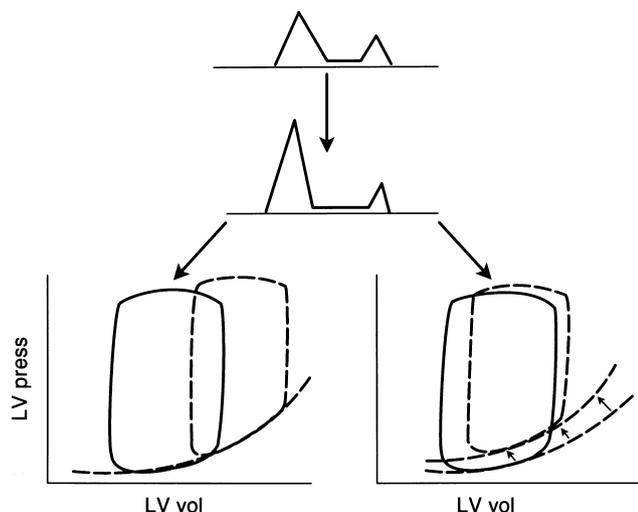


Figure 2. The effects of changes in operative compliance. **Top,** A decrease in operative compliance results in an increase in the initial E velocity and a shortening of the deceleration time on the mitral flow velocity curve. This can be caused by one of two mechanisms, as shown by the two pressure–volume loops. **Bottom left,** An increase in left ventricular volume (LV vol) may shift the pressure–volume loop to the right (**dashed loop**) on the same diastolic pressure–volume curve (**dashed line**). **Bottom right,** The diastolic pressure–volume curve can be shifted upward and to the left (**arrows**), causing a decrease in the effective operative compliance. This can be caused by either an increase in myocardial stiffness or a change in the extrinsic factors of the heart, such as an increase in pericardial restraint.

volume curve, a decrease in chamber compliance can be caused by 1) a shift of the curve upward and to the left because of either increased myocardial stiffness or increased pericardial restraint; or 2) a shift of the ventricle rightward to a steeper portion of the pressure–volume curve because of an increase in volume (Fig. 2). A decrease in chamber compliance caused by either mechanism will increase left ventricular filling pressure and mean left atrial pressure, which are the end result of diastolic dysfunction.

Doppler Flow Velocity Curves: Interpretation

In 1982, Kitabatake et al. (28) described the transmitral flow velocity curves obtained with Doppler echocardiography

in different disease states. Subsequent investigations have shown (28–30) that mitral flow velocity curves correlate well with the first derivative of diastolic volumetric flow rates obtained by other accepted methods, such as left ventriculography, radionuclide angiography and digitized M-mode echocardiography. On the basis of descriptive studies of transmitral flow velocity curves in disease states, a bimodal distribution of early peak filling rates was identified. In patients with known cardiac disease, the early peak filling rate was found to be slower than in those without heart disease (28,31–33). Therefore, low peak filling rates were thought to represent “diastolic dysfunction.”

There has been confusion in the published reports about this interpretation of mitral flow velocity curves. The concept of a bimodal distribution of peak filling rates can be misleading. In patients with abnormally low peak filling rates, the “normalization” of the peak filling rate by a drug or intervention was interpreted to represent improvement in the diastolic filling of the left ventricle (34–41). However, although acute administration of a drug such as a calcium channel blocking agent increases an abnormally low peak velocity, simultaneous invasive measurements have shown (42) that this is associated with an increase in left ventricular filling pressures and prolongation of tau. Thus, there may be a deterioration of diastolic function with “normalization” of an abnormal mitral velocity curve (Fig. 3).

To interpret the Doppler indexes of diastolic filling, it has been proposed (25,32,43–45) that the mitral flow velocity curves be considered as reflecting the relative driving force across the mitral valve. When a pulsed-wave sample volume is placed at the tip of the mitral leaflets, the measured peak velocity is indicative of the relative instantaneous change in pressure between the left atrium and left ventricle after the opening of the mitral valve. A sample volume can also be placed in the pulmonary vein to provide additional information about the filling of the left atrium and left ventricle (46,47). Similarly, right-sided filling can be interrogated with velocity curves obtained from transtricuspid and vena cava flow (48). It must be emphasized that Doppler flow velocity curves should not be interpreted as a measurement of all the complexities involved in diastolic function of the heart but rather as a

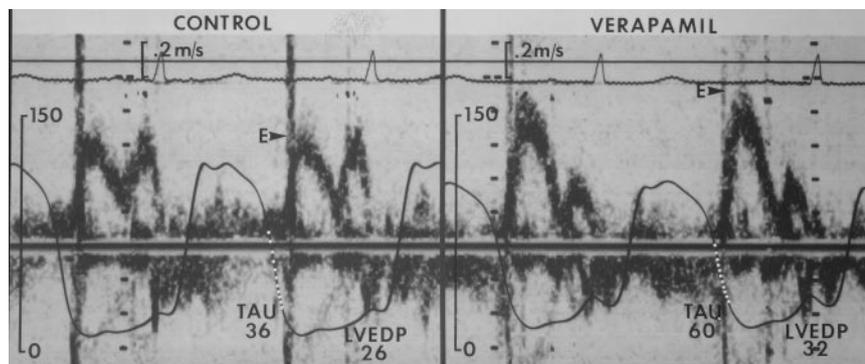


Figure 3. High fidelity left ventricular pressure curves and simultaneous mitral flow velocity curves in a patient (**left**) in the baseline state and (**right**) after intravenous administration of verapamil. The mitral flow velocity curve shows an increase in E velocity and a shortening of deceleration time after intravenous administration of verapamil. The mitral flow velocity curve has a “pseudonormal” pattern. In the left ventricular pressure curves, there is an increase in left ventricular end-diastolic pressure (LVEDP) and a prolongation of the time constant of relaxation (TAU), indicating deterioration of diastolic function. Reprinted, with permission, from Nishimura et al. (42).

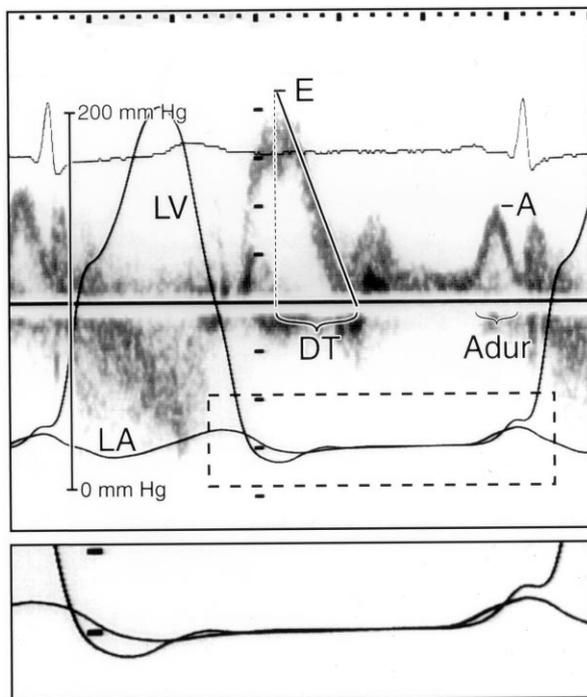


Figure 4. Simultaneous mitral flow velocity curve and high fidelity pressure curves of the left ventricle (LV) and left atrium (LA). Enlargement of the diastolic portion of the left atrial and left ventricular pressure curves is shown in the **bottom rectangle**. Measurements of the mitral flow velocity curves include E velocity (E), A velocity (A), deceleration time (DT) and A duration (Adur).

representation of the overall diastolic filling characteristics of the heart. However, these flow velocity curves can be useful in the diagnosis, prognosis and treatment of diastolic dysfunction (25,32,43).

The relation of the instantaneous pressure changes between the left atrium and left ventricle and the mitral flow velocity curve is shown in Figure 4. After contraction is completed in a normal ventricle, left ventricular pressure rapidly decreases during ventricular relaxation. When left ventricular pressure becomes less than the left atrial pressure, a driving force develops across the mitral valve from the left atrium to the left ventricle, and an acceleration of blood flow velocity is seen on the transmitral flow velocity curve (44,45,49-51). Left ventricular pressure continues to decrease because of further relaxation and a "suction" effect. In early diastole, left ventricular pressure reaches its nadir, which is followed by an increase in pressure caused by a combination of forces, such as the viscoelastic forces of the myocardium, pericardial restraint and ventricular interaction (5-7,17,18,20,49,52). Left ventricular pressure then equilibrates, or may even transiently exceed, left atrial pressure and causes a deceleration of the transmitral flow velocity curve. The rate of deceleration of flow depends on the effective operative compliance of the ventricle (26,27). During mid-diastole, the pressures are equilibrated, but forward flow continues because of inertial forces. Finally, atrial contraction produces an increase in left atrial pressure so that

it exceeds left ventricular pressure; this causes a reacceleration of flow on the transmitral flow velocity curve.

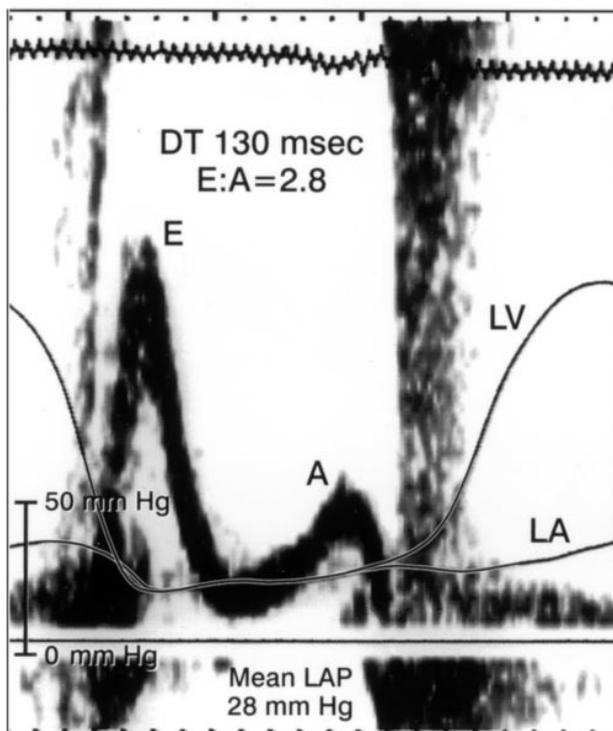
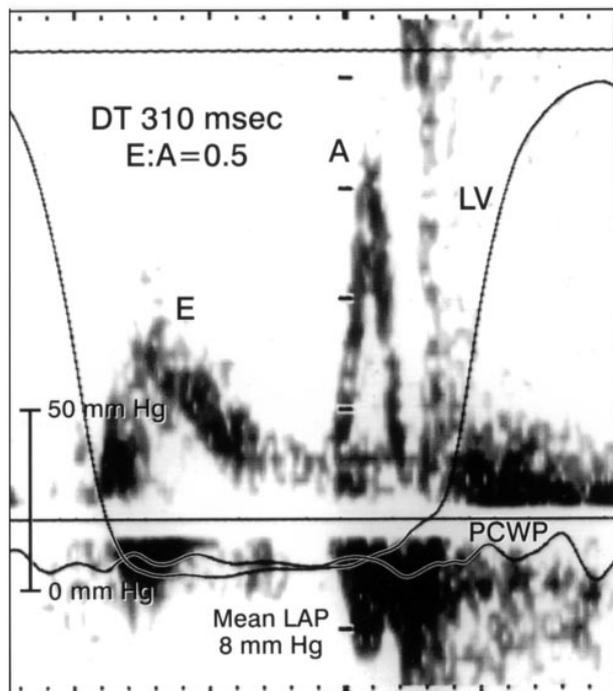
Simple measurements can be obtained from transmitral flow velocity curves (Fig. 4). The E velocity is the peak early filling velocity and is influenced by left atrial pressure at mitral valve opening, the relative driving force between the left atrium and left ventricle, minimal left ventricular diastolic pressure, compliance of the left atrium and the rate of ventricular relaxation (44,45,50,51,53,54). The rate of decrease of velocity following the E velocity is measured as the deceleration time. The deceleration of the mitral flow velocity curve is extrapolated to baseline, and the deceleration time is the interval between the peak E velocity and the intersection of the deceleration of flow with the baseline. The deceleration time depends on the rate of increase in left ventricular pressure in early diastole, after it has reached its nadir, and is a measure of the effective operative chamber compliance of the left ventricle (26,27). The A velocity is the velocity at atrial contraction. Because atrial contraction usually occurs after relaxation is completed, the peak velocity depends on left ventricular chamber compliance as well as the volume and contractility of the left atrium. The duration of the atrial contribution of the transmitral flow velocity curve is a useful measurement, especially in combination with pulmonary vein flow velocity curves (55-57).

The normal mitral flow velocity curve varies with loading conditions, age and heart rate (46,51,58-65). Published values for age and gender are available and should be used when interpreting these velocity curves. In a normal middle-aged subject, the E velocity is slightly larger than the A velocity, and the deceleration time is $\sim 200 \pm 40$ ms.

Usually, an abnormality of relaxation is the earliest manifestation of a disease process (Fig. 5, top). It is commonly present with hypertension and coronary artery disease and becomes more prominent in older subjects. A primary abnormality of relaxation produces specific changes in the mitral flow velocity curve. There is a slower decrease in the rate of decrease of left ventricular pressure, and the duration of relaxation is prolonged into mid- or even late diastole. A lower initial driving force across the mitral valve occurs because of this slower rate of ventricular relaxation and results in a low E velocity. The duration of ventricular relaxation may continue into mid- or late diastole, which means less filling of the left ventricle in mid-diastole and prolongation of the deceleration time on the transmitral flow velocity curve. There is a compensatory increase in transmitral flow at atrial contraction from the high residual atrial preload, and the result is a high A velocity. Thus, a mitral flow velocity curve of a heart with abnormal relaxation consists of a low E velocity, a high A velocity and a prolonged deceleration time.

In the late stages of disease, the effective operative chamber compliance decreases and causes increased mean diastolic pressures (Fig. 5, bottom). Patients with this abnormality have isolated severe diastolic abnormalities, as seen in restrictive cardiomyopathy or concomitant systolic dysfunction due to dilated cardiomyopathy or end-stage ischemic cardiomyopa-

Figure 5. Top, Simultaneous mitral flow velocity curves and high fidelity manometer-tipped pressures of the left ventricle (LV) and pulmonary capillary wedge pressure (PCWP) in a patient with abnormal prolonged relaxation. The time constant of relaxation is increased at 72 ms. The deceleration time (DT) is prolonged (310 ms), and the E/A ratio is low (0.5). There is a low mean left atrial pressure (LAP) of 8 mm Hg, as assessed indirectly by the pulmonary capillary wedge pressure. **Bottom,** Simultaneous mitral flow velocity curve and high fidelity left ventricular (LV) and left atrial (LA) pressure curves in a 60-year old patient with dilated cardiomyopathy and restriction to filling. Note the high left atrial pressure of 28 mm Hg in this patient. The deceleration time is short (130 ms), and the E/A ratio is high (2.8).



thy. A decrease in the effective operative chamber compliance of the left ventricle will affect the transmitral flow velocity curves in a specific manner. A high left atrial pressure at the time of mitral valve opening and a large left atrial-left ventricular gradient in early diastole will produce a fast acceleration in blood flow velocity into the left ventricle. A high E velocity will occur on the mitral flow velocity curve. A rapid increase in left ventricular pressure after its nadir will cause a rapid deceleration on the transmitral flow velocity curve. There will be a lower forward velocity at atrial contraction because a relatively greater filling of the left ventricle has occurred in early diastole. Also, a greater proportion of blood will flow back into the pulmonary veins during atrial contraction because there is a high afterload on the left atrium from higher left ventricular diastolic pressure. Thus, an abnormality of compliance, referred to as "restriction to filling," results in a high E velocity, a short deceleration time and a low A velocity on the mitral flow velocity curve (53,54).

There is an important concept that must be recognized to properly interpret mitral flow velocity curves. In a patient with abnormal relaxation, deterioration of diastolic function results in a higher left atrial pressure and a decrease in effective operative compliance of the left ventricle. This increases E velocity, shortens the deceleration time and produces a mitral flow velocity curve pattern that simulates a normal flow velocity curve (66). This pattern of a normal-appearing mitral flow velocity curve with increased filling pressures is called "pseudonormalization" (Fig. 6). Thus, "normalization" of an abnormal relaxation pattern may represent a deterioration of diastolic function of the heart. This may explain the confusion that has occurred in the published reports when mitral velocity curves have been used to determine the effects of a treatment.

Information from pulmonary vein velocity curves can be used clinically in conjunction with that from mitral flow velocity curves (46,47,67). Pulmonary vein velocity curves are obtained by placing a pulsed wave sample volume in the pulmonary veins where they enter the left atrium. A normal pulmonary vein velocity curve consists of systolic forward flow, diastolic forward flow and a reversal of velocity at atrial contraction. Systolic forward flow is influenced by left atrial compliance, atrial relaxation, mean left atrial pressure, descent of the annulus toward the left ventricular apex, right ventricular contraction and other factors, such as concomitant mitral regurgitation (67). In a patient with high left atrial pressures and poor left ventricular systolic function, the velocity of systolic forward flow is decreased (46). Diastolic forward flow occurs at the time when there is an open conduit between the pulmonary vein, left atrium and left ventricle. Thus, the contour of diastolic flow velocity is similar to that of the early part of the mitral flow velocity curve and is dependent on the same factors that influence the early mitral velocity curve (47). Isolated relaxation abnormalities cause a higher systolic/diastolic velocity ratio on the pulmonary velocity curves. Restriction to filling with a high left atrial pressure produces a low systolic/diastolic velocity ratio.

The reversal of velocity at atrial contraction in the pulmo-

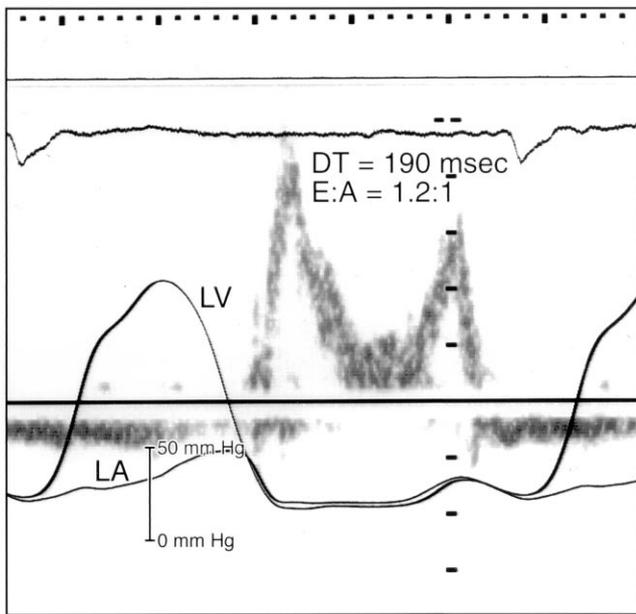


Figure 6. Simultaneous mitral flow velocity curve and left ventricular (LV) and left atrial (LA) high fidelity pressure curves in a 62-year old patient with dilated cardiomyopathy and a pseudonormalization pattern. The left atrial pressure is high at 32 mm Hg, and the rate of left ventricular relaxation is prolonged, with a time constant of relaxation of 68 ms. Deceleration time (DT) is normal (190 ms), as is the E/A ratio. However, this represents pseudonormalization rather than a normal flow velocity curve. Note early closure of the mitral valve because of first-degree atrioventricular block.

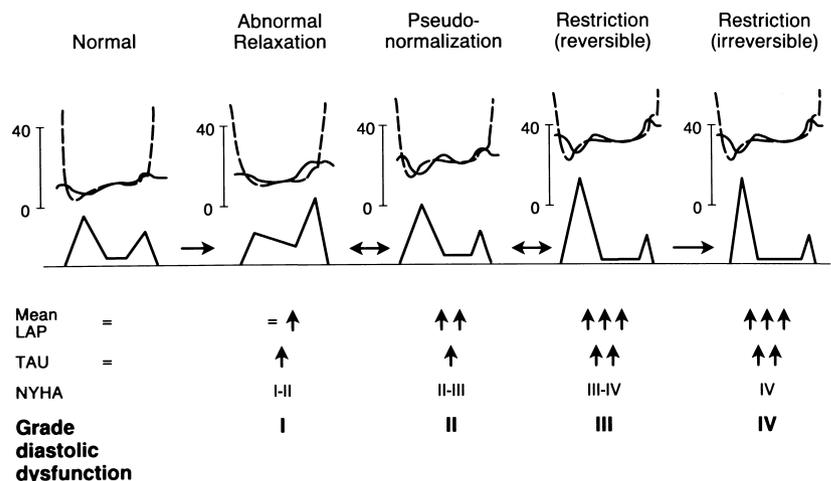
nary vein curves provides clinically relevant information that supplements that obtained from mitral flow velocity curves (55-57). At the time of atrial contraction, there continues to be an open conduit between pulmonary vein, left atrium and left ventricle. There is forward flow into the left ventricle, with blood also going retrogradely into the pulmonary veins. As the left ventricular filling pressure increases and left ventricular compliance decreases, a higher resistance to forward flow occurs during atrial contraction. This results in less forward flow into the left ventricle and reflux of a greater volume of

blood into the pulmonary vein during atrial contraction. Conversely, with low filling pressures and normal compliance of the left ventricle, there will be more forward flow into the left ventricle and reflux of a smaller volume of blood into the pulmonary vein during atrial contraction. Because ventricular relaxation usually is completed by the time of atrial contraction, the ratio between forward flow velocity into the left ventricle and retrograde flow into the pulmonary vein is an indirect indicator of ventricular compliance.

Progression of Disease Patterns

It has been hypothesized (25), and demonstrated in experimental models of heart failure (26,27), that the transmitral flow velocity curves show a progression over time with diseases involving the myocardium (Fig. 7). In a normal middle-aged subject, the mitral flow velocity curve consists of an E/A ratio slightly >1.0 and a deceleration time of ~200 ms. In the early stages of dysfunction, impaired (delayed) relaxation of the left ventricle predominates, and this decreases early diastolic filling. An abnormal relaxation pattern is seen on the mitral flow velocity curve and consists of a low E velocity, prolongation of the deceleration time and increased filling at atrial contraction. At this stage, there is little if any increase in rest left ventricular diastolic filling pressure. Increased filling pressure may develop with exercise because of shortening of the diastolic filling period. With disease progression, left atrial pressure increases, thus increasing the driving pressure across the mitral valve. There is a gradual increase in the E velocity on the mitral flow velocity curve. As effective operative compliance decreases, the deceleration time shortens, and a pseudonormal pattern appears. In more advanced disease, the left atrial pressure is higher and ventricular compliance is poor, producing a restriction to filling pattern. In patients with left ventricular systolic dysfunction, a restriction to filling pattern has been associated with a worse functional class and diminished exercise tolerance (68). The finding that the prognosis of patients with either dilated (69,70) or infiltrative (71) cardiomyopathy can be predicted by the mitral

Figure 7. Diagram of a proposed grading system for diastolic dysfunction based on the progression of disease patterns in patients with cardiac disease. Below the high fidelity left atrial and left ventricular pressure curves is a schematic representation of the mitral flow velocity curve. Below this is the mean left atrial pressure (LAP), time constant of relaxation (TAU) and New York Heart Association (NYHA) class associated with the various mitral flow velocity curves. The natural progression is from the normal pattern, to the abnormal relaxation pattern, to the pseudonormalization pattern, to a reversible restriction pattern and finally to an irreversible restriction pattern. The grade of diastolic dysfunction on a scale of I to IV is shown (see text for details).



deceleration time is of great interest. A short deceleration time (<140 to 150 ms) is indicative of a poor prognosis, independent of the degree of systolic dysfunction (69-71).

Mitral flow velocity curve patterns are influenced by loading conditions of the left ventricle (44,50-52,58,59,72). Different flow patterns may be seen only hours to days apart in the same person, depending on the left ventricular preload or afterload. An increase in preload increases the driving pressure at mitral valve opening. The effective operative compliance of the left ventricle decreases for two reasons (Fig. 2): 1) The diastolic pressure-volume relation is curvilinear, and a shift in the pressure-volume curve to the right because of a larger left ventricular volume results in a greater increase in pressure per unit volume during diastole (5,7). 2) If left ventricular volume increases, pericardial restraint occurs and shifts the diastolic pressure volume curve upward and to the left (5,7,19). Thus, an increase in preload increases the E velocity and shortens the deceleration time. Conversely, a decrease in preload decreases the E velocity and prolongs the deceleration time. An increase in afterload primarily prolongs the rate of left ventricular relaxation, which in turn lowers the E velocity and prolongs the deceleration time.

On the basis of this progression of disease patterns, we would like to propose a grading system for the severity of diastolic dysfunction as assessed with Doppler echocardiography (Fig. 7). Published values for the 95% confidence limits of the E/A ratio in deceleration time based on age and gender (62-64) should be used to define the transmitral flow velocity curves in individual patients. Using a scale of I to IV, *grade I* identifies a patient with an abnormal relaxation pattern and minimal or no symptoms of heart failure at rest. Patients with *grade I* diastolic dysfunction may develop dyspnea with moderate to extreme exertion or may develop symptoms of heart failure if the contribution from atrial contraction is lost, as occurs with development of atrial fibrillation. With *grade II* diastolic dysfunction, there is a pseudonormalization pattern on the mitral flow velocity curves and increased filling pressures at rest, producing symptoms with mild to moderate exertion. Patients with *grade III* diastolic dysfunction have a restrictive filling pattern on the mitral flow velocity curves, severe increase in filling pressures and symptoms at rest or with minimal exertion. The treatment of heart failure and decreasing preload may produce changes in the mitral flow velocity curve so that a patient with *grade III* diastolic dysfunction may move to *grade II* or even *grade I* diastolic dysfunction. Some patients with severe abnormalities of ventricular compliance and end-stage heart disease maintain a severe restrictive pattern even after aggressive diuresis. These are patients with the poorest prognosis; they have *grade IV* (irreversible) diastolic dysfunction (73).

Estimation of Left Ventricular Filling Pressures

The result of abnormal diastolic function is increased left ventricular filling pressures (5-7,18,74-76). Currently, cardiac

catheterization is necessary to directly measure left ventricular filling pressures. Because of advances in interpreting Doppler flow velocity curves, left ventricular filling pressures can be determined noninvasively in selected subsets of patients. However, there remain caveats and questions that must be answered before Doppler echocardiography can be used to estimate left ventricular filling pressures in all patients with suspected cardiac disease.

The Doppler determinants of mean left atrial pressure occur in early diastole and are measured by the E velocity and deceleration time. The initial E velocity is influenced mainly by the driving pressure from the left atrium to the left ventricle at the time of mitral valve opening (44,45,49-51), and the deceleration time is determined by the effective operative compliance of the left ventricle (26,27), both of which are related to mean left atrial pressure. Thus, in many patients with a high mean left atrial pressure, the E velocity is usually high and the deceleration time is short on the transmitral flow velocity curve. Conversely, if the left atrial pressure is low, the initial E velocity is usually low and deceleration time is prolonged. It has been shown (51,52,58,59,72,77) that specific changes in the mitral flow velocity curves follow changes in mean left atrial pressure. What is clinically important is whether a similar interpretation of mitral flow velocity curves may be applied to a patient to estimate mean left atrial pressure.

As shown in several studies of patients with severe left ventricular systolic dysfunction (78-80), the inverse correlation of the deceleration time with the mean left atrial pressure or pulmonary capillary wedge pressure is excellent. Short deceleration times (<150 ms) nearly always indicate a left atrial mean pressure >25 mm Hg. Conversely, a prolonged deceleration time correlates well with low or normal filling pressures (<15 mm Hg). Although less sensitive and specific than the deceleration time, a high E/A ratio (>2.5) is associated with high left atrial pressures, and a low E/A ratio is associated with low left atrial pressures in patients with left ventricular systolic dysfunction.

Caution must be used in applying these concepts of estimating left atrial pressure to other disease states (55,81,82). The relation of left atrial pressure with the E/A ratio and deceleration time depends on several assumptions. The first assumption is that the initial portion of the mitral flow velocity curve is dependent primarily on left atrial pressure. However, other factors influence this portion of the mitral velocity curve, including the rate of ventricular relaxation, diastolic suction and the compliance of both the left atrium and ventricle (44,45,50,51,53,54). In patients with left ventricular systolic dysfunction, there usually is a moderate to severe prolongation of relaxation and little contribution from diastolic suction. Thus, in this subset of patients, there is an inverse correlation between mean left atrial pressure and deceleration time. However, in patients with a disease such as hypertrophic cardiomyopathy, there is a wide range in the extent of prolongation of ventricular relaxation, and the hyperdynamic ventricle may have a large component of diastolic suction. This

produces a poor correlation between left atrial pressure and the values of the mitral flow velocity curve (83). The second assumption that is made in using these early mitral flow velocity curve variables is that patients with an entirely normal flow velocity curve are excluded from analysis. In the progression of mitral flow velocity curves in disease, the gradual increase in E velocity and the decrease in deceleration time (pseudonormalization) occur only after the onset of abnormal relaxation. Normal subjects, especially younger ones, have a relatively high E velocity and a short deceleration time, not because of the abnormality of diastolic filling but because of a rapid relaxation and rapid suction effect. In studies of a large number of patients, including those with normal systolic function, the correlation between deceleration time and left ventricular filling pressures is poorer, which makes it difficult to determine filling pressures in a specific patient on the basis of the mitral flow velocity curve alone.

Currently, research is focused on distinguishing between the normal pattern (normal filling pressures) and the pseudonormal pattern (increased filling pressures) seen on mitral flow velocity curves (84). Analysis of pulmonary vein velocity curves may be helpful in that the velocity of systolic forward flow is inversely related to left atrial pressure (43,46,56,67). However, systolic forward flow may still be preserved if the contraction of the atrium and ventricle is maintained despite a high left atrial pressure (47). The response of the mitral flow velocity curve to changes in load may be used to distinguish between a normal and a pseudonormal flow pattern (50,51,72,85,86). In a normal subject, the E and A velocities both decrease when the preload is lowered with a drug such as nitroglycerin or during the strain phase of the Valsalva maneuver. Conversely, when there is a lowering of the preload in the presence of a pseudonormal pattern, a low E but a high A velocity emerges as an abnormal relaxation pattern is unmasked. New techniques are being investigated, for example, color M-mode echocardiography, which measures the flow propagation into the left ventricle, and Doppler tissue imaging, which directly examines myocardial motion (82,87-91). Additional studies will be needed before these new techniques can be applied clinically (84).

Left ventricular end-diastolic pressure depends on atrial pressure at the onset of atrial contraction, atrial contractility and compliance of the left ventricle. The left ventricular end-diastolic pressure can best be estimated from the ratio between the duration of atrial contraction on the mitral flow velocity curve and the duration of the pulmonary venous velocity curve (55-57). In a normal subject, the duration of the pulmonary venous velocity curve is equal to or less than the duration of atrial contraction on the mitral flow velocity curve. In the presence of an abnormal compliance of the left ventricle and higher end-diastolic pressures, there is a cutoff of the duration of mitral flow velocity curve at atrial contraction as left ventricular pressure rapidly exceeds left atrial pressure. Blood will flow back into the pulmonary vein as atrial contraction continues, even after cessation of transmitral flow. A pulmonary vein duration greater than mitral duration at atrial contraction is highly sensitive and specific for increased left

ventricular end-diastolic pressure (>15 mm Hg). This relation is present with both left ventricular systolic dysfunction and normal systolic function.

Currently, left ventricular filling pressures can be assessed reliably from the mitral flow velocity curves alone in patients in normal sinus rhythm who have left ventricular systolic dysfunction. Short deceleration times are indicative of high filling pressures. In patients with normal systolic function, more information is required in addition to the transmitral velocity curve for estimation of left ventricular filling pressures. If the pulmonary vein "A" velocities can be obtained, the relative duration compared with the mitral A velocity is useful for estimating filling pressures. Other methods for aiding in estimation of filling pressures in patients with normal systolic function are still under investigation.

Treatment

The treatment of diastolic dysfunction has been difficult and confusing. Only with increased understanding of the mechanism of diastolic dysfunction has it been possible to treat diastolic dysfunction. The treatment of this disorder can be divided into 1) general guidelines, 2) specific therapy based on Doppler flow velocity curves, and 3) dual-chamber pacing.

General therapy. The general therapy of diastolic dysfunction has several goals (5,7,19,81). If the size of the left ventricle is enlarged, a decrease in size will shift the pressure-volume curve downward and to the right by decreasing the preload and reducing pericardial constraint. This is most effective if there is an increase in right-sided diastolic pressures at baseline. If systolic contractility is reduced, an increase in systolic contractility will improve the rate of relaxation and shift the left ventricular pressure-volume loop leftward on its diastolic pressure-volume curve. A high afterload prolongs ventricular relaxation, and an attempt should be made to normalize blood pressure if it is increased.

Specific therapy. Specific therapy may be based on Doppler flow velocity curves. In patients with abnormal relaxation (grade I), there is a decrease in early filling of the heart, when a large proportion of the left ventricle fills at atrial contraction. These patients usually are not symptomatic at rest because their filling pressure is normal or only mildly increased. However, they may become symptomatic with exercise as the diastolic filling period shortens, because relaxation may not become complete before the onset of atrial contraction. An optimal therapy for these patients would be a medication that would increase the diastolic filling period and allow the ventricle more time to fill and allow relaxation to be completed before the onset of atrial contraction. Drugs such as beta-adrenergic or calcium channel blocking agents with negative chronotropic properties should be administered for symptomatic benefit. Calcium channel blockers do not appear to improve directly the rate of relaxation (42). For patients with abnormal relaxation caused by left ventricular hypertrophy due to hypertension, drugs that can produce regression of the hypertrophy may be beneficial in the long term. Angiotensin-

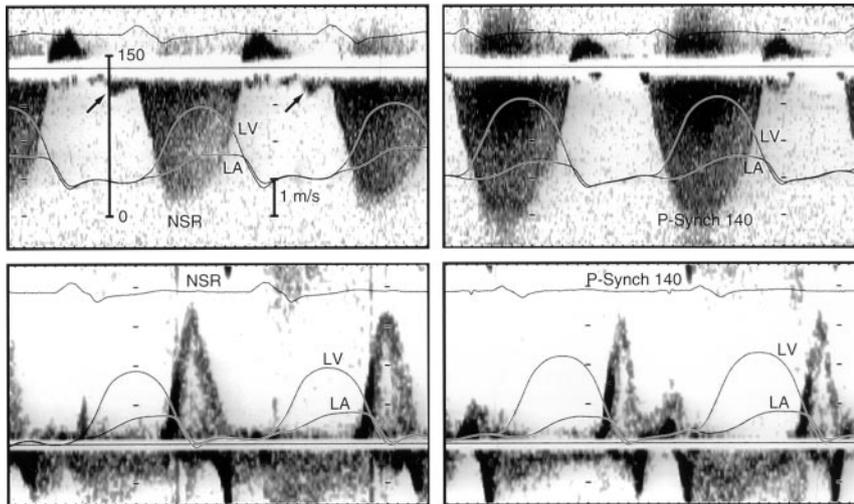


Figure 8. Continuous wave Doppler echocardiographic tracings of mitral regurgitation (**top**) and transmitral flow velocity curves (**bottom**) in a patient with severe heart failure due to dilated cardiomyopathy. **Left**, In the baseline state, there is first-degree atrioventricular (AV) block that causes early cessation of diastolic forward flow on the transmitral velocity curve and diastolic mitral regurgitation (**arrows**) on the continuous wave Doppler recording of mitral regurgitation. This is due to premature contraction and relaxation of the left atrium, which causes left atrial (LA) pressure to drop below left ventricular (LV) pressure in mid-diastole. NSR = normal sinus rhythm. **Right**, Dual-chamber pacing with a short AV interval results in the reestablishment of optimal AV synchrony, with diastolic forward flow continuing until the time of the onset of ventricular contraction. The diastolic mitral regurgitation is abolished, and in this example, there is a 40% increase in forward stroke volume. Modified, with permission, from Symanski JD, Nishimura RA. The use of pacemakers in the treatment of cardiomyopathies. *Curr Probl Cardiol* 1996;21:385-44.

converting enzyme inhibitors may have a direct beneficial effect on both relaxation and compliance (92). For patients who lose atrial contraction because of atrial arrhythmias, aggressive therapy should be directed at keeping the patient in normal sinus rhythm.

For patients with restriction to filling (grades III and IV), most of the filling of the left ventricle occurs in early diastole. Any measure that would prolong diastolic filling in these patients would not be beneficial, and the end result would be a decrease in cardiac output caused by decreasing the heart rate. The mainstay in therapy in these cases is the cautious use of venodilators and diuretic drugs to reduce the left ventricular preload. The reduction in preload not only shifts the pressure-volume curve leftward but relieves pericardial restraint if there is a concomitant increase in right-sided diastolic pressures. In patients with grade IV diastolic dysfunction, caution must be used because a reduction in preload may be at the expense of a decrease in forward cardiac output.

Dual-chamber pacing. Dual-chamber pacing has been used to treat selected subgroups of patients with severe left ventricular systolic dysfunction (93). The mechanism by which dual-chamber pacing works is restoration of proper atrial ventricular synchrony. The patients who respond best to dual-chamber pacing are those in whom atrial ventricular synchrony is ineffective because of a long first-degree atrioventricular (AV) block (Fig. 8). This results in abbreviated diastolic filling, and as left ventricular pressure increases above left atrial pressure at mid-diastole, diastolic mitral regurgitation may occur to further reduce the preload of the left ventricle. Therefore, at the time of onset of ventricular contraction, there is a lower preload, and decreased forward output is present. By reestablishing optimal AV synchrony with dual-chamber pac-

ing at a short AV delay, forward cardiac output can be increased in selected patients.

Summary

Doppler echocardiography has emerged as a noninvasive modality that can be used to assess diastolic filling of the heart. To apply this in clinical medicine, mitral flow velocity curves must be properly interpreted. It now is possible to predict prognosis, estimate filling pressures and guide therapy by analyzing mitral flow velocity curves. Additional studies with a large number of patients will be required to determine the ultimate role of Doppler echocardiography in population-based studies of diastolic dysfunction.

References

1. Yusuf S, Thom T, Abbott RD. Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension* 1989;13 Suppl:174-9.
2. Wilson JR, Martin JL, Schwartz D, Ferraro N. Exercise intolerance in patients with chronic heart failure: role of impaired nutritive flow to skeletal muscle. *Circulation* 1984;69:1079-87.
3. Wilson JR, Ferraro N. Exercise intolerance in patients with chronic left heart failure: relation to oxygen transport and ventilatory abnormalities. *Am J Cardiol* 1983;51:1358-63.
4. Packer M. Abnormalities of diastolic function as a potential cause of exercise intolerance in chronic heart failure. *Circulation* 1990;81 Suppl III:III-78-86.
5. Gaasch WH, Levine HJ, Quinones MA, Alexander JK. Left ventricular compliance: mechanisms and clinical implications. *Am J Cardiol* 1976;38:645-53.
6. Grossman W, Barry WH. Diastolic pressure-volume relations in the diseased heart. *Fed Proc* 1980;39:148-55.
7. Grossman W, McLaurin LP. Diastolic properties of the left ventricle. *Ann Intern Med* 1976;84:316-26.

8. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. *Am J Cardiol* 1984;54:778-82.
9. Dodek A, Kassebaum DG, Bristow JD. Pulmonary edema in coronary-artery disease without cardiomegaly: paradox of the stiff heart. *N Engl J Med* 1972;286:1347-50.
10. Fink LI, Wilson JR, Ferraro N. Exercise ventilation and pulmonary artery wedge pressure in chronic stable congestive heart failure. *Am J Cardiol* 1986;57:249-53.
11. Franciosa JA, Baker BJ, Seth L. Pulmonary versus systemic hemodynamics in determining exercise capacity of patients with chronic left ventricular failure. *Am Heart J* 1985;110:807-13.
12. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol* 1985;55:1037-42.
13. Tresch DD, McGough MF. Heart failure with normal systolic function: a common disorder in older people. *J Am Geriatr Soc* 1995;43:1035-42.
14. Benjamin EJ, Levy D, Anderson KM, et al. Determinants of Doppler indexes of left ventricular diastolic function in normal subjects (the Framingham Heart Study). *Am J Cardiol* 1992;70:508-15.
15. Sagie A, Benjamin EJ, Galderisi M, et al. Reference values for Doppler indexes of left ventricular diastolic filling in the elderly. *J Am Soc Echocardiogr* 1993;6:570-6.
16. Brutsaert DL, Sys SU. Relaxation and diastole of the heart. *Physiol Rev* 1989;69:1228-315.
17. Gilbert JC, Glantz SA. Determinants of left ventricular filling and of the diastolic pressure-volume relation. *Circ Res* 1989;64:827-52.
18. Levine HJ, Gaasch WH. Diastolic compliance of the left ventricle. II: Chamber and muscle stiffness, the volume/mass ratio and clinical implications. *Mod Concepts Cardiovasc Dis* 1978;47:99-102.
19. Little WC, Downes TR. Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 1990;32:273-90.
20. Mirsky I, Pasipoularides A. Clinical assessment of diastolic function. *Prog Cardiovasc Dis* 1990;32:291-318.
21. Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation* 1984;69:836-41.
22. Brutsaert DL. Nonuniformity: a physiologic modulator of contraction and relaxation of the normal heart. *J Am Coll Cardiol* 1987;9:341-8.
23. Brutsaert DL, Housmans PR, Goethals MA. Dual control of relaxation: its role in the ventricular function in the mammalian heart. *Circ Res* 1980;47:637-52.
24. Brutsaert DL, Rademakers FE, Sys SU. Triple control of relaxation: implications in cardiac disease. *Circulation* 1984;69:190-6.
25. Appleton CP, Hatle LK. The natural history of left ventricular filling abnormalities: assessment of two-dimensional and Doppler echocardiography. *Echocardiography* 1992;9:437-57.
26. 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.
27. 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.
28. Kitabatake A, Inoue M, Asao M, et al. Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease—a study by pulsed Doppler technique. *Jpn Circ J* 1982;46:92-102.
29. Friedman BJ, Drinkovic N, Miles H, Shih WJ, Mazzoleni A, DeMaria AN. Assessment of left ventricular diastolic function: comparison of Doppler echocardiography and gated blood pool scintigraphy. *J Am Coll Cardiol* 1986;8:1348-54.
30. Spirito P, Maron BJ, Bonow RO. Noninvasive assessment of left ventricular diastolic function: comparative analysis of Doppler echocardiographic and radionuclide angiographic techniques. *J Am Coll Cardiol* 1986;7:518-26.
31. Labovitz AJ, Pearson AC. Evaluation of left ventricular diastolic function: clinical relevance and recent Doppler echocardiographic insights. *Am Heart J* 1987;114:836-51.
32. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II: clinical studies. *Mayo Clin Proc* 1989;64:181-204.
33. Hanrath P, Mathey DG, Siegert R, Bleifeld W. Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: an echocardiographic study. *Am J Cardiol* 1980;45:15-23.
34. Szlachcic J, Tubau JF, Vollmer C, Massie BM. Effect of diltiazem on left ventricular mass and diastolic filling in mild to moderate hypertension. *Am J Cardiol* 1989;63:198-201.
35. Scognamiglio R, Fasoli G. Effects of nifedipine on left ventricular diastolic dysfunction after myocardial infarction. *Cardiovasc Drugs Ther* 1990;4 Suppl 5:923-8.
36. Petrella RJ, Nichol PM, Cunningham DA, Paterson DH. Verapamil improves left ventricular filling and exercise performance in hypertensive and normotensive elderly individuals. *Can J Cardiol* 1994;10:973-81.
37. Myreng Y, Myhre E. Effects of verapamil on left ventricular relaxation and filling dynamics in coronary artery disease: a study by pulsed Doppler echocardiography. *Am Heart J* 1989;117:870-5.
38. Lee RT, Lord CP, Plappert T, Sutton MS. Effects of nifedipine on transmitral Doppler blood flow velocity profile in patients with concentric left ventricular hypertrophy. *Am Heart J* 1990;119:1130-6.
39. Gambelli G, Amici E, Selvanetti A. Effects of nifedipine on left ventricular diastolic function in hypertension; echo Doppler study. *Cardiovasc Drugs Ther* 1990;4 Suppl 5:951-5.
40. Granier P, Douste-Blazy MY, Tredez P, Conte D, Galinier F. Improvement in left ventricular hypertrophy and left ventricular diastolic function following verapamil therapy in mild to moderate hypertension. *Eur J Clin Pharmacol* 1990;39 Suppl 1:S45-6.
41. Betocchi S, Cuocolo A, Pace L, et al. Effects of intravenous verapamil administration on left ventricular diastolic function in systemic hypertension. *Am J Cardiol* 1987;59:624-9.
42. Nishimura RA, Schwartz RS, Holmes DR Jr, Tajik AJ. Failure of calcium channel blockers to improve ventricular relaxation in humans. *J Am Coll Cardiol* 1993;21:182-8.
43. Appleton CP. Doppler assessment of left ventricular diastolic function: the refinements continue [editorial]. *J Am Coll Cardiol* 1993;21:1697-700.
44. Courtois M, Vered Z, Barzilai B, Ricciotti NA, Perez JE, Ludbrook PA. The transmitral pressure-flow velocity relation: effect of abrupt preload reduction. *Circulation* 1988;78:1459-68.
45. Courtois M, Kovacs SJ Jr, Ludbrook PA. Transmitral pressure-flow velocity relation: importance of regional pressure gradients in the left ventricle during diastole. *Circulation* 1988;78:661-71.
46. Kuecherer HF, Kusumoto F, Muhiudeen IA, Cahalan MK, Schiller NB. Pulmonary venous flow patterns by transesophageal pulsed Doppler echocardiography: relation to parameters of left ventricular systolic and diastolic function. *Am Heart J* 1991;122:1683-93.
47. Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Relation of pulmonary vein to mitral vein flow velocities by transesophageal Doppler echocardiography: effect of different loading conditions. *Circulation* 1990;81:1488-97.
48. Appleton CP, Hatle LK, Popp RL. Superior vena cava and hepatic vein Doppler echocardiography in health adults. *J Am Coll Cardiol* 1987;10:1032-9.
49. Thomas JD, Weyman AE. Echocardiographic Doppler evaluation of left ventricular diastolic function: physics and physiology. *Circulation* 1991;84:977-90.
50. Choong CY, Abascal VM, Thomas JD, Guerrero JL, McGlew S, Weyman AE. Combined influence of ventricular loading and relaxation on the transmitral flow velocity profile in dogs measured by Doppler echocardiography. *Circulation* 1988;78:672-83.
51. Choong CY, Herrmann HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;10:800-8.
52. Thomas JD, Choong CYP, Flachskampf FA, Weyman AE. Analysis of the early transmitral Doppler velocity curve: effect of primary physiologic changes and compensatory preload adjustment. *J Am Coll Cardiol* 1990;16:644-55.
53. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:757-68.
54. 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.
55. 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.
56. 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.
 57. Matsuda Y, Toma Y, Matsuzaki M, et al. Change of left atrial systolic pressure waveform in relation to left ventricular end-diastolic pressure. *Circulation* 1990;82:1659-67.
 58. Takahashi T, Iizuka M, Sato H, et al. Doppler echocardiographic-determined changes in left ventricular diastolic filling flow velocity during the lower body positive and negative pressure method. *Am J Cardiol* 1990;65:237-41.
 59. Triulzi MO, Castini D, Ornaghi M, Vitolo E. Effects of preload reduction on mitral flow velocity pattern in normal subjects. *Am J Cardiol* 1990;66:995-1001.
 60. Appleton CP, Carucci M, Henry CP, Olajos M. 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.
 61. Harrison MR, Clifton GD, Pennell AT, DeMaria AN. Effect of heart rate on left ventricular diastolic transmitral flow velocity patterns assessed by Doppler echocardiography in normal subjects. *Am J Cardiol* 1991;67:622-7.
 62. Kitzman DW, Sheikh KH, Beere PA, Philips JL, Higginbotham MB. Age-related alterations of Doppler left ventricular filling indexes in normal subjects are independent of left ventricular mass, heart rate, contractility and loading conditions. *J Am Coll Cardiol* 1991;18:1243-50.
 63. Spirito P, Maron BJ. Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988;59:672-9.
 64. 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.
 65. Yamamoto K, Masuyama T, Tanouchi J, et al. Effects of heart rate on left ventricular filling dynamics: assessment from simultaneous recordings of pulsed Doppler transmitral flow velocity pattern and haemodynamic variables. *Cardiovasc Res* 1993;27:935-41.
 66. Iga K, Hori K, Matsumura T, Tomonaga G, Gen H, Tamamura T. Left ventricular filling pattern in congestive heart failure patients with normal sinus rhythm—a decreased ratio of peak mitral flow velocity in atrial systole relative to that in early diastole may reflect markedly increased left ventricular end-diastolic pressure. *Jpn Circ J* 1990;54:473-7.
 67. Keren G, Sherez J, Megidish R, Levitt B, Laniado S. Pulmonary venous flow pattern—its relationship to cardiac dynamics: a pulsed Doppler echocardiographic study. *Circulation* 1985;71:1105-12.
 68. Xie GY, Berk MR, Smith MD, DeMaria AN. Relation of Doppler transmitral flow patterns to functional status in congestive heart failure. *Am Heart J* 1996;131:766-71.
 69. 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;90:2772-9.
 70. 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.
 71. Klein AL, Hatle LK, Taliencio CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiography study. *Circulation* 1991;83:808-16.
 72. Nishimura RA, Abel MD, Housmans PR, Warnes CA, Tajik AJ. Mitral flow velocity curves as a function of different loading conditions: evaluation by intraoperative transesophageal Doppler echocardiography. *J Am Soc Echocardiogr* 1989;2:79-87.
 73. 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 Cardiol* 1997;29:604-12.
 74. Braunwald E, Brockenbrough EC, Frahm CJ, Ross J Jr. Left atrial and left ventricular pressures in subjects without cardiovascular disease: observations in eighteen patients studied by transseptal left heart catheterization. *Circulation* 1961;24:267-9.
 75. Braunwald E, Frahm CJ. Studies on Starling's law of the heart. IV. Observations on the hemodynamic functions of the left atrium in man. *Circulation* 1961;24:633-42.
 76. Rahimtoola SH, Ehsani A, Sinno MZ, Loeb HS, Rosen KM, Gunnar RM. Left atrial transport function in myocardial infarction. Importance of its booster pump function. *Am J Med* 1975;59:686-94.
 77. Nishimura RA, Abel MD, Hatle LK, et al. Significance of Doppler indices of diastolic filling of the left ventricle: comparison with invasive hemodynamics in a canine model. *Am Heart J* 1989;118:1248-58.
 78. Brunazzi MC, Chirillo F, Pasqualini M, et al. Estimation of left ventricular diastolic pressures from precordial pulsed-Doppler analysis of pulmonary venous and mitral flow. *Am Heart J* 1994;128:293-300.
 79. Chenzbraun A, Keren A, Stern S. Doppler echocardiographic patterns of left ventricular filling in patients early after acute myocardial infarction. *Am J Cardiol* 1992;70:711-4.
 80. Giannuzzi P, Imparato A, Temporelli PL, et al. Doppler-derived mitral deceleration time of early filling as a strong predictor of pulmonary capillary wedge pressure in postinfarction patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 1994;23:1630-7.
 81. DeMaria AN, Wisenbaugh T. Identification and treatment of diastolic dysfunction: role of transmitral Doppler recordings [editorial]. *J Am Coll Cardiol* 1987;9:1106-7.
 82. Takatsuji H, Mikami T, Urasawa K, 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.
 83. 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.
 84. Nishimura RA, Appleton CP. "Diastology": beyond E and A [editorial]. *J Am Coll Cardiol* 1996;27:372-4.
 85. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG Jr. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. *Am J Cardiol* 1991;68:515-9.
 86. Berk MR, Xie GY, Kwan OL, et al. Reduction of left ventricular preload by lower body negative pressures alters Doppler transmitral filling patterns. *J Am Coll Cardiol* 1990;16:1387-92.
 87. Stugaard M, Risoe C, Ihlen H, Smiseth OA. Intracavitary filling pattern in the failing left ventricle assessed by color M-mode Doppler echocardiography. *J Am Coll Cardiol* 1994;24:663-70.
 88. Stugaard M, Brodahl U, Torp H, Ihlen H. Abnormalities of left ventricular filling in patients with coronary artery disease: assessment by colour M-mode Doppler technique. *Eur Heart J* 1994;15:318-27.
 89. Stugaard M, Smiseth OA, Risoe C, Ihlen H. Intraventricular early diastolic filling during acute myocardial ischemia, assessment by multigated color M-mode Doppler echocardiography. *Circulation* 1993;88:2705-13.
 90. Brun P, Tribouilloy C, Duval AM, 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.
 91. Cohen GI, Pietrolungo JF, Thomas JD, Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol* 1996;27:1753-60.
 92. Friedrich SP, Lorell BH, Rousseau MF, et al. Intracardiac angiotensin-converting enzyme inhibition improves diastolic function in patients with left ventricular hypertrophy due to aortic stenosis. *Circulation* 1994;90:2761-71.
 93. Nishimura RA, Hayes DL, Holmes DR Jr, Tajik AJ. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. *J Am Coll Cardiol* 1995;25:281-8.