A clinical approach to the assessment of left ventricular diastolic function by Doppler echocardiography: update 2003

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Patients with heart disease frequently have abnormalities of systolic function. However, it is now well recognised that abnormalities of diastolic function play a major role in producing the signs and symptoms of heart failure. Thirty to fifty per cent of patients with heart failure have normal systolic function, implicating diastolic dysfunction as a major pathophysiologic abnormality. It is important to understand and recognise abnormalities of diastolic filling of the heart for proper diagnosis, prognosis, and institution of treatment. Doppler echocardiography has become the primary tool for the assessment of diastolic function and left ventricular filling pressures. The purpose of this review is to summarise the physiology of diastole and develop a practical clinical approach for the non-invasive assessment of diastolic filling of the heart.

DEFINITION OF DIASTOLE AND DIASTOLIC DYSFUNCTION

Cellular definition

At the cellular level diastole can be considered as beginning when ATP hydrolyses and actin–myosin crossbridges become unlinked allowing for sarcomeric relaxation. This is integrally related to decreasing intracellular concentrations of calcium owing to enhanced sarcoplasmic reuptake of calcium. These cellular processes actually occur in some cells while other cells are still demonstrating active contraction. Thus cellular diastole may actually begin while left ventricular pressure is still rising.

Dysfunction at the cellular level is mediated principally via decreased ATP hydrolysis and/or impaired uptake of the intracellular calcium. When the actin–myosin interaction is prolonged, there is a delay and prolongation of sarcomeric expansion. Additionally, in the case of regional ischaemia, there may be regional cellular impairment such that the heart ceases to function as a syncytium.

Mechanical definition

Mechanically, diastole is considered to begin when the pressure within the left ventricle begins to fall—that is, during the isovolumic relaxation phase. This would occur after a significant number of myocardial cells had entered cellular diastole and is a metabolically active phase. The left ventricular pressure will continue to fall rapidly, with continued relaxation involving the ATP dependent uptake of intracellular calcium into the sarcoplasmic reticulum. Elastic recoil and suction then occur after mitral valve opening and result in rapid flow across the mitral valve. Left ventricular compliance (distensibility) is higher than atrial compliance during diastole and further favours filling of the ventricle (that is, the atrium acts as a conduit). This results in rapid myocardial relaxation velocity and rapid, unimpeded flow across the valve. These changes in the relation of left ventricular and left atrial pressures are reflected in the mitral valve inflow velocities, derived from Doppler echocardiography. There is a rapid velocity early inflow that occurs with mitral valve opening (E wave) followed by deceleration of...
flow as left ventricular pressure rises to meet left atrial pressure. This may be followed by a brief period where there is no pressure gradient across the valve (diastasis). At end diastole, with the contraction of the atrium there is a second wave (A wave) of blood flow into the ventricle.

The initial abnormality of diastolic function is loss of the elastic recoil/suction forces in early diastole. This and subsequent slowing of the energy requiring myocardial relaxation can be identified by a decreased left atrial—left ventricular (LA-LV) pressure gradient and increased reliance on atrial contribution to left ventricular filling. In this state, the mitral E velocity is decreased and flow into the ventricle continues throughout diastole. Because of incomplete atrial emptying (and therefore increased atrial preload), there is an increase in the velocity and importance of the A wave. The Doppler velocity curve of a low E/A ratio and prolongation of deceleration time represents grade I diastolic dysfunction (abnormal relaxation pattern). These patients may have normal or only mildly increased filling pressures at rest but may develop symptomatic increases in filling pressures with exercise as the diastolic filling time shortens.

As disease progresses, there is further decline of active myocardial relaxation and the onset of operative compliance abnormalities. Filling of the left ventricle becomes increasingly dependent on the LA-LV pressure gradient (driving force) which can be maintained only by increasing left atrial pressure. In this state, left atrial pressure is raised throughout the cardiac cycle with a transient decrease as the atrium empties in ventricular diastole. Increased mean left atrial pressure “pseudonormalises” the flow from the left atrium to left ventricle with an increase in the early inflow velocity and shortening of the deceleration time. This state of diastole is characterised by mitral inflow signals that are similar to that of the normal state: rapid early inflow (increased E wave) and less prominent flow at atrial contraction (A wave). This is grade II diastolic dysfunction (pseudonormal pattern).

In the latter stages of diastolic deterioration, left ventricular chamber compliance is severely impaired such that there is a larger increase in pressure for small increases in ventricular volume. Here the early mitral inflow is very rapid (high E wave) with rapid equilibration of left atrial and left ventricular pressure that truncates the E wave (very short deceleration time). The pressures and operating compliance are such that there is very little contribution to filling the ventricle from atrial contraction (small A wave). This is the restrictive pattern, representing grade III—IV of diastolic dysfunction. An individual patient may progress or regress between grades I, II, and III diastolic dysfunction depending upon the state of compensation in filling pressures at the time of the echocardiographic examination. However, in
severe end stage disease, the restrictive pattern persists despite manipulation of filling pressures and may be irreversible (grade IV).

The change in the mitral flow velocity patterns with advancing diastolic dysfunction has been described particularly in those with concomitant systolic dysfunction.\(^4\)\(^5\) In this group of patients there is a strong correlation between mitral inflow parameters and filling pressures allowing prediction of elevated filling pressures with high specificity (fig 3).\(^6\)\(^7\) Furthermore, worsening mitral inflow patterns have been correlated with worsening prognosis in several sets of patients (fig 4).\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)

**COMPREHENSIVE DOPPLER EXAMINATION**

Although the mitral inflow velocity curves are predictive of filling pressures and can determine prognosis in subgroups of patients, there are major pitfalls that can limit the utility of mitral inflow in the general assessment of diastolic function. First, prediction of left ventricular filling pressures by mitral valve inflow velocities appears to be accurate only in those patients with systolic dysfunction, as patients with normal systolic function show wide scatter of filling pressures.\(^4\)\(^11\) This is related to the progression of disease that occurs, so that in an advanced state of diastolic dysfunction the mitral inflow pattern looks identical to the normal state. The reason for the confusing similarity is that normal hearts have rapid relaxation and fall in left ventricular pressure such that blood is “sucked” across the mitral valve. Those with grade II diastolic dysfunction display a “pseudonormal” mitral inflow from the raised left atrial pressure where blood is “pushed” across the valve. There also are data that demonstrate that patients with an E/A ratio < 1 can have raised left ventricular filling pressures as they transition to higher degrees of diastolic abnormality.\(^14\)\(^15\) The distinction of normal versus pseudonormal filling is difficult using the mitral inflow alone and in most patients other parameters will be necessary to complete the assessment.

**Preload alteration**

Reducing left ventricular preload, using glyceryl trinitrate or the Valsalva manoeuvre, has been used as a means of unmasking patients with elevated filling pressures. Those patients with a normal pattern and filling pressure will simply show a hypovolaemic response (reduction in all
velocities) (fig 5). The reduction of preload (left atrial pressure) in patients with “pseudonormal” flow (raised filling pressures coupled with abnormal relaxation) should reveal the underlying abnormal relaxation pattern.7 14–17 Reported data suggest that patients who can reduce the E/A ratio by an absolute value of 0.5 (that is, from 1.3 to 0.8) or more have raised filling pressures, independent of systolic function. Unfortunately, preload alteration is not universally practical in clinical practice. Some patients are not able to perform an adequate Valsalva manoeuvre and careful attention to signal acquisition and measurement is crucial. In a recent series adequate signals were obtained in only 61% of patients.7 The administration of nitrates to alter preload, while more predictable, is not feasible in many practice settings.

Pulmonary venous Doppler velocities

Pulmonary venous flow is used as an adjunct to mitral inflow. Pulmonary venous flow pattern has also been well characterised and provides additive insight to diastolic filling of the left ventricle.18–24 The pattern of flow (systolic versus diastolic predominance) has been proposed as a predictor of left atrial pressure but is not applicable in unselected patients because of the multiple contributions to these velocities.7 Comparison of the duration of flow at atrial contraction across the mitral valve (on the mitral inflow velocity curve) and the duration of reversal flow back into the pulmonary veins (on the pulmonary venous velocity curves) has been repeatedly demonstrated to reflect the left ventricular end diastolic pressure.7 As filling pressures and therefore operating chamber characteristics worsen, a worsening relative compliance of the left ventricle compared with the pulmonary venous circuit is observed. Transmitral flow at atrial contraction is shortened while retrograde flow at atrial contraction into the low resistance pulmonary venous circuit continues for a longer duration. If the duration of atrial reversal flow in the pulmonary vein exceeds by more than 30 ms the duration of flow across the mitral valve, raised left ventricular end diastolic pressure can be diagnosed with high specificity (fig 6).7 13 14 The major limitations to the use of the pulmonary venous signals are that these signals are difficult to obtain and interpret. The technical feasibility of obtaining adequate signals has been reported at less than 80% of unselected patients.7

Tissue Doppler velocities

The velocity of the mitral annulus, representing velocity of changes in left ventricular long axis dimensions, has been related to measures of systolic and diastolic left ventricular performance.25–28 The diastolic velocity has been proposed as representing the intrinsic speed of myocardial relaxation.

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**Figure 7** The tissue Doppler velocity of the mitral annulus can help distinguish between normal and abnormal filling. These examples are from two patients with normal systolic function and similar mitral inflow signals. On the left, a normal mitral annular velocity and E/e′ ratio indicate normal filling pressures. On the right, the mitral annular e′ velocity is reduced and the E/e′ ratio elevated in a patient with high left atrial pressure. A, mitral filling at atrial contraction; a′, late mitral annulus diastolic velocity; E, mitral early filling wave; e′, early mitral annulus diastolic velocity; E/e′, ratio of mitral early filling wave to early mitral annulus velocity; LA p, left atrial pressure.

**Figure 8** Cut-off values using the ratio of mitral early filling wave to early mitral annulus velocity (E/e′) can be used to group patients according to filling pressures. Those with high ratios (> 15) have high filling pressures, while those with very low ratios tend to have normal filling pressures. The intermediate group requires additional information to correctly classify diastolic function. The closed circles represent those patients with other Doppler parameters suggesting high filling pressures. Reproduced from Ommen et al,7 with permission.
Figure 9  Screening assessment for diastolic function and filling pressures. Two dimensional and Doppler echocardiographic variables can be used to readily classify diastolic function. In general, high filling pressures should be confirmed with multiple parameters (that is, E/e', E/Vp, A-dur difference, response to Valsalva manoeuvre, TR velocity, etc).

This may then be used to determine the difference between the effect of “suction” (normal E wave and rapid early mitral annular velocity) versus “pushing” with high left atrial pressure causing an increase in transmitral flow (normal E wave with reduced early mitral annular velocity).

The ventricle elongates in two distinct phases. The annular velocities recorded during these two phases are called e' and a', which correspond temporally with the mitral E and A waves. The velocity of e' has been modestly correlated to the time constant of relaxation. A pattern of progression of diastolic dysfunction of the Doppler tissue velocities can be seen (fig 2). In the initial stages of diastolic dysfunction, the relaxation velocity (e') decreases and remains reduced throughout the remaining stages of impaired diastole.24

Subsequent investigations have shown that combining the mitral inflow with the mitral annular velocity into a ratio (E/e') can predict left ventricular filling pressure (fig 7).21–32 The ability of this ratio to predict filling pressure has been demonstrated in patients with normal sinus rhythm, sinus tachycardia, preserved systolic function, atrial fibrillation, and in patients with hypertrophic cardiomyopathy. This combination may resolve the issue of discriminating normal from pseudonormal filling. Patients with diastolic dysfunction and a normal appearing mitral inflow pattern will also have a reduced mitral annular velocity (e') and an elevated E/e' ratio. Again, cut off values can easily be selected from published data. If E/e' is > 15, left ventricular filling pressure is raised, and when E/e' is < 8 filling pressure is low (fig 8). However, between 8–15 there is considerable variability in filling pressure.7

Flow propagation
Assessment of flow propagation into the left ventricle is another technique that provides better ability to predict filling pressures.13–16 In the normal state, flow rapidly propagates into the left ventricular (fig 2). Early stage relaxation abnormalities show a blunting of flow propagation. The propagation velocity does not show a pseudonormalisation and therefore can be used in all levels of systolic function.

Similar to the tissue Doppler velocities, colour M mode flow propagation has been combined in a ratio with the mitral E velocity to provide an “adjusted” parameter (E/Vp) with strong correlation to filling pressures and prognosis.12 14–17 The chief limitations of this tool are lack of consensus on technique and theoretical concerns that this will be invalid in small left ventricular cavities.

APPLICATION TO CLINICAL PRACTICE
These findings described herein can be incorporated into clinical practice to provide a non-invasive assessment of diastolic filling of the heart (fig 9). Diastolic function should always be viewed in context of ventricular size and function, as well as left atrial size.24 For example, patients with preserved systolic function and normal left atrial size will almost always have normal diastolic filling pressures and normal diastolic function. The mitral inflow and mitral annulus velocity signals can be obtained in over 90% of patients. Thus these two Doppler parameters, in conjunction with the two dimensional echocardiographic findings, represent the most efficient means of initial diastolic assessment. The diagnosis of diastolic dysfunction and raised filling pressures should always be considered in the context of the clinical presentation and other features (estimated pulmonary artery pressures, for example).

Impaired systolic function
For patients with reduced systolic function, diastolic function is abnormal and the mitral inflow parameters are predictive of filling pressure. If the mitral deceleration time is less than 150 ms and E/A > 1.5 the filling pressures are raised. Among these patients, those who can reduce their E/A ratio by at least 0.5 can be called grade III diastolic dysfunction while those with an unchanged E/A ratio are grade IV. Patients with a low E/A ratio (< 0.75) and prolonged DT (> 240 ms) can be said to have low to normal filling pressure and grade I diastolic dysfunction. Patients that fall in between are called grade II. The E/e' ratio can also be applied in this group as described above. Patients with grade I dysfunction should have a lower E/e' ratio, while grade II–IV will have a raised E/e' ratio. This stepwise approach facilitates classification of diastolic function and filling pressures in most patients.

Preserved systolic function
Patients with E/e' < 8 can be classified as normal filling pressure and if there is a normal left atrial size, normal diastolic function can be diagnosed. Those with E/e' > 15 have raised filling pressure. In the intermediate group (E/e' 8–15), abnormal filling pressure can be predicted only if other Doppler variables meet high specificity cut-off values.
Therefore, a patient with intermediate E/e’ can be classified as raised filling pressure if the E/A ratio decreases by more than 0.5 during the Valsalva manoeuvre, or the pulmonary venous A wave duration exceeds the mitral A wave duration by at least 30 ms. If neither of these conditions is met and the left atrial size is normal, filling pressure is likely to be normal.

**CONCLUSION**

Diastolic abnormalities of the left ventricle result in significant morbidity and adverse outcomes. Assessment of true myocardial and cellular level diastole is complex and elusive; however, clinically meaningful information regarding chamber characteristics is available. The assessment of diastolic function and left ventricular filling pressures continues to evolve. Using a stepwise, evidence based approach involving readily obtained Doppler echocardiographic variables, left ventricular filling pressures and the stage of diastolic dysfunction can be obtained in most patients.

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