

Echocardiographic assessment of diastolic function

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Abnormal diastolic function is increasingly appreciated as a major contributor to cardiac morbidity and mortality. Accurate noninvasive assessment of the presence and severity of diastolic impairment is crucial to the broad application and understanding of this common condition. Echocardiographic parameters have become the backbone of this noninvasive assessment. Active investigation into both old and new Doppler variables will provide the framework that can lead to a more uniform assessment and reporting that will be essential as we prepare to confront clinically the next frontier in cardiac pathophysiology. This review discusses the clinical impact of recent echocardiographic contributions to the field of diastology. *Curr Opin Cardiol* 2001, 16:240–245 © 2001 Lippincott Williams & Wilkins, Inc.

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Abbreviations

MVI mitral valve inflow
Vp propagation velocity
PV pulmonary veins

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The impact of diastolic dysfunction on cardiac morbidity and mortality is becoming increasingly understood [1–9]. Although the prevalence of diastolic dysfunction among patients with common comorbidities (*eg*, hypertension, diabetes) has been under-appreciated, it has become apparent that significant proportions of patients presenting with signs and symptoms of congestive heart failure have primary diastolic dysfunction. Interestingly, those patients with isolated abnormalities of diastole are equally impaired as those patients with CHF due to systolic dysfunction, and have a poor prognosis [3,4,10].

Although there have been recent gains in treating systolic heart failure, the treatment of diastolic dysfunction is lagging. Large-scale treatment trials have not occurred in this patient group and there is no precise definition of diastolic heart failure [11,12•]. This is in part because of the complex physiology of diastole with complex interactions between cellular derangements, mechanical myocardial stiffness/compliance, filling pressure, pericardial constraint, etc. Although “diastolic heart failure” will need to be a clinical diagnosis, a better understanding and application of noninvasive testing should provide an important component in the diagnosis and treatment of diastolic dysfunction.

Historically, invasive hemodynamics have provided useful information with respect to diastolic filling pressures (*eg*, left atrial pressure, left ventricular end-diastolic pressure), left ventricular relaxation (time constant of relaxation, $-dP/dt$), and operant chamber stiffness (pressure-volume loops, diastolic pressure contour). However, advances in echocardiographic assessment of left ventricular diastolic function can lead to the replacement of invasive hemodynamics in the vast majority of patients.

Assessment of transmitral blood flow velocities has served as the backbone of diastology from an echocardiographic standpoint. The velocity profile is directly related to the pressure gradient between the left atrium and left ventricle. Well-characterized patterns of mitral valve inflow (MVI) have been related to invasive measures of diastole as well as to prognosis [13,14]. There are, however, significant limitations to the use of MVI in clinical practice. The most recognized problem is a parabolic, or J-shaped, progression of MVI patterns with advancing diastolic dysfunction such that the pattern seen in healthy individuals is quite similar to those patients

with moderately impaired diastolic function and elevated filling pressures (Fig. 1). This led to important advancement of other complementary variables, particularly the pattern of flow from the pulmonary veins (PV) into the left atrium. Newer techniques such as assessment of flow propagation in the left ventricle, Doppler assessment of myocardial velocities, and simple bedside manipulation of loading conditions have provided further insights. The second major problem, one that is not as recognized, is that most of the characterization of the mitral inflow pattern and its significance has occurred in the context of coexistent systolic and diastolic dysfunction.

This review focuses on recent investigation into the echocardiographic assessment of diastolic function and attempts to provide a framework for its application in clinical practice. To this end, it can be useful to examine specific echocardiographic parameters in terms of their association with measures of myocardial relaxation, prediction of left ventricular filling pressures, and measures of clinical outcome.

Mitral valve inflow

The pattern of MVI is well established as reflecting the pressure gradient between left atrium and left ventricle during diastolic filling. The change in the MVI pattern with advancing diastolic dysfunction has been described, particularly in those with concomitant systolic dysfunction [13,14]. Worsening diastolic dysfunction has been correlated with worsening prognosis in several sets of patients [15–18]. Recently, the pattern of MVI was once again confirmed to be a very significant predictor of subsequent mortality after myocardial infarction [19•]. This study examined 110 consecutive patients and reported that mitral deceleration time was an independent predictor of in-hospital heart failure and was the strongest predictor of 35-day mortality.

However, there are important limitations that must be recognized. In addition to the J-shaped, or parabolic, pro-

gression of MVI patterns, there are difficulties in its use in relative tachycardia and atrial fibrillation. The bulk of data supporting correlation between MVI pattern and left ventricular filling pressures (and outcome as well), has been collected from patients with impaired systolic function. The relationships between deceleration time or E/A ratio (ratio of early to late transmitral flow velocity) and filling pressures are not as strong in those patients with normal systolic function [20,21•]. Additionally, there are data that clearly demonstrate, contrary to general perceptions, that patients with E/A ratio less than 1 can have elevated left ventricular filling pressures [22,23]. These facts make it imperative to utilize other Doppler parameters in assessing diastolic function.

Pulmonary vein flow

Pulmonary vein flow patterns have been used to complement the MVI. Like the MVI, there is a well-characterized progression of the PV pattern with worsening disease [14]. Unlike the MVI, the progression is not J-shaped. Specifically, the reversal of flow into the PV with atrial contraction tends to increase in velocity and the duration of flow with atrial contraction tends to lengthen (relative to mitral A wave flow duration) with worsening diastolic properties. This is the result of a worsening relative compliance of the left ventricle compared with the pulmonary venous circuit. At atrial contraction, a poorly compliant ventricle will have a steep pressure rise for a small volume of transmitral flow and result in equalization of pressures and cessation of flow. Meanwhile, flow can continue into the pulmonary venous circuit. The correlation between PV pattern and filling pressures is not as dependent on systolic function as is the MVI pattern [20–22].

There is important prognostic information in the PV flow pattern. Among 145 patients with depressed LV systolic function, those with restrictive MVI pattern (deceleration time < 130 ms) had only 23:1 survival at 2 years. Those patients with deceleration time greater than

Figure 1. Progression of diastolic dysfunction



Progression of diastolic dysfunction as established in patients with decreased left ventricular systolic function. a', late mitral annular velocity; A, late diastolic mitral inflow velocity; e', early mitral annular velocity; a', late mitral annular velocity; E, early diastolic mitral inflow velocity; LAP, left atrial pressure.

130 ms could be further stratified based on difference in flow duration at atrial contraction between the PV and MVI ($\Delta A\text{-dur} = \text{PV A-dur} - \text{MVI A-dur}$). Those patients with $\Delta A\text{-dur}$ greater than 30 ms had a 2-year survival of 37%, while those patients with $\Delta A\text{-dur}$ less than 30 ms had 86% survival at 2 years. This was the strongest predictor among the variables considered, including level of systolic function [24•].

Despite these important observations in the PV, some limitations must be realized. The most problematic limitation is the overall feasibility of obtaining interpretable PV signals. Several studies have documented that complete PV analysis, including systolic and diastolic forward flow as well as atrial reversal flow, is possible in only 64% to 73% of patients [21,22,24,25]. Even among patients with adequate PV signals, the ability of PV parameters to detect elevated left ventricular filling pressures is somewhat limited. Two recent studies compared PV signals and invasively measured LV filling pressures and found diagnostic accuracy ranging from 56 to 82% for various variables [21,22]. Thus, even under the best circumstances, up to 20% of patients would be misclassified and another 25% could not be assessed at all by PV analysis. This does not mean that the PV should be ignored. Recent work confirms that, when the PV signal is available, elevated LVEDP can be detected with very high specificity (100%) if $\Delta A\text{-dur}$ greater than 30 ms [21].

Preload manipulation

Simple bedside maneuvers that alter preload can also be used to complement the MVI pattern [26,27]. Patients with “pseudonormal” MVI have a primary abnormality of LV relaxation in combination with elevated mean LV filling pressure. The Valsalva maneuver, which decreases preload, can unmask the diastolic dysfunction by converting the “pseudonormal” pattern to that of abnormal relaxation. Several studies have recently examined the utility of obtaining MVI during the Valsalva maneuver [21–23]. One study examined 20 consecutive patients and found that the change in the A-wave velocity correlated with LVEDP [23]. The hypothesis is similar to that of the A-wave duration difference: Valsalva will decrease preload and LV filling in early and mid-diastole. This means that LV pressure and operating compliance at atrial systole are improved and flow velocity will increase. Another study examined 80 patients for the relative utility of MVI during Valsalva compared with resting PV analysis [22]. A decrease in E/A ratio from rest to Valsalva of greater than 40% or an increase in the duration of mitral A-wave duration both had reasonable diagnostic accuracy (85 and 86%, respectively) for the detection of increased LVEDP. These two studies also emphasized those patients with E/A less than 1 can have elevated filling pressure and that this can be detected

using the Valsalva response. The diagnostic accuracy for the detection of increased LVEDP was 88% using a decrease in E/A greater than 40%, and 90% using increase in A-duration for patients with resting E/A less than 1 [22]. A third study examined 100 consecutive patients and found that the response to Valsalva maneuver could be used to predict (specificity = 100%) elevated filling pressure if E/A decreased by an absolute 0.5 (*ie*, from 1.2 at rest to 0.7 during Valsalva)[21]. This finding was not altered by degree of systolic function. The overall accuracy of response to Valsalva was marginally better than PV analysis in the two studies that reported the relative accuracy [21,22].

Like the PV, the ability to assess response to Valsalva is limited by technical feasibility. The ability to accurately measure A-wave duration and true A-wave velocity can be hindered by the fusion of the E and A-wave during the relative tachycardia of the Valsalva maneuver.

Color flow propagation

The MVI and PV flow patterns reflect a composite of inter-related physical properties including (but not limited to) pressure gradients, differential compliance, and myocardial relaxation. The noninvasive assessment of myocardial relaxation, independent of loading conditions is an important goal that would facilitate accurate diastolic assessment. The propagation of flow into the LV cavity in early diastole, as assessed using color M-mode echocardiography, has been shown to correlate with the invasively measured time constant of relaxation (τ) [28]. A chamber with normal relaxation (small τ) demonstrates quick flow propagation into the cavity; a slowly relaxing ventricle (large τ) demonstrates blunted flow propagation.

Based on several recent publications, it would appear that the propagation velocity (V_p) is relatively load independent. One paper examined 30 “normals” and 30 patients with LV systolic dysfunction after myocardial infarction [29]. Although this study did not measure directly the LV filling pressures, a series of maneuvers, known to produce changes in filling pressure (*eg*, Valsalva, passive leg lift, nitroglycerine), were used. The transmitral parameters all varied significantly during the various manipulations, while the V_p was statistically unchanged. The level of systolic performance did not alter this relation.

A second report looked at effects of manipulation of lusitropy and preload in animals and humans [28]. A multivariate analysis of the hemodynamic changes in animals revealed that V_p is determined by τ , heart rate, and ejection fraction. Likewise, in humans undergoing preload manipulation (partial cardiopulmonary bypass),

multivariate analysis suggested that tau was the only independent determinant of V_p .

The impact of altered flow propagation was examined in 125 consecutive myocardial infarction patients [30]. Using a combination of the mitral deceleration and V_p patients were characterized as normal (DT (mitral deceleration time) 140-240 ms and $V_p > 45$ cm/s), impaired relaxation (DT > 240 ms), pseudonormal (DT 140-240 ms and $V_p < 45$ cm/s), or restrictive (DT < 140 ms). The 1-year mortality was best in normals (0%), worsening with each successive diastolic grade: impaired relaxation (13%), pseudonormal (48%), and restrictive (65%). On multivariate analysis, pseudonormal (relative risk = 4) and restrictive (relative risk = 5.5) filling patterns were the only independent predictors of death.

A ratio of mitral E velocity to V_p (E/V_p) has been studied in its relationship to survival as well. Again, the E velocity is dependent on both filling pressure and myocardial relaxation. The use of the E/V_p ratio is one method of "adjusting" the E velocity for the effects of relaxation and in essence yields an estimate of filling pressure. (The E/e' ratio using tissue Doppler is another method, discussed later.) When examined in the context of 110 patients presenting with myocardial infarction, E/V_p greater than 1.5 was the single best predictor of in-hospital heart failure (Killip Class II or greater) [19]. Additionally, mitral deceleration time and E/V_p were the strongest predictors of subsequent mortality even when considering systolic function.

There is a technical learning curve to its incorporation in clinical practice. There is not yet a consistent method of measuring V_p and the various techniques reported are not interchangeable. Additionally, the influence of rapid hearts with fusion of early and late diastolic flow is not yet understood. However, accurate determination of V_p is a promising variable for the comprehensive assessment of diastolic function.

Tissue Doppler imaging of the mitral annulus

Assessment of mitral annular velocities in diastole has also been studied recently as a relatively load-insensitive estimator of myocardial relaxation [31–33]. Although the speed of ascent of the mitral annulus in early diastole (e') correlates with tau, the most significant impact appears to be in its combination with the transmitral blood flow E velocity. The E/e' ratio is another method of adjusting the E velocity for the effects of speed of myocardial relaxation (or recoil). Basic hemodynamic principles govern that the mitral annulus must move in the opposite direction of myocardial blood flow with a speed that is proportional to the speed of blood flow [34]. This rela-

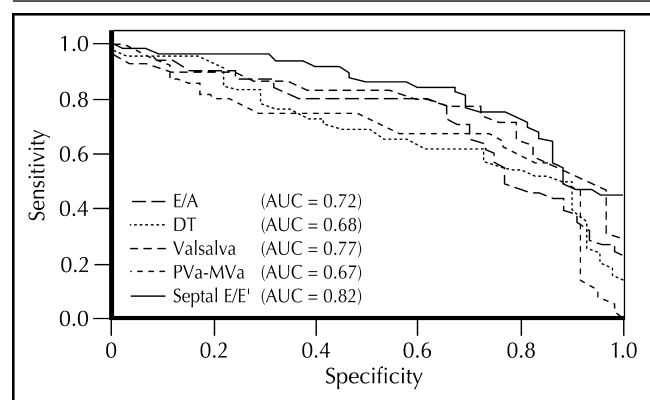
tionship is altered by changes in distending or filling pressure.

In clinical terms, among 100 consecutive patients, E/e' was the single best predictor of LV filling pressure [21]. The E/e' ratio was independent of systolic function and was the most easily obtained parameter. Groups of patients with high and low pressures were easily identified using cut-off values (for high sensitivity or specificity) that have been observed in other studies [32,35,36]. Patients with E/e' greater than 15 have elevated LV filling pressure; patients those with E/e' less than 8 tend to have low or normal filling pressure (85%)[21]. This study also highlights that no single Doppler parameter is sufficient to completely assess diastolic function (Fig. 2).

Of particular importance, the E/e' ratio and its relationship to LV filling pressures has been shown to remain valid in patients with preserved systolic function, fused MVI signals due to tachycardia [33,36], and in patients with atrial fibrillation [35]. The cut-off values are similar to that observed in normal sinus rhythm.

The tissue Doppler signal is an easily obtained high-amplitude, low velocity signal that is available in almost all patients ($> 95\%$)[21]. Various reports have sampled different portions of the annulus (septal [21,31], lateral [21,32], average of several [21], etc.) but the basic relation to filling pressures does not appear to be significantly altered by sample site [21]. For patients with significant regional wall motion abnormalities it is reasonable to sample several sites. At present, because of its ease of use and impact in difficult patient groups (*eg*, preserved ejection fraction, atrial fibrillation, and hy-

Figure 2. Prediction of elevated filling pressure



Receiver operator characteristics of common Doppler variables for the prediction of elevated left atrial pressure. DT, mitral deceleration time; E/A, ratio of early to late peak diastolic transmitral velocities; E/E' , ratio of early diastolic transmitral velocity to early diastolic mitral annular velocity; Pva-Mva, difference in duration of flow at atrial contraction. Modified from [21].

peritrophic cardiomyopathy), the E/e' ratio may offer the best general applicability to clinical echocardiography.

Application to clinical practice

Because of the tremendous impact of diastolic dysfunction on clinical morbidity and mortality, diastolic function screening should be a part of nearly every echocardiogram. No single parameter or Doppler pattern can be used in isolation to accurately assess diastolic function. Comprehensive Doppler and two-dimensional features all must be considered. The degree of systolic function is a key component of assessment of diastole. Those patients with depressed systolic function are generally accepted to also have diastolic dysfunction. Thus, if the ejection fraction is low, there will not be the difficulty in discerning normal from pseudonormal. Filling pressures can be reasonably estimated from the MVI in this group with supporting evidence from E/e' , E/Vp , ΔA -dur, and/or elevated tricuspid regurgitant velocity.

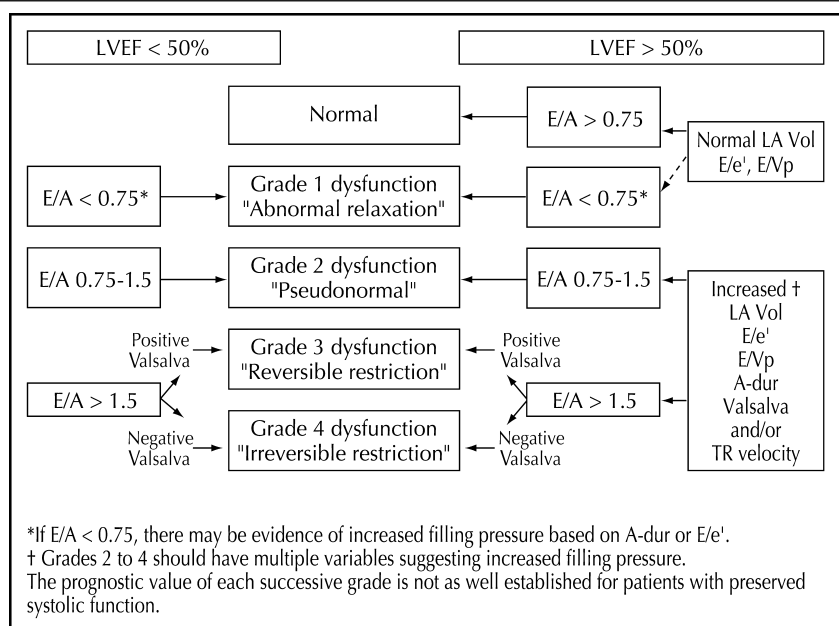
The patients with preserved systolic function will be more problematic because any degree of diastolic dysfunction is possible. Another complementary two-dimensional feature, the left atrial size, can be useful [37]. The left atrial size can serve as a barometer of chronic loading conditions such that patients with normal left atrial size are unlikely to have had significant, lasting elevations of filling pressures. Conversely, those patients with enlarged atria have likely had, at some point, increased left atrial pressure. The Doppler data can provide insight to the present loading conditions. When systolic function is preserved it will be best to have multiple parameters to support any diagnosis of elevated filling pressure. Although diastolic abnormalities represent a continuum

and no diagnostic algorithm can account for every contingency, Figure 3 represents one possible guide based on the available data. This is based on the initial application of those parameters that are easiest to obtain and have proven discriminatory value: LV systolic function, MVI, tissue Doppler E/e' , and left atrial volume. Confirmatory evidence can be obtained from the other variables. To avoid confusion of descriptive language, a numerical grading system may provide more insight into the severity of the diastolic abnormality. Although the grades of diastolic dysfunction have not been as rigorously associated with outcome in those patients with preserved systolic function, a consistent reporting system will facilitate general understanding of the hemodynamic derangements. The assessment of diastolic dysfunction is more difficult in the presence of native valvular heart disease, valvular prostheses, and high-output states that will alter the blood flow velocities even in the absence of myocardial relaxation and compliance abnormalities.

The increase in the understanding of the impact of diastolic dysfunction is an important advance. The progress and investigations into newer, easily applied, reproducible Doppler variables will set the stage for a more uniform diastolic assessment and report. This will enhance the understanding of diastolic abnormalities and its relation to other prominent disease states allowing preclinical detection. Future trials and therapies aimed at diastole are the next step, not only in improving outcomes in heart failure, but also in potentially preventing the development of heart failure. Doppler echocardiography will continue to provide the backbone for the attack on the next great challenge in cardiology.

Figure 3. Assessment of diastolic function

Potential diagnostic guidelines for assessment of diastolic function for patients with normal sinus rhythm and no significant valvular heart disease. A-dur, difference of pulmonary venous flow duration and transmitral flow duration at atrial contraction; E/A, ratio of early to late diastolic transmitral blood flow velocity; E/e' , ratio of early transmitral blood flow velocity to early mitral annular velocity; E/Vp , ratio of early transmitral blood flow velocity to color Doppler m-mode flow propagation velocity; LA Vol, left atrial volume; LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.



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