

REVIEW

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The Pathophysiology and Diagnostic Approaches for Diastolic Left Ventricular Dysfunction: A Clinical Perspective

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ABSTRACT

Heart failure with a normal ejection fraction is interchangeably termed diastolic heart failure. This condition is often unrecognized and it does have diagnostic, prognostic and therapeutic implications that are distinct from those conditions with systolic dysfunction. It is clinically important to understand and assess the diastolic function to reliably manage the patients suffering with heart failure. With the results of randomized trials for this distinct clinical syndrome, as well as the probability of better diagnostic testing in the future, physicians will in a better position not only to diagnose diastolic dysfunction or heart failure, but also to manage it more effectively. In this review, the physiology of the diastole and how to evaluate the abnormalities of the diastolic function will be discussed. (**Korean Circulation J 2005;35:865-876**)

KEY WORDS : Pathophysiology ; Diastolic dysfunction ; Heart failure.

Epidemiology

Heart failure is the most common hospital diagnosis for patients 65 or older at the time of discharge, and it is a major cardiovascular disorder that's still increasing in prevalence. In the early 20th century, 4% of the population reached 65 years of age; however, by the year 2010, it is predicted that 35% of the population will be older than 65 years of age.¹⁾ Cardiovascular disease is the most common cause of morbidity and mortality for the elderly. Investigators have traditionally focused on systolic functional abnormalities to explain the signs and symptoms of heart failure. However, it has become increasingly evident that diastolic functional abnormalities also play a major role for precipitating heart failure and determining the prognosis.²⁻⁵⁾

Four epidemiological investigations have demonstrated that nearly half of the congestive heart failure subjects in the community have normal systolic function.⁶⁻⁹⁾ Some researchers have argued that apparent "diastolic heart failure" may actually be undetected transient systolic dysfunction that is caused by an acute afterload mismatch that's induced by hypertension or this is caused by ischemia. In a recent study of 38 consecutive

patients who had acute pulmonary edema and marked systolic hypertension, their heart failure was due to exacerbation of the diastolic dysfunction via hypertension, and not by transient systolic dysfunction or mitral regurgitation.¹⁰⁾ However, this condition, which commonly referred to as diastolic dysfunction, is often unrecognized and it does have diagnostic, prognostic and therapeutic implications that are distinct from those patients with systolic dysfunction. Thus, it is clinically important to understand and assess the diastolic function to reliably manage those patients with heart failure. In this review, we will discuss the physiology of the diastole and how to evaluate abnormalities of diastolic function.

Physiology of Diastole

Abnormalities of ventricular relaxation and filling contribute to heart failure because these features result in an abnormally high ventricular diastolic pressure in relation to the diastolic volume. The most important factors that determine the relation between pressure and volume during ventricular diastole are the rate and extent of myocardial relaxation and the generation of restoring forces. Both are important determinants of early diastolic filling, and the passive pressure-volume relationship of the ventricle determines the mid-late diastolic filling after the relaxation is completed.¹¹⁻¹⁴⁾

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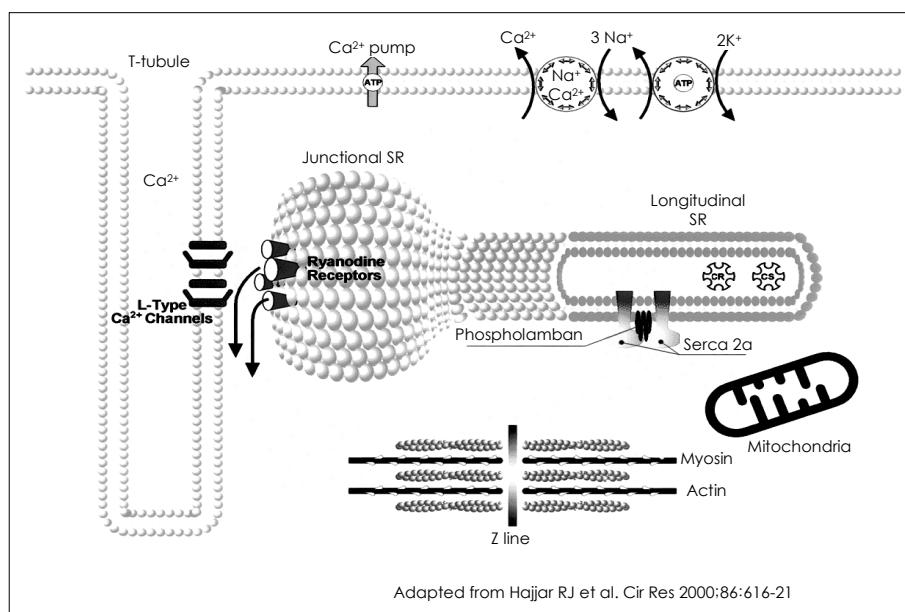


Fig. 1. The Ca^{2+} handling proteins involved in Ca^{2+} movement (adapted from Hajjar RJ et al. Cir Res 2000;86:616-21). SR: sarcoplasmic reticulum.

Myocardial relaxation

The normal cardiac contraction/relaxation cycle requires a precise, transient rise and fall in the level of intracellular calcium ions. The sarcoplasmic reticulum (SR) has a central role in orchestrating the movement of calcium during each contraction and relaxation.¹⁵⁾¹⁶⁾ Contraction of the cardiac muscle is initiated by the cellular action potential that causes opening of the L-type sarcolemmal calcium channels through which the calcium ions enter the cytosol. Influx of calcium ions through the L-type channels results in the release of large amounts of calcium ions from the adjacent SR through the ryanodine receptor channels, and this process is termed calcium-induced calcium release. These calcium ions bind to troponin C that ultimately disinhibits the interaction of actin and myosin with the resultant cross-bridge formation (Fig. 1).¹¹⁾¹²⁾ Myocardial relaxation is primarily accomplished by the removal of calcium ions from troponin C by an enzyme located in SR, which is called SR calcium ATPase or SERCA₂, and the sarcolemmal sodium-calcium exchanger. In humans, approximately 75% of calcium ions are removed by SERCA₂ and 25% are removed by the Na/Ca exchanger.¹⁷⁾ The activity of SERCA₂ is modulated by phospholamban, another SR protein located near SERCA₂. The calcium ion uptake by SERCA₂ is enhanced via phosphorylation by protein kinase A and other kinases.¹⁸⁾ Failure of the normal mechanisms for the reuptake and extrusion of calcium ions that are released during contraction can result in slowing of relaxation or an inability to return the cytosolic calcium concentration to normal diastolic levels. The latter causes a diastolic calcium overload and incomplete relaxation with excessive diastolic tension or stiffening.¹⁹⁻²¹⁾ In an experimental model of senescence,

it has been demonstrated that there is a decrease of the SR Ca^{2+} uptake during relaxation, and this is associated with a decrease in the content and activity of SERCA₂.²²⁾ More recently, SERCA₂ protein levels were found to be significantly decreased in senescent human myocardium.²³⁾ This decrease in SERCA₂ levels was associated with impaired myocardial function at the study's baseline and further deterioration occurred during hypoxic conditions.²³⁾ Thus, a decrease in the SERCA₂ content and the associated decrease in the SR Ca^{2+} uptake have been suggested to play a major role in the diastolic dysfunction. The vulnerability of calcium reuptake is a contributing factor for the abnormal left ventricular relaxation that's been noted early in cardiac disease states, and this is despite the normal systolic function.

Myocardial relaxation is also modulated by factors at the extracellular and organ levels. Endocardial and vascular endothelial modulators have been proposed as being important factors in the physiology of myocardial relaxation.¹¹⁾²⁴⁾ The vascular endothelium also appears to play an important role in these responses. In an experiment with papillary muscle preparation, Brutsaert et al. have found that denudation of the endocardium resulted in earlier and rapid relaxation in conjunction with a very modest reduction of the developed force.¹¹⁾ Although its effects are less clear in normal hearts, angiotensin II has been shown to slow myocardial relaxation in hypertrophied hearts.²⁴⁾ Other locally released substances that may influence myocardial relaxation include endothelin-1, natriuretic peptides, prostaglandins and adenylyl purines. The physiologic and pathophysiologic significance of these modulators of relaxation remains to be elucidated.

It's interesting that the relevance of caffeine for fa-

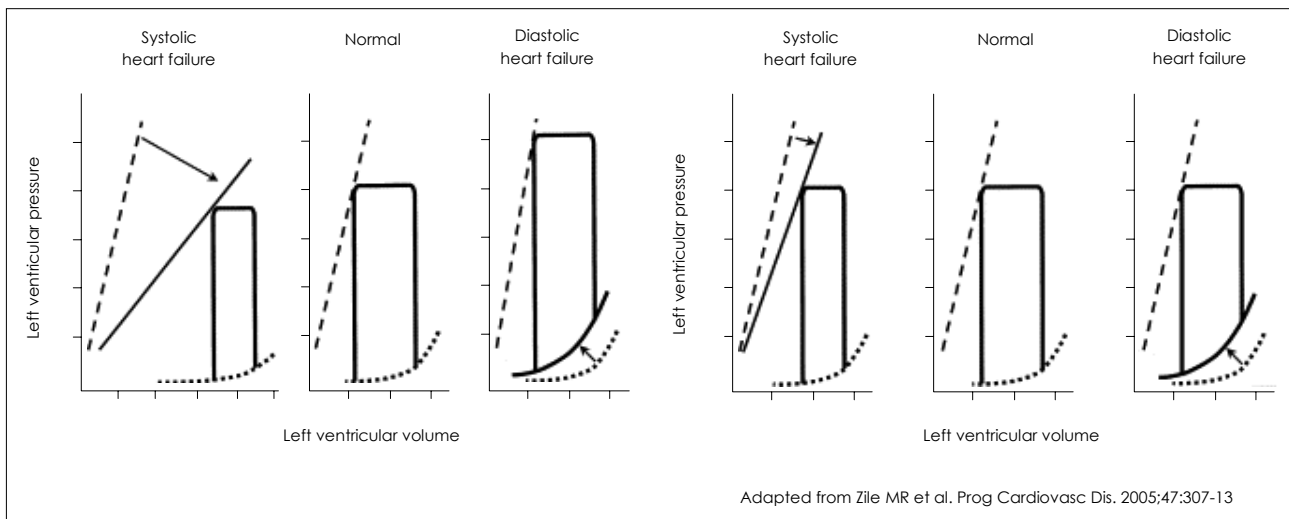


Fig. 2. The left ventricular end-diastolic pressure-volume relationship describes the diastolic properties of the left ventricle. The slope of the relationship indicates the passive chamber stiffness. Shifting the pressure-volume curve leftward indicates a stiffer ventricle, whereas a rightward shift indicates greater compliance (adapted from Zile MR et al. *Prog Cardiovasc Dis.* 2005;47:307-13).

cilitating diastolic dysfunction in the intact heart was demonstrated in the experimental canine model of demand ischemia.²⁵⁾ It was also suggested that caffeine favorably affected myocardial relaxation without altering contractility.²⁶⁾

Restoring forces

Restoring forces are generated when the ventricle contracts to an end-systolic volume (ESV) that is less than its equilibrium volume (V_0), which is the volume in the fully relaxed state when the transmural pressure is zero, thereby storing energy by compressing the elastic elements in the myocardium.¹³⁾²⁴⁾ The physical properties of the normal ventricular chamber allow potential energy to be stored during systole in the form of a lower ventricular pressure. This potential energy is converted to kinetic energy in the form of elastic recoil with the resultant suction of blood from the left atrium into the ventricle early during diastole.²⁷⁾ Other factors, especially complex shape changes during systole, may also play a role in causing suction during the subsequent diastole.²⁸⁾ During systole the left ventricle demonstrates a counter clockwise twist extending from the apex to the base, and in early diastole the left ventricle untwists clockwise to release the stored energy and this creates a suction force not unlike the release of a compressed spring. Suction is most important under conditions of stress when contractility is high and the ESV is small, and when filling must be enhanced such as during exercise. Conversely, when contractility is impaired, the ESV is larger and the suction is reduced or lost as a mechanism of filling.²⁹⁾

The passive pressure-volume relation of the ventricle

Laplace's law provides for the relationship between pressure and the chamber geometry when a stress is

applied to the ventricle. In the simplest case of a sphere, Laplace's law states that pressure is proportional to the radius of the chamber divided by its wall thickness. Thus, a chamber with thicker walls requires a larger distending pressure to achieve a given volume. The intrinsic stiffness of the tissue in the ventricular wall is the other key determinant of the distending force that's required to passively fill the chamber. The elastic properties are most responsible for wall stiffness at low filling pressures.³⁰⁾ At higher distending pressures, the myocardial connective tissue matrix assumes a key role. The intrinsic passive stiffness of any tissue, including the myocardium, can be quantified as the change in stress required for producing a given change in stretch (or strain). Biologic tissues have a curvilinear passive stress-strain relationship. The amount of blood contained within the vessels in the heart wall is also a determinant of the stiffness of the myocardial tissue, which contributes to the pressure-volume relationship (PVR).³¹⁾ As a result, a greater distending pressure is required to fill the chamber when the myocardial blood volume increases. The PVR of the passive ventricle is curvilinear, paralleling the passive stress-strain relationship. At any point on this curve, the ratio of the change in pressure to the change in volume is represented as the operating chamber stiffness; its inverse is the operating compliance. Like the stress-strain relationship, the PVR can be converted into a linear relationship by plotting the operating chamber stiffness versus pressure (Fig. 2). The slope of this relation is the chamber-stiffness constant. The parietal pericardium and right ventricle form external constraints to filling, and this influences the PVR as well. The parietal pericardium has a very compliant PVR at low volumes, but then it makes a sharp transition to a very steep relationship. Increases in the right ventricular dia-

stolic volume and pressure influence the left ventricular PVR similarly, albeit more modestly because the right ventricular changes are transmitted to the left ventricle via the ventricular septum. This phenomenon is termed diastolic-ventricular interaction and it is based on the fact that the total cardiac volume within the pericardial sac remains constant; hence, overfilling of the right ventricle will result in reduced filling of the left ventricle and vice versa. This is manifested most dramatically in constrictive pericarditis. The ventricular and pericardial effects on the left ventricular PVR are often linked.

Diagnostic Evaluation by Echocardiography

Doppler echocardiography has been successfully applied in the past decade to assess diastolic filling, and it has become a reliable, reproducible and practical noninvasive method for the identification and longitudinal follow-up of those patients with diastolic dysfunction.³²⁾

Mitral valve inflow

Assessment of transmitral blood flow velocities has served as the backbone for evaluating the diastolic function via Doppler echocardiography since its first description by Kitabatake in 1982.³³⁾ The velocity curve is influenced by several parameters, including the preload, afterload, contractile state, heart rate, myocardial relaxation and the left ventricular compliance. Theoretical models, computer simulation and experimental animal models have shown that the left atrial pressure, the rate of isovolumic ventricular relaxation (τ), the end-systolic volume and the left ventricular minimal pressure are

the major determinants of transmitral Doppler filling.³⁴⁻³⁸⁾ Impairment of left ventricular relaxation, which is the earliest manifestation of diastolic dysfunction, results in a prolongation of the isovolumic relaxation time and a reduction in the early transmitral flow velocity (E) with prolongation of the E-wave deceleration time and an augmented A velocity. In contrast, increasing filling pressures result in shortening of the isovolumic relaxation time, an increased early transmitral gradient and consequently, a high early transmitral flow velocity, shortening of the deceleration time and a reduction in the atrial flow velocity. Since the mitral flow Doppler profile depends on both of the above parameters, progressive elevation of the left atrial pressure in the ventricles with reduced isovolumic relaxation will reverse the classic pattern of impaired myocardial relaxation towards a "normal" appearing profile; i.e., the so called pseudonormal pattern.

Transmitral flow velocity curves show a progression over time, and this demonstrates the natural progression of the underlying myocardial dysfunction. 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 diastolic dysfunction, which is referred to as mild diastolic dysfunction, impaired (delayed) relaxation of the left ventricle predominates and this results in the most typical mitral flow velocity profile. At this stage, there is little if any increase in the rest left ventricular diastolic pressure or the mean left atrial pressure. Increased filling pressure may develop with exercise because of shortening of the diastolic filling period. With progression of disease, the filling pressure in the particular left atrial pressure starts

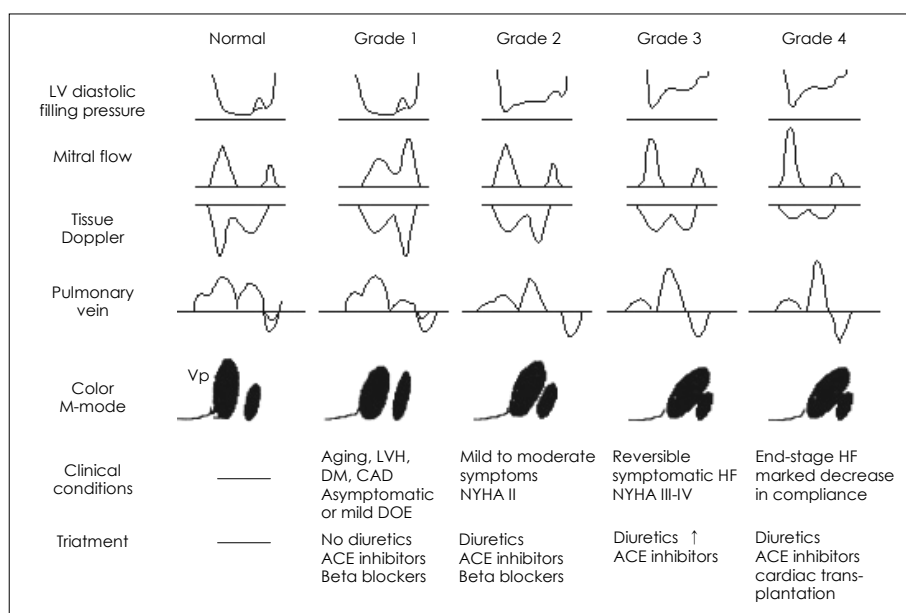


Fig. 3. Diagram of a proposed grading system for diastolic dysfunction, as based on the progression of disease patterns in the patients with cardiac disease. LV: left ventricle, LVH: left ventricular hypertrophy, DM: diabetes mellitus, CAD: coronary artery disease, DOE: dyspnea on exertion, ACE: angiotensin converting enzyme, NYHA: New York Heart Association, HF: heart failure, Vp: early diastolic propagation velocity.

to increase at rest; thus, this increases the driving pressure across the mitral valve. This has the effect of normalizing the E velocity and the DT of the E velocity. This phase represents moderate diastolic dysfunction. In more advanced disease, as the effective operative compliance decreases, the left atrial pressure becomes even higher and this produces a restrictive filling pattern that's characterized by a tall E velocity, a shortened DT and a small A velocity; this all indicative of severe diastolic dysfunction. In patients with left ventricular systolic dysfunction, a restricted filling pattern has been associated with a worse functional class and exercise intolerance.³⁹⁾ A short deceleration time (<140 ms) is indicative of a poor prognosis that's independent of the degree of systolic dysfunction.⁴⁰⁻⁴²⁾ On the basis of this progression of disease patterns, a grading system has been proposed for the severity of diastolic dysfunction as assessed with Doppler echocardiography (Fig. 3).⁴³⁾ 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. The patients with grade I diastolic dysfunction may develop dyspnea with moderate or greater exertion or they may develop symptoms of heart failure if the contribution from atrial contraction is lost, as occurs with the 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; this produces symptoms with mild to moderate exertion. Patients with grade III diastolic dysfunction have a restrictive filling pattern on the mitral flow velocity curves, a severe increase in the filling pressures and they experience symptoms with minimal exertion or at rest. The treatment of heart failure or such bedside maneuvers that result in a decrease preload (an upright sitting posture or a Valsalva maneuver) may produce changes in the mitral flow velocity curve so that for a patient with grade III diastolic dysfunction, the velocity profile may revert to grade II or even grade I diastolic dysfunction, which is indicative of a good prognosis. On the other hand, some patients with severe abnormalities of ventricular compliance and end-stage heart disease maintain a severely restrictive pattern even after optimal medical therapy. These patients have the poorest prognosis and they are classified as having grade IV (irreversible) diastolic dysfunction.⁴⁴⁾

Because of the opposing effects on these variables according to the relaxation and filling pressures, it is difficult to evaluate the relaxation properties of the left ventricle when the left atrial pressure is unknown. Moreover, the relationships between the deceleration time or E/A ratio and the filling pressures are not as strong in those patients with normal systolic function.⁴⁵⁾⁴⁶⁾ Therefore, it is desirable to have additional variables to complement the mitral inflow velocity during the evaluation

of diastolic function.

Additional echocardiographic parameters can assess ventricular relaxation and the filling pressure since these are the two most prominent components of diastolic dysfunction. Impaired ventricular relaxation indicates the presence of diastolic dysfunction, and the level of filling pressure elevation indicates the extent of the diastolic dysfunction. Ventricular relaxation is assessed via the mitral annular velocity recording by performing tissue Doppler echocardiography (TDE), and the mitral inflow propagation velocity is assessed by color M-mode and less directly by the preload reduction. The left ventricular filling pressure is estimated by the mitral inflow deceleration time (especially when there is left ventricular systolic dysfunction), pulmonary vein flow velocity analysis, comparison of the flow duration (the mitral A wave vs the pulmonary venous atrial flow reversal), and the ratio of the transmitral flow velocity to the mitral annular velocity, which will be discussed later. Demonstration of impaired relaxation and/or increased filling pressures by any of the above modalities signifies the presence and severity of diastolic dysfunction. In addition, the two-dimensional echocardiographic features such as increased left ventricular wall thickness, left atrial enlargement and ventricular interaction reflect the presence of diastolic dysfunction.

Tissue Doppler echocardiography

TDE is a recent Doppler application that allows direct measurement of myocardial velocities. TDE uses low-velocity and high-amplitude Doppler signals, in contrast to the mitral inflow, which uses high-velocity and low-amplitude signals.⁴⁷⁾ TDE is the easiest and most reproducible method to evaluate myocardial relaxation by measuring the mitral annulus velocity during diastole. The mitral annulus velocity reflects shortening and lengthening of the left ventricular myocardial fibers along a longitudinal plane (from the base to the apex plane). With prolonged myocardial relaxation, the ratio of the mitral annulus motion during atrial systole to the total diastolic annular motion is increased. It has been shown that the early diastolic mitral annulus velocity (E'), as determined by TDE, is relatively independent of the preload, especially in those patients showing reduced myocardial relaxation, and it is useful in differentiating a pseudonormal from a normal mitral inflow velocity pattern.⁴⁸⁾⁴⁹⁾ As the left ventricular filling pressure increases, the mitral E velocity becomes progressively higher whereas the E' velocity remains reduced. Therefore, the assessment of mitral annular velocity by employing TDE may be useful for the evaluation of diastolic dysfunction, and TDE has overcome some of the inherent difficulties in assessing diastolic function with utilizing transmitral inflow velocities alone. Nagueh et al.⁴⁹⁾ have recently shown that when the mitral E velocity was cor-

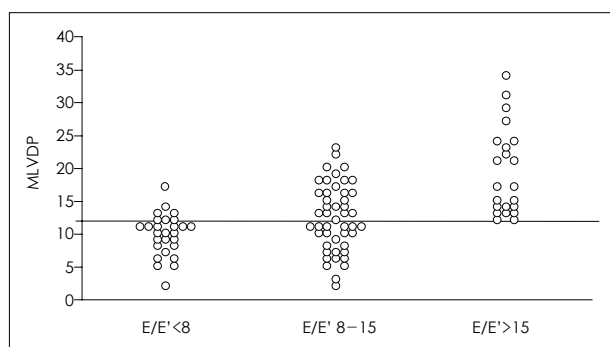


Fig. 4. The mean LV diastolic pressure versus groups defined by values of the septal E/E'. An E/Ea ratio of 15 is highly specific for an elevated LA pressure, whereas a ratio of 8 is very specific for normal to low filling pressures. LA: left atrium, MLVDP: mean left ventricular diastolic pressure.⁴⁶⁾

rected for the influence of myocardial relaxation (i.e. the E/E' ratio), it was found to be well correlated with the mean pulmonary capillary wedge pressure (PCWP). In their study, an E/E' (lateral annulus) ratio of >10 detected a mean PCWP >15 mm Hg with a sensitivity of 97% and specificity of 78%. Ommen et al. have assessed the association between E' (septal annulus) and the left ventricular filling pressures in 100 consecutive patients who were referred for cardiac catheterization, and they found that an E/E' ratio >15 identified an increased left ventricular filling pressure (Fig. 4).⁴⁶⁾ Nagueh et al.⁵⁰⁾ have also showed that E' remained unchanged with an increased transmitral gradient in those subjects with diastolic dysfunction, whereas it is increased in the subjects with a normal tau.

A very exciting observation was recently published showing that myocardial contraction and relaxation velocities, as assessed by TDE, were reduced in the patients with familial hypertrophic cardiomyopathy mutations (the positive genotype), but they were without the left ventricular hypertrophy phenotype.⁵¹⁾ Early detection of mutation-positive subjects may allow therapeutic interventions to prevent the later development of left ventricular hypertrophy, which is a major determinant of mortality and morbidity in these patients. Although much work is still required to link the genetic defects in the cardiac sarcomere with a clinical, noninvasive measure of global left ventricular function, this preliminary observation has introduced a possible future application of this technique that will contribute to the better understanding and management of the patients suffering with hypertrophic cardiomyopathy or premature diastolic dysfunction.

It was recently shown that E', as measured by TDE, is reduced in the patients suffering with restrictive cardiomyopathy (RCM), whereas it is relatively normal or even accentuated in the patients suffering with constrictive pericarditis (CP).⁵²⁻⁵⁴⁾ Recording of E' by using TDE is another useful means to diagnose CP when the mitral

inflow velocity reveals a restrictive filling pattern without sufficient respiratory variation. When the mitral inflow velocity shows a high E, a shortened deceleration time and no respiratory variation, then the diagnostic possibilities are normal (in healthy young individuals), restriction or constriction; however, E', as measured by TDE and the hepatic vein flow velocity, in addition to the 2-dimensional echocardiographic findings, should be able to distinguish them.⁵⁵⁾ Therefore, the recording of E' via TDE should be an essential part of the echocardiographic Doppler evaluation for all the patients suffering with heart failure, especially when CP is suspected.

Color flow propagation

The propagation of flow into the left ventricular cavity during early diastole by the color M-mode has been shown to correlate with the invasively measured time constant of relaxation, τ .^{56,57)} A chamber with normal relaxation will demonstrate rapid flow propagation from the inflow to the left ventricular apex, while a slowly relaxing ventricle will demonstrate prolonged flow propagation. It has also been shown that the propagation velocity is relatively load independent.⁵⁸⁾ However, there is not yet a consistent method for measuring propagation velocity, and the various reported techniques are not interchangeable. In addition, the influence and challenge of a rapid heart rate along with the fusion of the early and late diastolic flow is not yet fully understood. The flow propagation velocity may erroneously appear to be normal in the patients suffering with diastolic dysfunction and a preserved left ventricular systolic function. This is particularly so when the left ventricular size is small and the heart rate is fast. Therefore, in small ventricles, this index may not accurately reflect the relaxation properties of the left ventricle.

Pulmonary venous flow velocity

Pulmonary vein flow patterns have been used to complement the mitral inflow velocity profiles. A normal pulmonary venous flow velocity curve consists of systolic forward flow, diastolic forward flow and a reversal flow during atrial contraction. The systolic forward flow is influenced by the left atrial relaxation, the left atrial compliance, the mean left atrial pressure, the descent of the annulus toward the left ventricular apex, the right ventricular contraction and the presence of significant mitral regurgitation. The diastolic forward flow occurs at the time when there is an open conduit between the pulmonary vein, the left atrium and the left ventricle. At the time of atrial contraction, there continues to be an open conduit between the pulmonary vein, the left atrium and the left ventricle. There is forward flow into the left ventricle, with blood also traveling in a retrograde fashion into the pulmonary veins. When the left

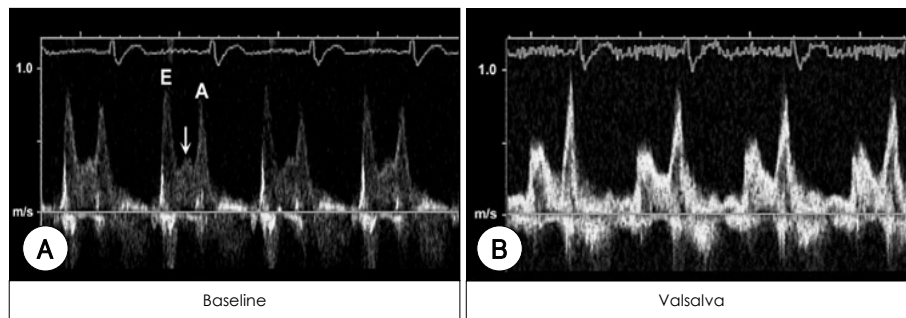


Fig. 5. Pulsed-wave Doppler echocardiography of the transmitral inflow in a 62-year-old man with ischemic cardiomyopathy. A: triphasic mitral inflow velocity with prominent mid-diastolic filling (indicated by arrow). B: a Valsalva maneuver unmasked a delayed relaxation pattern and the mid-diastolic filling disappeared during the Valsalva maneuver. E denotes the peak velocity of early filling; A is the peak velocity of late filling during atrial contraction.

atrial pressure is normal, most flow into the left atrium occurs during systole. However, when the left atrial pressure increases, the systolic forward flow decreases and flow occurs predominantly during diastole, resulting in a reversal of the systolic (S)/diastolic (D) ratio with blunting of the pulmonary venous S wave and an increase in the amplitude and duration of the atrial reversal (AR) wave. This pattern has been used to distinguish normal from “pseudonormal” transmitral Doppler filling. However, in those healthy young adults and athletes for whom the atrial contribution to the left ventricular filling is minimal and the left atrium behaves more as a “passive” conduit, blunting of the S wave is also commonly seen. The AR wave is usually shorter in amplitude and duration in normal subjects,⁵⁹⁾ but it may also be reduced in some patients suffering with moderate or severe diastolic dysfunction, which is possibly caused by atrial mechanical failure.⁶⁰⁾ A recent study that investigated the correlation between the deceleration time of the diastolic pulmonary venous flow and of the early filling mitral flow, and the pulmonary capillary wedge pressure in patients suffering with acute myocardial infarction showed that the deceleration time of the diastolic pulmonary venous flow correlated even better than did the deceleration time of the mitral E velocity with the pulmonary capillary wedge pressure.⁶¹⁾ However, the most challenging aspect in practice is the overall feasibility of obtaining interpretable pulmonary venous flow signals. Several studies have documented that this assessment is possible in only 64-73% of patients. Moreover, even for the patients with adequate pulmonary venous flow signals, the ability of the pulmonary venous flow parameters to detect elevated left ventricular filling pressures is inconclusive or it’s sometimes confusing. Additionally, similar to the mitral inflow velocity, its accuracy for predicting left ventricular filling pressures is dependent upon the presence of sinus rhythm.

Preload manipulation

Preload manipulation can also be used to comple-

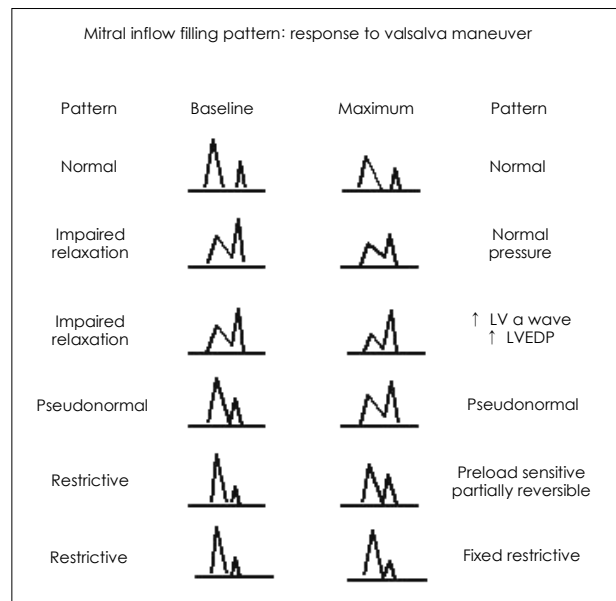


Fig. 6. Various responses of the mitral inflow to a Valsalva maneuver. LV: left ventricle, LVEDP: left ventricular end-diastolic pressure.

ment the mitral inflow pattern. A reduction in preload by having the patient sit, by performing a Valsalva maneuver or by administering sublingual nitroglycerin may be able to unmask the underlying impaired relaxation of the LV (Fig. 5, 6), and so decrease the E/A ratio to less than 1.0. Conversely, an increase in preload by performing a leg raise may result in deterioration of the diastolic function and the LV filling pattern. Fig. 7 shows the transmitral inflow velocity tracing obtained by pulsed-wave Doppler echocardiography in a 71-year-old man with restrictive cardiomyopathy. The mitral flow pattern at baseline (left panel) showed that the early filling (the E wave) is lower than the filling during atrial contraction with a prolonged deceleration time, which is consistent with a pattern of impaired relaxation (grade I). After elevating both legs for 3 minutes (the middle panel), the mitral flow pattern changed with prominent mid-diastolic filling, an increased E/A ratio and a shortened deceleration time of the E wave (grade II).

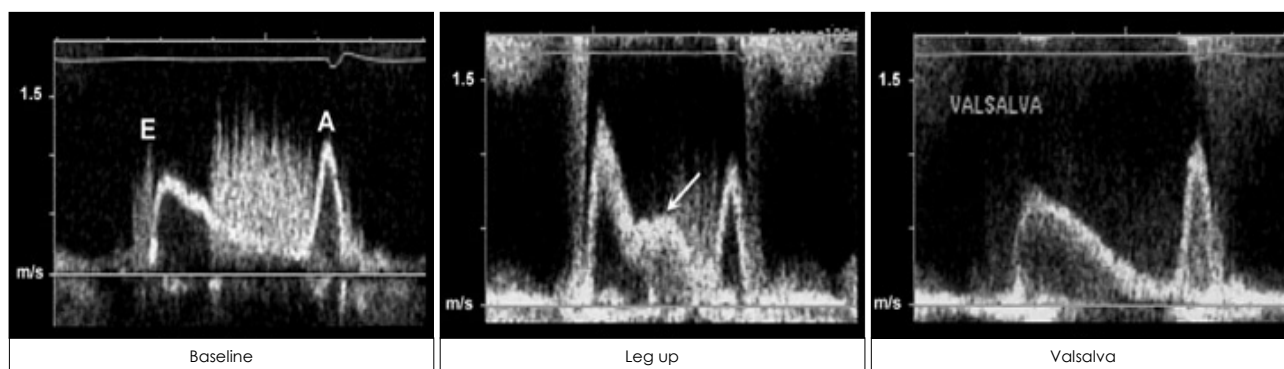


Fig. 7. Transmitral inflow velocities obtained by pulsed-wave Doppler echocardiography in a 71-year-old man suffering with restrictive cardiomyopathy. The mitral flow pattern at baseline (left panel) showed that the early filling (the E wave) was lower than the filling during atrial contraction with a prolonged deceleration time, which was consistent with a pattern of impaired relaxation. After elevating both legs for 3 minutes (middle panel), the mitral flow pattern was changed with prominent mid-diastolic filling, an increased E/A ratio and a shortened deceleration time of the E wave. The mitral inflow pattern returned to baseline during a Valsalva maneuver. The abbreviations are the same as in Fig. 5.

The mitral inflow pattern returned to baseline during performance of a Valsalva maneuver. However, similar to the pulmonary venous flow pattern, the ability to assess the response to a Valsalva maneuver is limited by the technical feasibility. The fusion of the E and A wave during the relative tachycardia of the Valsalva maneuver may hinder any accurate measurement.

Flow duration during atrial contraction

The comparison of flow duration between mitral inflow and pulmonary venous flow during atrial contraction is helpful for determining an elevated left ventricular end-diastolic pressure. The reversal of flow into the pulmonary vein during atrial contraction tends to increase in velocity and duration (relative to mitral A wave duration) with the worsening diastolic properties. This is the result of the worsening relative compliance of the left ventricle compared with the pulmonary venous conduit. Upon atrial contraction, a poorly compliant ventricle will manifest a steep end diastolic pressure rise for a small volume of transmitral flow, and this results in rapid and early equalization of the left ventricular pressure and the left atrial pressure, and cessation of forward flow will prematurely occur. Meanwhile, flow will continue into the pulmonary venous circuit. An elevated left ventricular end-diastolic pressure can be detected with high specificity if the atrial reversal flow duration is >30 msec of the mitral A duration.⁵⁹⁾⁶²⁾

Index of myocardial performance (Tei index)

The integrated assessment of the systolic and diastolic left ventricular function would be ideal for the evaluation of heart failure. An index of myocardial performance (IMP) has been devised to incorporate both the systolic and diastolic time intervals for expressing global performance, and this is referred to as the Tei index. This is estimated as the sum of the isovolumic contraction time and the isovolumic relaxation time divided by the ejection time. It can be easily obtained

and it's been shown to be reproducible.⁶³⁾ Both systolic and diastolic dysfunction results in abnormality of myocardial relaxation, which prolongs the isovolumic relaxation period. IMP has been demonstrated to predict morbidity and mortality in dilated cardiomyopathy,⁶⁴⁾ cardiac amyloidosis,⁶⁵⁾ primary pulmonary hypertension,⁶⁶⁾ and myocardial infarction.⁶⁷⁾ Whether this index is useful for diagnosing and predicting the clinical outcome of primary diastolic dysfunction needs to be validated with future studies.

The interval between the onset of mitral E and the annular early diastolic velocity (E') as determined by tissue Doppler echocardiography

The different responses of the E and E' velocities to an increase in preload illustrate the different mechanisms generating the E and Ea velocities: when the LV myocardial relaxation is normal, E begins with the LV diastolic suction that's induced by rapid relaxation, and this results in a simultaneous onset of E and E'. However, if myocardial relaxation is impaired, early diastolic filling is initiated by the left atrial pressure at the time of the mitral valve opening, and the E' velocity starts later as a result of the delayed myocardial relaxation. Garcia and colleagues have shown that the onset of E' occurred 7.5 ± 3.5 ms after the peak mitral inflow velocity in 7 patients suffering with restrictive cardiomyopathy, whereas the E' started 22 ± 19 ms earlier than did the E in the normal group.⁵²⁾ Subsequently, the interval between the onset of the mitral E and E', as determined by TDE ($T_{E-E'}$), has been shown to correlate with the time constant of the LV relaxation (τ); this was demonstrated by Hasegawa and associates in their rather elegant animal experiment.⁶⁸⁾ With worsening of heart failure by inducing rapid pacing, E' progressively decreased in velocity and it was delayed in onset. Rivas-Gotz et al.⁶⁹⁾ demonstrated that the pulmonary capillary wedge pressure was closely related to $IVRT/T_{E-E'}$, and an $IVRT/T_{E-Ea} < 2$ was found to have a sensitivity of 91% and a

specificity of 89% for detecting a PCWP >15 mm Hg. However, Sohn and associates could not find a delay in the onset of mitral annulus velocity compared with the onset of the mitral inflow over a wide range of τ (31 to 70 ms); therefore, they found no correlation between $T_{E-E'}$ and τ .⁷⁰ They also pointed out that the equation $IVRT/T_{E-E'}$ could not be applied with a zero denominator when the onset of E and E' was simultaneous. A potential limitation of clinically applying this ratio is the necessity for measuring the cardiac time intervals at different locations and different cardiac cycles.⁷¹ An approach to simultaneously record the onset of E and E' may allow this approach to be more attractive for clinical use. Nevertheless, this new parameter, $T_{E-E'}$ or $IVRT/T_{E-E'}$, can be useful to assess the LV filling pressure, and especially when E/E' is indeterminate. Further clinical investigations and experience will be needed to determine the reliability and the role of $IVRT/T_{E-E'}$ for assessing the filling pressure.

Assessment of left ventricular torsion

During systole, the left ventricular apex rotates counterclockwise (as viewed from the apex), whereas the base rotates clockwise, and this creates a torsional deformation originating in the dynamic interaction of the oppositely-wound epicardial and endocardial myocardial fiber helices.⁷² Left ventricular torsion is an important aspect of such cardiac biomechanics as ejection and suction. However, this has been difficult to measure. It has been recently shown that speckle tracking imaging can assess left ventricular torsional deformation.⁷³ Assessment of left ventricular torsion may help understand the relationship between molecular changes and the left ventricular performance, and it may provide new concepts for the superior management of patients suffering with heart failure.

Evaluation of left atrium

The left atrial size and function is frequently altered by various cardiac disorders; however, this has not received as much attention as it should have. This is now receiving its proper attention as it is now commonly realized that the left atrium is invariably dilated in the patients with left ventricular diastolic dysfunction. The left atrium is commonly enlarged in the patients suffering with mitral stenosis due to flow obstruction at the mitral valve level during diastole. During diastolic dysfunction, flow resistance occurs at the level of the left ventricle, and this results in left atrial enlargement. Therefore, the left atrial size is a faithful mirror of the elevated left ventricular and left atrial filling pressures in the absence of any mitral valve disease. The left atrial volume has been shown to provide a more accurate assessment of the left atrial size than does the M-mode left atrial dimension. The left atrial volume usually gives indirect evidence for the increased left atrial pressure

that's observed over an extended period of time rather than tracking acute changes in the left atrial pressure that are akin to the glycosylated hemoglobin level in the patients suffering with diabetes mellitus. Diastolic dysfunction is associated decreased passive left atrial emptying; this results in a larger left atrial volume at the onset of atrial systole, which helps to maintain left atrial ejection. With the increase in the left atrial pressures, atrial stretch and enlargement of the chamber occur, and this leads to remodeling of the left atrial structure along with changes of the physiologic properties and electrical milieu of the left atrium; all this finally culminates in the development of atrial fibrillation. Tsang et al. have shown that the left atrial volume appears to be a strong predictor of incident atrial fibrillation, and this is incremental to the clinical risk factors.⁷⁴

Future Directions in the Assessment of Diastolic Function

Patients with significant heart disease may have entirely normal diastolic hemodynamics, as assessed in the resting state. Because most cardiac symptoms are precipitated by exertion, it may also be quite important to assess hemodynamic performance during some form of stress. The lack of a relation between the left ventricular filling pressure and peak oxygen consumption has been reported and in a similar fashion, there appears to be almost no relation between the left ventricular function, as measured by the rest ejection fraction, and the resting cardiac output with the exercise capacity. Thus, an evaluation both at rest and during exercise should enable physicians to assess the cardiovascular reserve and the relationship between specific symptoms and any hemodynamic impairment. Furthermore, the physiologic information so obtained is often valuable for differentiating patients with cardiac causes of exercise intolerance from the patients with non-cardiac causes of exercise intolerance, and this may also be helpful in prescribing specific medical therapy and estimating the

During exercise		
	Control	Diastolic dysfunction
Mitral E	↑	↑↑
Annulus E'	↑	—, ↑
E/E'	—	↑
Mitral DT	↓	↓↓

Fig. 8. Changes of the mitral inflow E and mitral annular E' velocities for diastolic dysfunction during exercise. DT: deceleration time.

prognosis. It is also conceivable that those patients with exertional dyspnea that can not be explained by the resting parameters of the left ventricular systolic and diastolic functions would have steep left ventricular pressure-volume relations during exercise as compared to those patients who have no symptoms of exertional dyspnea despite their similar degrees of left ventricular systolic and diastolic functions at rest.

A standard method for assessing the diastolic functional reserve, which can be defined as the capacity of the ventricle to accommodate the diastolic filling that's necessary for increased demand as imposed by exercise without resulting in any marked increase in filling pressures. Therefore, for those patients suspected of having diastolic dysfunction with exertional dyspnea and they also have normal ventricular systolic and diastolic functions, exercise could unmask the diastolic abnormalities that were not evident under rest conditions.⁷⁵⁾ Patients with severe exercise limitation may be found to have a relatively preserved diastolic function even during exercise; this points to other etiologies such as pulmonary disease or deconditioning as the cause of the patient's symptom. Alternatively, there may be patients who have a relatively normal or mildly impaired diastolic function at rest, but they have the development of significant deterioration of the diastolic function during exercise. In this setting, it is important to assess the diastolic function during stress or exercise with the provocation of symptoms. The development of a "diastolic stress test" would be helpful for achieving better assessment and management of the patients with dyspnea (Fig. 8).⁷⁶⁾⁷⁷⁾

Diastolic dysfunction represents a growing clinical challenge to develop novel therapeutic approaches. Improvements in our understanding of the molecular pathogenesis of diastolic dysfunction and its incorporation into the diagnostic and therapeutic approaches will enhance patient management in this disease population. Novel approaches that will evolve in the future will undoubtedly improve our evaluation and treatment of this entity. This makes it even more important to assess the diastolic function and its functional reserve. Despite the high prevalence, substantial morbidity and significant mortality of diastolic heart failure, there has been no prospective, randomized, blinded pharmacologic trial data for guiding clinical decisions. Fortunately, large outcome studies are now ongoing to investigate the role of angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers for patients suffering with diastolic heart failure or heart failure with preserved left ventricular systolic function. With the results of these trials, as well as the better diagnostic testing that will be available in the future, physicians should be in a better position to not only to diagnose diastolic dysfunction or heart failure, but also to manage it more effectively.

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