Diastolic dysfunction as a cause of left heart failure and as a powerful predictor of cardiovascular events is now well established. Diastolic dysfunction is present in over 25% of adults over 40 years of age and is the primary cause of approximately 50% of heart failure cases. The potential of using Doppler techniques as a means of studying diastolic function has been recognized for over 25 years and has contributed significantly to our understanding of this condition. Among patients with symptoms, Doppler, combined with two-dimensional echocardiography, is the best method to ascertain whether or not diastolic dysfunction is present and a likely cause of those symptoms. This provides a comprehensive, noninvasive approach to evaluate diastolic dysfunction and to assess its severity and hemodynamic consequences. As such, an assessment of diastolic function should be a part of every comprehensive adult echocardiographic examination.

Normal Diastolic Function

Systole and diastole are intrinsically linked as the left ventricle alternately serves as pump and reservoir. For this reason, it is not appropriate to think of systole and diastole as separate and independent. Figure 7.1 illustrates some of the differences between systolic and diastolic heart failure using pressure-volume loops. Although isolated systolic or diastolic dysfunction can occur, in most patients, elements of both contribute to the overall clinical status and symptom complex. Furthermore, the main causes of diastolic dysfunction are the same conditions that result in systolic dysfunction. Hypertension, coronary disease, and valvular heart disease are common causes of both conditions. In an individual patient with one or more of these diseases, detectable abnormalities of both systole and diastole frequently coexist although manifestations of one of the other may predominate.

**FIGURE 7.1.** Diastolic filling and systolic ejection can be demonstrated using pressure-volume loops. By tracing a loop counterclockwise, the entire cardiac cycle depicting the interplay between pressure and volume is illustrated. In this example, the changes that occur with systolic versus diastolic heart failure are contrasted.

It is also important to recognize the contribution of both upstream and downstream factors, relative to the left ventricle, as contributors to diastolic function. Upstream, left atrial function has an important effect on left ventricular filling. Since the left atrium acts as both conduit and pump, its ability to transfer blood to the ventricle essentially defines left ventricular filling. This explains why left atrial volume is now established as a useful indicator of the presence, chronicity, and severity of left ventricular diastolic dysfunction. Downstream, effective arterial elastance is related to both systolic and diastolic function of the left ventricle. Although afterload is more directly related to systolic function, it should be recognized that chronic elevation in arterial pressure will also affect left ventricular relaxation and chamber compliance.

Left ventricular diastole begins when the aortic valve closes and includes isovolumic relaxation, rapid early ventricular filling, diastasis, and left atrial contraction (see Fig. 7.2). The...
Initial phase, prior to mitral valve opening, involves the rapid, energy-dependent relaxation of the left ventricular myocardium to its resting unstressed length. This process is associated with a brisk decline in left ventricular pressure. Once ventricular pressure falls below left atrial pressure (which is rising), the mitral valve opens. The interval between aortic valve closure and mitral opening is referred to as isovolumic relaxation. The next step involves filling the left ventricle as rapidly as possible without resulting in a significant increase in pressure. After the mitral valve opens, ventricular pressure continues to fall, creating a pressure gradient between the left atrium and the left ventricle, and blood is literally pulled through the mitral valve (Fig. 7.3). As the left ventricle begins to fill, the pressure within the chamber rises and the rate of inflow slows. Continued filling in mid-diastole occurs only if left ventricular compliance is sufficiently low, or if left atrial pressure is sufficiently high, to allow the forward flow of blood. The final phase of left ventricular filling results from atrial contraction and ends with mitral valve closure. If diastolic pressure rises too quickly, left ventricular filling will be reduced and prematurely terminated. If a compensatory increase in left atrial pressure is required to maintain left ventricular filling, pulmonary venous pressure will rise as a result, leading to symptoms.

Conceptually, it is helpful to regard diastolic filling as a process of transporting blood through the mitral valve from one reservoir (the left atrium) to another (the left ventricle). This process depends on creating and maintaining a pressure gradient between the two chambers, the magnitude of which determines the rate of flow. Blood can be either pulled through the mitral valve, by rapidly lowering left ventricular pressure below left atrial pressure (injection), or pushed through the valve by raising atrial pressure above ventricular pressure. Both occur in the normal heart. In early diastole, flow is initiated by the rapidly relaxing left ventricle resulting in a suction of blood from the left atrium, through the mitral valve. In late diastole, the continued forward flow of blood is accomplished by a pushing mechanism, the result of atrial contraction. The concept of pulling versus pushing blood through the mitral valve is fundamental to understanding some of the pathophysiologic principles of diastolic function, which are discussed below.

### Stages of Diastolic Dysfunction

It is helpful to consider diastolic dysfunction as a continuum of disease that progresses from mild to more advanced stages, eventually becoming severe and irreversible. These stages, along with the pathophysiologic changes that characterize each, are summarized in Table 7.1. Although such a “natural history” is helpful to our understanding of the pathophysiology, it is a generalization. Not all patients progress linearly along the pathway and reversal of the path is possible. For example, preload reduction or treatment of hypertension can improve diastolic function, shifting the patient from a more advanced to a less advanced stage. In addition, changes in systolic function will also affect diastole. Conceptually, it is useful to define several stages of abnormal diastolic function. Although they are described below as distinct and separate, in reality they represent a continuum. In an individual patient, therefore, it is sometimes difficult to precisely assign a label, as he or she transitions from one stage to the next.

#### Normal Diastolic Function

Diastolic function changes with age, so the Doppler criteria used to define normal and abnormal function must account for this factor. Regardless of age, however, normal diastolic function can be characterized as the complete and efficient filling of the left ventricle at physiologic pressures. This implies that an abnormally high left atrial pressure is not required and that the left ventricle can fill completely without an associated abnormal increase in pressure during filling. Following isovolumic relaxation, the mitral valve opens and most filling occurs in the first third of diastole, the result of elastic recoil and active relaxation of the chamber. This phase is referred to as the E wave (Fig. 7.4A). This rapid early filling is associated with a similar brisk motion of the mitral annulus as the chamber expands to accommodate the inflow of blood. This process can be recorded and quantified using tissue Doppler as the e’ wave (Fig. 7.4B). Little filling occurs in mid-diastole, the diastasis, the duration of which is heart rate dependent; that is, it shortens or disappears with increasing heart rate. This is followed by atrial systole (the A wave), which contributes a relatively small amount of additional inflow.

### Table 7.1: Stages of Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Grade</th>
<th>Stage</th>
<th>Dominant Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Impaired relaxation</td>
<td>Delayed LV early diastolic active relaxation, low opening LA-LV pressure gradient, elevated LA pressure</td>
</tr>
<tr>
<td>2</td>
<td>Pseudonormalization</td>
<td>Diminished LV relaxation, mildly elevated LA pressure, low opening LA-LV pressure gradient, reduced LA suction force</td>
</tr>
<tr>
<td>3</td>
<td>Restrictive filling</td>
<td>Diminished LV relaxation, elevated LA pressure, low opening LA-LV pressure gradient, elevated LA suction pressure</td>
</tr>
<tr>
<td>4</td>
<td>Restrictive filling</td>
<td>Diminished LV relaxation, elevated LA pressure, low opening LA-LV pressure gradient, elevated LA suction pressure</td>
</tr>
</tbody>
</table>

LA, left atrium; LV, left ventricle.
failing. As such, the A-wave peak velocity and area under the curve (time velocity interval) are less than the E wave. As blood enters the ventricle through the mitral valve, it propagates rapidly toward the apex, a parameter that is evaluated using color Doppler M-mode, and termed the propagation velocity or $V_p$. Consistent with left ventricular filling, left atrial filling occurs via the pulmonary veins. Normal pulmonary venous flow consists of a systolic and diastolic component followed by a brief reversal of flow during atrial systole (Fig. 7.5). Finally, normal diastolic function is associated with a normal left atrial volume.

**Impaired Relaxation, Grade I**

For most patients who have diastolic dysfunction, the initial or earliest abnormality is termed **impaired relaxation**. This results from the loss of elastic recoil of the left ventricle in early diastole leading to a reduction in the force by which blood is sucked through the mitral valve. Hemodynamically, this leads to a delay or prolongation of the left ventricular pressure curve during isovolumic relaxation. This prolongation, in turn, causes a delay in mitral valve opening and a prolongation of the isovolumic relaxation time (IVRT). With the decrease in suction during early diastole, the left atrial to left ventricular (LA-LV) pressure gradient at the time of mitral valve opening is also decreased (Fig. 7.6). The rate of deceleration of early mitral inflow diminishes (i.e., deceleration time is prolonged, unless left ventricular stiffness is significantly increased) and the slope of the early diastolic flow propagation profile is also reduced. Antegrade flow across the mitral valve continues through mid-diastole. In contrast, mitral flow velocity during atrial systole is increased. This occurs through a combination of increased atrial preload and a more forceful atrial contraction, a compensatory mechanism. The auscultatory equivalent of this is the S4 gallop. At this early
FIGURE 7.7. The effect of an increase in mean left atrial pressure on Doppler inflow velocity. On the left, in the setting of normal left atrial pressure, a typical mitral inflow velocity pattern is shown. On the right, when left atrial pressure is elevated, isovolumic relaxation time (IVRT) is reduced and an increased left atrial-left ventricular pressure gradient results in a higher E wave. See text for details.

stage, pulmonary venous flow and the E/e’ ratio usually are normal, consistent with normal filling pressures at rest.

Pseudonormalization, Grade II

With further deterioration of diastolic function, a decrease in chamber compliance (increased stiffness) adds to the continued delay in relaxation. Transmitral flow is increasingly dependent on maintaining a high left atrial pressure rather than active relaxation (i.e., pushing as opposed to pulling blood into the left ventricle). This results in an increase in mean left atrial pressure which has two subsequent effects. First, it contributes to a shortening of IVRT. The reasons for this are illustrated graphically in Figure 7.7. Second, in contrast to impaired relaxation, the early mitral inflow velocity is restored back to the normal range. This increase is because the high left atrial pressure results in a larger LA-LV pressure gradient at the time of mitral valve opening. In most patients, left atrial contractility is maintained. As a result of these factors, the mitral inflow pattern appears similar to the normal state (Fig. 7.8). Thus, this phase is often referred to as pseudonormalization. Pulmonary venous flow usually shows diastolic predominance. A very small systolic wave (less than 50% of the diastolic wave) suggests elevated filling pressures. The important concept here is that the mitral inflow velocity pattern resembles the normal state due to the combined effects of high filling pressure and impaired relaxation.

Restrictive Filling (Reversible), Grade III

With further deterioration in diastolic function, left ventricular chamber compliance becomes increasingly abnormal. To maintain forward flow, left atrial filling pressure must continue to increase. This results in a further shortening of the IVRT and a marked increase in the early diastolic mitral inflow velocity (Fig. 7.9). Although the early mitral inflow velocity is very high, the rate of deceleration of flow is marked, the result of a noncompliant left ventricular chamber loading to a rapid equilibration of the LA-LV pressure gradient early in diastole. Pressure equilibration prevents the continuation of flow during mid-diastole. Filling velocity during atrial contraction is also reduced through a combination of elevated left ventricular pressure and failing left atrial contractility. Pulmonary venous flow during systole is greatly reduced relative to diastolic flow and there is usually prominent flow reversal during atrial systole. The retrograde pulmonary venous A-wave duration (Ar) is typically longer than the mitral A-wave duration (Ar – A > 30 ms), indicating high filling pressures. This phase of diastolic dysfunction is called restrictive filling or restrictive physiology. In some patients, this stage may be reversible. That is, with diuresis (or other forms of preload reduction), the restrictive filling pattern may revert one of the earlier stages of diastolic dysfunction, usually resembling pseudonormalization. This occurs because of an intervention that lowers left atrial pressure and reduces the LA-LV pressure gradient.

FIGURE 7.8. A pseudonormal mitral inflow velocity pattern. As the name suggests, without additional information, this pattern appears normal.

FIGURE 7.9. A mitral inflow velocity pattern in the setting of a restrictive physiology. This is characterized by an increased E-wave velocity due to a high left atrial-left ventricular pressure gradient, a short deceleration time, and a low A-wave velocity. See text for details.
Restrictive Filling (Irreversible), Grade IV

In later stages of the restrictive filling stage, the pattern may become irreversible. In such cases, preload manipulation no longer leads to an improvement in the filling pattern or the clinical status. This late-stage of irreversible restrictive physiology is often associated with a marked intolerance to volume manipulation. Those patients often survive within a very narrow range of volume tolerance. In such patients, maintaining the precarious balance between volume overload and hypoperfusion can be very difficult.

Echo-Doppler Parameters of Diastolic Function

The progressive stages of diastolic dysfunction can be characterized using various Doppler parameters which are summarized in Table 7.2. Note that each parameter reflects a specific component of diastolic function, but that no marker, by itself, completely captures all the information necessary to characterize an individual patient.

Isovolumic Relaxation Time

IVRT measurement provides insight into the rate of early left ventricular relaxation. When relaxation is prolonged, mitral valve opening is delayed and IVRT is increased. Conversely, when left atrial pressure is elevated, mitral valve opening will occur earlier and IVRT will be shortened. These concepts are illustrated in Figure 7.10. Isovolumic relaxation time does not directly measure the rate of relaxation but rather the duration of relaxation prior to mitral valve opening. It is derived using pulsed Doppler from a modified apical four-chamber view. The goal is to adjust the image to allow simultaneous visualization of left ventricular inflow and outflow. Once this view is obtained, the Doppler sample volume is placed midway between the inflow and outflow areas so that mitral and aortic flows are

![Diagram](https://example.com/diagram.png)
Feigenbaum's Echocardiography

- Apical 4C
- PW or CW Doppler
- SV= 3-4 mm
- Alignment between AV & MV
- 100 sweep speed
- Normal 70-90 ms

captured simultaneously (Fig. 7.11). The sample volume size can be adjusted to permit optimal recording, and generally a relatively large sample volume is host. Isovolumic relaxation time is most easily obtained by measuring the time from middle of the aortic closure click to the onset of the E wave of mitral flow. Gain and wall filters should be adjusted to allow precise definition of aortic closure and mitral opening. Generally, a fast sweep speed is used and measurements are performed at end-expiration. At least three measurements of IVRT should be obtained and averaged.

Isovolumic relaxation time is an indicator of the rate of myocardial relaxation. A major limitation is the fact that multiple factors influence the duration of the IVRT. For example, impaired relaxation lengthens IVRT while increases in left atrial pressure shorten IVRT. Furthermore, IVRT increases with age and is sensitive to changes in both heart rate and systolic function. All of these factors contribute to the nonspecificity of IVRT, which should never be used in isolation as a predictor of diastolic function.

Mitral Inflow

An accurate recording of mitral inflow velocity is the single most important parameter for the assessment of diastolic function. The use of mitral inflow Doppler recordings to assess diastolic function is based on the premise that the velocity curve throughout the cardiac cycle reflects the instantaneous pressure gradient between the left atrium and ventricle (see Figs. 7.2 and 7.3). The greater the pressure difference, the higher the velocity at that point in time. If no gradient exists, then flow will cease. Thus, mitral inflow provides unique insight into left ventricular filling throughout the entire period of diastole.

Mitral inflow is recorded from the apical four-chamber view. Once the view is properly aligned, the sample volume is positioned at the tips of the mitral leaflets. Sample volume size should be small, about 2 mm. Care should be taken to avoid placing the sample volume too close to the mitral annulus which will result in lower velocities and an inaccurate E/A ratio. By moving the sample volume up and down relative to the mitral tips, the true peak velocity in early and late diastole can be recorded with confidence (Fig. 7.12). In addition, continuous wave Doppler can also be performed to confirm that maximal velocities are in fact recorded. Spectral gain and wall filter settings should be adjusted to ensure that a clean envelope is
recorded and to facilitate the accurate timing of the beginning and end of mitral inflow. The Doppler recording should be performed at both a slow and a fast sweep speed. The slow speed is useful for evaluation of respiratory variation, whereas the fast speed is used to obtain measurements. These measurements should be recorded at end-expiration and multiple beats should be averaged.

Once the Doppler recording is optimized, a variety of measurements should be obtained. The primary measurements include the peak early filling velocity (E wave), peak filling velocity during atrial systole (A wave), the E/A ratio, and the deceleration time of the early filling velocity (Fig. 7.13). Deceleration time is defined as the time interval from early peak inflow velocity (the E wave) to the cessation of the rapid early filling phase (Fig. 7.14). It is inversely proportional to chamber stiffness and is obtained by tracing the deceleration curve from the maximal E-wave velocity to the baseline which represents the time of pressure equalization between the two chambers (when inflow ends and velocity is zero). In many patients, the deceleration limb of the E wave does not reach the zero line. In these cases, the line should be extrapolated to the baseline in order to define the deceleration time (Fig. 7.15). Factors that affect the mitral inflow pattern include sinus tachycardia and first-degree atrioventricular (AV) block, which tend to fuse the E and A waves, atrial fibrillation, which eliminates the A wave, and mitral valve disease, which independently alters the velocity pattern.

**Color M-mode Flow Propagation Velocity (Vp)**

When the mitral valve opens, flow accelerates from the valve orifice toward the apex of the left ventricle. Propagation velocity (Vp) throughout diastole can be measured with color Doppler M-mode. Although a variety of parameters can be obtained, by convention, the slope of the early diastolic valve-to-apex contour is used most often. From the four-chamber view, the M-mode cursor is placed in the center of the column of mitral inflow, as parallel as possible to flow direction (Fig. 7.16). Temporally, this is performed in early diastole, coincident with the E wave. By shifting the color baseline to a low Nyquist limit, an aliasing border (blue to red, representing the first aliasing velocity) near the center of the column is obtained. Although this border is not truly linear, a tangent is drawn from the mitral valve to a point 4 cm distal, representing the early diastolic flow propagation velocity.

The slope of this line corresponds to the velocity gradient from left ventricular base to apex. The primary determinant is the rate of myocardial relaxation or elastic recoil of the chamber in early diastole. Thus, impaired relaxation will slow the propagation of blood and thereby reduce the slope of the line. However, several other factors affect this simple measurement. These include ventricular geometry, chamber volume, regional dysynchrony, systolic function, and the complexity of flow vortex patterns once blood enters the chamber. It is recommended that propagation velocity should never be used in isolation and
should only be assessed in the setting of a dilated left ventricle with reduced systolic function.

**Tissue Doppler Mitral Annular Velocity**

The velocity of the mitral annulus can be recorded throughout the cardiac cycle using the tissue Doppler method (Fig. 7.17). From the four-chamber view, the sample volume is positioned on the annulus, near the insertion site of the mitral valve. Both the septal (medial) and lateral sites should be recorded. Because of the high amplitude of the signal, spectral gain should be lowered to ensure a crisp, reproducible tracing. Because of the low velocity, the velocity scale should also be adjusted to maximize the size of the curve, thereby permitting accurate determination of velocity throughout the cardiac cycle. The sweep speed should be high, between 50 and 100 cm/sec. Measurement of three or more consecutive cycles should be obtained at end-expiration. Using this approach, accurate, reproducible recordings are possible in the majority of patients.

Although several velocity measurements can be made, the most useful is the peak annular velocity in early diastole. It has been given a variety of names, but the current recommendation is $e'$. The $e'$ velocity primarily depends on left ventricular relaxation. When diastolic function is abnormal, $e'$ is relatively independent of preload. However, when diastolic function is normal, $e'$ increases with higher filling pressure. For this reason, the use of the $e'$ has limitations in normal subjects. In patients with diastolic dysfunction, however, $e'$ can be used to mitigate the effect of left ventricular relaxation on the E-wave velocity. The practical importance of this observation will be discussed subsequently.

In practice, $e'$ is not often reported in isolation. Instead, it is usually combined with the E-wave velocity into the familiar ratio, E/e' (Fig. 7.18). A measure of $e'$ should be made from both septal and lateral locations. In most patients, lateral $e'$ will be higher than the septal value. Thus, the E/e' will be lower if the lateral position is used for $e'$ and higher if the septal value...
FIGURE 7.19. The e′ velocity will be different when it is recorded from the septal versus the lateral location. In panel A, the septal e′ is less than the lateral e′ velocity (panel B). A higher lateral velocity is typical.

is used (Fig. 7.19). Debate continues over which e′ should be reported. The range of normal and abnormal E/e′ ratios published in the literature was initially generated using the septal value. However, it was subsequently shown that the lateral e′ may correlate better with filling pressures in the setting of a normal ejection fraction. Furthermore, a regional wall motion abnormality will tend to affect the adjacent annular velocity. For all these reasons, it is recommended that e′ and E/e′ be reported as the average of the septal and lateral values.

The main use of the E/e′ ratio is to predict filling pressure in the setting of abnormal diastolic function (Figs. 7.20–7.22). A considerable amount of data has emerged validating this approach for estimating pulmonary capillary wedge pressure (Fig. 7.23). A limitation of this approach is that the two measurements, E and e′, are obtained from different cardiac cycles and at different times. To minimize variability, the recording of the mitral inflow and annular velocities should be performed in close temporal proximity. Additional limitations exist. Age, preload, and systolic function can affect these parameters. The ratio may not be predictive in normal subjects, presumably because of the sensitivity of e′ to preload in the normal heart. Finally, prosthetic mitral valves, annular rings, and significant annular calcification can create technical problems in measuring e′.

Pulmonary Venous Flow Patterns

Pulmonary venous flow velocity can be recorded at the junction of the veins and left atrium, providing insight into the factors that affect left atrial filling. To obtain pulmonary venous flow, the apical four-chamber should be used. Some superior angulation of the view is often required and color Doppler is helpful to identify the entrance of the veins into the chamber. Then, a pulsed Doppler sample volume should be positioned within the vein approximately 5 mm from its junction with the atrium (Fig. 7.24). To optimize the recording, wall filter settings should be lowered and a fast sweep speed should be employed. Measurements should be obtained over three consecutive cycles at end-expiration. Of all the Doppler parameters...
FIGURE 7.21. This example, taken from a patient with elevated left ventricular filling pressure, demonstrates an abnormally high E/e\textsuperscript{'} ratio of approximately 18. Note that a different E/e\textsuperscript{'} ratio is obtained depending on whether the septal (panel B) or lateral (panel C) e\textsuperscript{'} value is utilized.

FIGURE 7.22. From a patient with restrictive cardiomyopathy, the E/e\textsuperscript{'} ratio of 25 is consistent with elevated left ventricular filling pressure.

\[ \frac{E}{e'} = \frac{100}{4} = 25 \]
Chapter 7 Evaluation of Left Ventricular Diastolic Function

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Pulmonary venous flow consists of three main components: an antegrade systolic wave (which often has two peaks, S1 and S2), a diastolic wave (D), and a retrograde wave (Ar) corresponding to atrial systole (Fig. 7.25). Both the time velocity integral and the peak velocity of each component can be measured. In addition, the duration and peak velocity of the retrograde atrial wave can be quantified. The systolic fraction is defined as the ratio of systolic to the diastolic time velocity integral (i.e., the ratio of areas under the velocity curves). The most commonly reported value is the ratio of the peak antegrade velocities (S1 and S2) present, as in the presence of bradycardia and first-degree block, it is recommended that the second (or S2) value be used. The pulmonary venous flow pattern is affected by several factors. Young normal subjects have a predominant diastolic wave. With increasing age, the S/D ratio increases (Figs. 7.26 and 7.27). As left atrial compliance decreases and pressure rises, the S/D ratio decreases and the systolic fraction is usually less than 40%. The duration of the retrograde atrial wave, Ar, also increases with increased filling pressure. Furthermore, differences in duration of Ar and the mitral A wave (Ar – A) have been shown to correlate with left ventricular end-diastolic pressure (Fig. 7.28). As left atrial pressure rises, Ar duration lengthens and Ar – A difference increases. Although technically challenging to measure, the Ar – A difference may be sensitive and useful in the assessment of elevated left atrial pressure. A value of >30 ms indicates elevated left ventricular end-diastolic pressure and more severe left atrial pressure becomes abnormal. This may be useful in patients with abnormal relaxation to separate those with normal from those with elevated filling pressures. There are significant limitations to the routine use of pulmonary venous patterns in hemodynamic studies. In addition to the technical challenges in obtaining the recordings, age, heart rate, PR interval, mitral regurgitation, and systolic function also affect pulmonary venous flow. It has been shown that these parameters have limited accuracy in the setting of normal systolic function. For all these reasons, these parameters have been subjugated to a minor role in the practical assessment of diastolic function.

Left Atrial Volume

Although not a hemodynamic parameter, left atrial volume determination is an essential part of the diastolic function assessment. An increase in left atrial size is the morphologic expression of chronic diastolic dysfunction. Although admittedly nonspecific, it reflects both the duration and the severity of
disease. Chamber volume should be obtained using the biplane approach, from the apical four- and two-chamber views. The left atrial area should be measured at end-systole, just prior to mitral valve opening, when volume is greatest.

Two approaches to volume calculation have been reported (Fig. 7.29). The area-length method requires planimetry of the chamber and measurement of the distance from the annular plane to the superior border of the chamber. The length and area are obtained in both orthogonal views and then combined to derive volume. The second approach uses the Simpson’s method for volume determination and requires only planimetry of the chamber from the two views (i.e., linear dimensions are not involved). The echocardiographic planes should be adjusted to ensure that maximal area of the left atrium is captured. When performing the planimetry, care must be taken to exclude the pulmonary veins. Also, by convention, the mitral annulus is used as the inferior border when tracing left atrial area (Fig. 7.30). Because of the relationship between atrial size and body size, it is recommended that volume be corrected for body surface area, and reported in mL/m².

The superiority of volume over simple linear dimensions for assessing left atrial size is now well established. With careful attention to technique, accurate determination of volume is feasible in most patients. However, the limitations of deriving volume from tomographic images should be apparent. For this reason, three-dimensional imaging will likely play an increasing role for this purpose in the future.

Left atrial volume has both diagnostic and prognostic value in the assessment of diastolic function. However, left atrial enlargement may also result from other factors, thereby reducing its specificity. In particular, mitral valve disease will often lead to left atrial dilatation. This possibility should be considered whenever left atrial volume is increased in the setting of normal Doppler markers of diastolic function.
### Chapter 7 Evaluation of Left Ventricular Diastolic Function

**The Valsalva Maneuver**

Preload manipulation is an integral part of the comprehensive diastolic function examination. This is most often accomplished using the Valsalva maneuver. This involves forced expiration against a closed nose and mouth. During the strain phase, left ventricular preload is reduced. The most important and practical application of this maneuver is in conjunction with mitral inflow velocity assessment. For example, in the setting of a normal appearing mitral inflow pattern, preload reduction can unmask a pseudonormal state (Fig. 7.31). In normal subjects, Valsalva maneuver leads to a general reduction in velocity, affecting the E and A wave to a similar degree. Thus, the E/A ratio is unchanged. In the pseudonormal stage of diastolic dysfunction, the Valsalva maneuver will change the pattern to one resembling impaired relaxation. This is because pseudonormalization causes a moderate increase in filling pressure superimposed on delayed relaxation. By lowering preload, the delayed relaxation pattern is unmasked. Thus, during the Valsalva strain phase, a decrease in the E/A ratio of >50% is a useful indicator of elevated filling pressure. However, in the setting of irreversibly elevated filling pressure (the restrictive filling pattern), this decrease in E/A may not occur.

**Other Markers of Diastolic Dysfunction**

Strain and strain rate can be measured using Doppler or speckle tracking methods. Although strain can be recorded during diastole and may provide unique information on diastolic function, its value for this purpose has yet to be established. Because regional strain (and strain rate) are typically assessed, it may be possible to use this approach to assess diastolic function locally. This may have relevance in the setting of acute ischemia, dyssynchrony, or viability assessment. Currently, however, there is no evidence to support the routine use of this technique for diastolic function assessment.

Twisting and untwisting (or torsion) have been recognized as important factors in ventricular function. This type of motion occurs because of the presence of obliquely oriented subepicardial fibers and contributes importantly to the efficiency of contractility and relaxation. Speckle tracking now provides a
FIGURE 7.30. Examples of left atrial volume calculation. In each case, planimetry of the left atrial area from the two-chamber view is used. The chamber volume is corrected for body surface area, yielding the left atrial volume index (LAVI). A range of volume measurements is shown in the three examples provided.

A Comprehensive Approach to Diastolic Dysfunction

The assessment of diastolic function is a complex, inexact science in which multiple factors must be assessed and integrated.
with clinical information. For each parameter, a range of values exist that define normal and each of the stages of dysfunction. This is due to the fact that multiple factors, in addition to diastolic function, affect each marker. In all cases, some degree of overlap exists. This means that no one parameter can be used in isolation. Instead, a number of markers must be evaluated, including the clinical scenario. An example of this is the finding of a high E/A ratio. This may indicate restrictive filling and elevated left atrial pressure. It may also be seen in a healthy young athlete. Distinguishing between the two can and should be made on clinical grounds.

Thus, the diagnosis of diastolic dysfunction is most helpful when viewed in clinical context and in the setting of a plausible anatomic substrate. Over the past 25 years, multiple Doppler parameters have been proposed for the assessment of diastolic function. Each has its strengths and limitations. In some respects, the sheer number of potential measurements has created confusion and even frustration for users. One of the problems is the lack of a gold standard and the challenge of validating each individual noninvasive marker against an appropriate benchmark. In one study (Kasner et al., 2007), a group of patients with heart failure and normal ejection fraction and
a group of control patients were studied with sophisticated in-
vasive techniques, including pressure-volume loop recordings and
derivation of Tau (τ, the time constant of relaxation), to
define the presence and severity of diastolic dysfunction. Then
these findings were compared to Doppler and tissue Doppler
parameters. Most Doppler markers, including E/A ratio, IVRT,
and deceleration time, correlated modestly with the various in-
vasive measures. The parameter that correlated best was E/e′
(using the lateral annulus). Using a cut point of 8, E/e′ (lateral)
had a specificity of 92% and a sensitivity of 83% for the detection
of diastolic dysfunction. This study underscores the complexity
of diastolic function and reminds us that no single parameter, 
either invasive nor Doppler, can completely characterize di-
astolic function. Instead, a comprehensive and systematic ap-
proach is recommended to fully address this important clinical
problem.

When applying these techniques in the clinical arena, sev-
eral factors must be taken into account. Abnormalities of relax-
ation and/or filling pressure may occur with either normal or
abnormal systolic function. Such abnormalities may or may not
produce symptoms. Whether they do or do not produce depends
in part on the magnitude of elevation of left atrial pressure and
whether diastolic function worsens significantly during ex-
ercise. In the natural history of diastolic dysfunction, patients
may initially be symptomatic only with exercise. In these early
stages, impaired relaxation and mild elevation of left ventricu-
lar end-diastolic pressure may be the predominant abnor-
malities. These may result from some combination of left ventricular
hypertrophy, increased afterload, prolonged ejection, or abnor-
malities of left ventricular shape.

Using the techniques outlined in the previous section, a com-
prehensive approach to diastolic function is possible (Fig. 7.33).
Through the systematic application of these principles, the
stages and severity of diastolic dysfunction can be determined
(see Table 7.3). The first step involves the analysis of the mitral
inflow pattern. As discussed previously, the earliest form of di-
astolic dysfunction is usually impaired relaxation, the result of
delayed pressure decline following aortic valve closure. This is
associated with a reversal of the E/A ratio (usually <1) and a
prolonged deceleration time (>240 ms). This pattern is highly
specific for impaired relaxation. In most cases, filling pressures
are still normal at this stage, although it should be noted that
this mitral inflow pattern does not preclude the possibility of a
modest increase in preload. Impaired relaxation is usually as-
sociated with a prolonged IVRT, although the multiple factors
that affect IVRT limit the specificity of this finding. At this stage,
E/e′ is usually normal (indicating normal filling pressure) and
left atrial volume is mildly increased. An example of impaired
relaxation is presented in Figure 7.34. This case involved a 65-
year-old male with untreated hypertension and exertional dys-
nea. Left ventricular systolic function was mildly reduced and
the left atrium was moderately dilated (LA volume index > 35
mL/m²). The case illustrates the E/A reversal and IVRT prolon-
gation typical of impaired relaxation.

With progression of disease, filling pressure rises, leading to
the pseudonormal phase. Here, the E/A ratio and deceleration
time are within the normal range (hence the name). Table 7.4
lists some of the markers that can be used to differentiate be-
tween normal and pseudonormal. Among the most helpful, the
Valsalva maneuver can unmask the underlying relaxation ab-
normality. A decrease in E/A > 30% during the strain phase is
indicative of increased filling pressure and serves to distinguish
normal from pseudonormal function. At this stage, the IVRT
may fall within the normal range because of the combined
and offsetting effects of increased left atrial pressure and de-
layed relaxation. Furthermore, the E/e′ will be increased for the
same reason. In almost patients at this stage of chronic diastolic
dysfunction, left atrial volume will be significantly increased.
Additional clues to the pseudonormal state include a reduced
propagation velocity slope and a pulmonary venous systolic-to-
diastolic ratio <1. Figure 7.35 is an example of pseudonormal
diastolic dysfunction in a patient with end-stage renal disease
and severe hypertension. Although the E/A ratio is normal at
baseline, impaired relaxation is unmasked with the Valsalva
maneuver. In addition, the left atrium is significantly enlarged.
A low septal e′ (6 cm/sec) and a high E/e′ (18) indicate elevated
filling pressure. This is further suggested by the prolonged pul-
monary venous A wave (Ar) relative to the mitral inflow A wave.
With the development of restrictive filling, the E/A ratio in-
creases (usually >2, an indication of a high LA-LV pressure
gradient at the time of mitral opening) and the deceleration
time becomes very short (<160 ms, due to a noncompliant left
ventricle). This results from the loss of elastic recoil and the in-
creased reliance on pushing rather than suction of blood into

![Diagram of diastolic function](image-url)
the left ventricle. The left atrium is invariably enlarged and an RV/e′ ratio greater than 15 confirms elevated filling pressure. If the stage of dysfunction is reversible, a decrease in the E/A ratio will occur with the Valsalva maneuver. An additional clue to this stage is a small or absent pulmonary venous systolic wave, that is, a predominant diastolic wave. As this phase of restrictive filling progresses to irreversibility, the E/A ratio becomes fixed and unresponsive to Valsalva (as well as other preload reducing strategies, including diuresis). An example of restrictive physiology is presented in Figure 7.36. These images are from a patient with ischemic cardiomyopathy and pulmonary edema. The left atrium is severely enlarged and the mitral inflow pattern is consistent with restrictive filling. The lack of responsiveness of the mitral pattern to Valsalva indicates irreversible restrictive filling. The E/e′ ratio of 22 indicates elevated filling pressure. The pulmonary venous inflow pattern is also strikingly abnormal.

A practical approach to the individual patient is shown in Figure 7.37. It begins with an assessment of left atrial volume, Ar – A, and the E/A ratio response to Valsalva (see figure) are used to categorize patients as having impaired relaxation (grade I), pseudonormal (grade II), or restrictive (grade III) filling.

### Estimating Left Ventricular Filling Pressures

In assessing individual patients for diastolic function abnormalities, it is helpful to distinguish between those with normal and abnormal systolic function, usually defined as a left ventricular ejection fraction greater than or less than 50%, respectively. This is based on the presumption that, among patients with abnormal systolic function, diastolic function is invariably abnormal, and the clinical question is whether or not filling pressures are elevated (and if so, to what degree). The approach to this group of patients with systolic dysfunction is outlined in Figure 7.38. By simply using the mitral inflow pattern (E-wave velocity; E/A ratio, and deceleration time), most patients with a reduced echocardiographic fraction can be categorized as having normal or elevated filling pressures. In patients with intermediate values, the E/A ratio is most helpful to predict filling pressure. The response of the E/A pattern to the Valsalva maneuver is also instructive. Additional parameters that may be useful include the pulmonary venous S/D ratio and the Ar – A difference.

In patients with a normal ejection fraction, the estimation of filling pressures begins with the E/e′ ratio (Fig. 7.39). If less than or equal to 8, left atrial pressure is normal. If greater than or equal to 15, filling pressure is elevated. In between these values, left atrial volume, Ar – A, and the E/A ratio response to Valsalva maneuver may be used to distinguish normal from abnormal filling pressures. Another clue is the presence or absence of pulmonary hypertension.

### Stress Testing to Assess Diastolic Function

The diastolic stress test has several applications. It is useful in patients who report exertional dyspnea in the setting of normal pulmonary function. It is also helpful to evaluate filling pressures in patients with known diastolic dysfunction with no or
FIGURE 7.34. A case study from a 65-year-old patient with long-standing hypertension. On two-dimensional imaging, there was left ventricular hypertrophy and mild global hypokinesis. Left atrial volume index was moderately increased and the Doppler findings are consistent with impaired relaxation. See text for details. IVRT, isovolumic relaxation time; LAVI, left atrial volume index.
FIGURE 7.35. A case study from a patient with pseudonormal diastolic dysfunction. The patient had end-stage renal disease and severe hypertension. The left atrium is severely dilated and Doppler indices are consistent with the pseudonormal stage of diastolic dysfunction. See text for details. IVRT, isovolumic relaxation time; LAVI, left atrial volume index.
FIGURE 7.36. These images were recorded from a patient with ischemic cardiomyopathy, moderate systolic dysfunction, and a significantly enlarged left atrium. Doppler indices are remarkable for restrictive physiology that does not respond to preload reduction. These findings suggest elevated left ventricular filling pressure and an irreversible stage of restrictive filling. See text for details. DT, deceleration time; LAVI, left atrial volume index.


mild symptoms. Often, patients in the early stages of diastolic dysfunction have only symptoms or limitations with exertion. In all these situations, the noninvasive evaluation of diastolic function can be useful. Among the various parameters that can be assessed during exercise, the E/e' ratio is most practical. In normal subjects, with exercise, both E and e' increase and the E/e' ratio remains unchanged or decreases slightly. In patients with impaired relaxation, mitral E velocity increases during exercise, while e' increases minimally if at all. Thus, the ratio will increase significantly, an indicator of a rise in left atrial pressure. Because the changes in mitral E velocity usually persist for several minutes after termination of exercise, they can be detected postexercise, even after wall motion assessment has been completed. A brief delay in recording mitral inflow also avoids the problem of fused E and A waves that occurs at high heart rates. Thus, combining an assessment of diastolic function with routine exercise echocardiography is feasible and may be of particular value in those patients with exertional dyspnea. Figure 7.40 illustrates the relationship between the E/e' ratio and left ventricular diastolic pressure during stress. At rest, diastolic pressure is within the normal range and the E/e' ratio is 12. Postexercise, an abnormal increase in diastolic pressure is associated with an E/e' of 17. Thus, exercise-induced changes in Doppler diastolic parameters, such as E/e', may be useful in the evaluation of patients with exertional symptoms and may explain reduced exercise capacity in patients with normal resting hemodynamics.

Finally, whenever stress testing is done for the purpose of dyspnea assessment, it is also prudent to record the tricuspid regurgitation velocity, before and after exercise. Like the diastolic parameters, determination of pulmonary pressures during stress in the group of patients can be very useful to answer clinical questions. If either pulmonary systolic pressure or left ventricular filling pressures increases significantly during exercise, the etiology of the patient's symptoms is usually established.

### The Differential Diagnosis of Heart Failure with Normal Ejection Fraction

Diastolic dysfunction is an important cause of heart failure with normal ejection fraction. Among patients with heart failure symptoms, the demonstration of diastolic dysfunction is often cited as evidence for a cause-and-effect relationship. However, several other conditions may also lead to symptoms of fatigue and exertional dyspnea and must therefore be considered in the differential diagnosis. Pericardial disease, particularly constrictive pericarditis, should be considered when heart failure and normal systolic function coexist. It is appropriate to consider constrictive pericarditis as having an element of diastolic dysfunction, since filling pressures are elevated and the mitral inflow velocity usually demonstrates a restrictive filling pattern. The distinction is important, however, because the treatment is totally different. Findings that suggest constrictive pericarditis include a normal or high e' velocity, which is very unusual in other causes of restrictive filling, and abnormal hepatic vein flow, which usually shows marked, respiratory-dependent flow reversal (see Fig. 7.41). This is not seen in most other causes of diastolic dysfunction. Table 7.5 lists several features that can be used to differentiate restrictive cardiomyopathy from constrictive pericarditis.

Among patients with normal systolic function and heart failure symptoms, several other conditions should be considered. In most cases, these are diseases in which diastolic dysfunction is the primary cause—or a major contributor—to symptoms. They are important, however, because specific treatment, sometimes curative, is available. These include mitral valve disease (both stenosis and regurgitation), restrictive cardiomyopathy, anemia, hypertrophic cardiomyopathy, and transient ischemia.

### Evaluation of Diastolic Dysfunction in Specific Patient Groups

#### Sinus Tachycardia

Most Doppler parameters perform less well in the setting of sinus tachycardia, especially in patients with normal systolic function. For example, fusion of the E and A waves of the mitral inflow pattern makes it difficult to measure the E/A ratio and deceleration time. In addition, fusion of the E and A waves will tend to increase A-wave velocity and reduce the E/A ratio. The parameter that is most useful in sinus tachycardia is the E/e' ratio, which retains its ability to predict filling pressures at higher heart rates. This is true whether or not ejection fraction is reduced.
Mitrval Valve Disease

Most patients with mitral stenosis have normal or low left ventricular diastolic pressure and elevated left atrial pressure. The mitral inflow pattern reflects the valvular disease rendering the usual Doppler markers of limited value in assessing diastolic function. However, left atrial pressure is often a clinically important question. In these patients, shortening of IVRT and increased mitral E-wave velocity correspond to an elevated early left atrial pressure. A more complex parameter, IVRT/(T1 – T2), has been reported to correlate reasonably well with mean left atrial pressure. This is the ratio of IVRT to the time difference between the mitral E-wave peak velocity and the annular e’ velocity. A ratio of less than 2 suggests elevated left atrial pressure (see Figs. 7.38 and 7.39). In patients with mitral stenosis, E/e’ has not been useful to predict left atrial pressure.

Mitral regurgitation is usually associated with increased compliance of both the left atrium and the ventricle. When severe, it is associated with a high E-wave velocity, reflecting the high LA-LV pressure gradient in early diastole and the increased antegrade diastolic flow. The pulmonary venous systolic wave is often blunted. In these patients, the E/e’ may be useful to predict filling pressures but only in the presence of a depressed ejection fraction. As in mitral stenosis, the ratio of IVRT/(T1 – T2) correlates reasonably well with pulmonary capillary wedge pressure.

Hypertrophic Cardiomyopathy

Neither the E/A ratio nor the mitral deceleration time are helpful in hypertrophic cardiomyopathy. Similarly, E/e’ seems to exhibit greater variability (and less predictability) in this population. Of the parameters that have been studied, the time difference between mitral A-wave duration and pulmonary venous A-wave duration (Ar – A), may correlate best with filling pressure. Other parameters that may prove of some value include pulmonary artery pressure and left atrial volume. Clearly, this represents a challenging area for the noninvasive prediction of diastolic function and filling pressures.

Atrial Fibrillation

Atrial fibrillation creates two distinct problems, absence of the mitral A-wave and beat-to-beat variability. In patients with atrial fibrillation and systolic dysfunction, the deceleration time correlates modestly with filling pressures. A deceleration time <150 ms predicts not only an elevated filling pressure but also a poor prognosis. In addition, the E/e’ ratio retains its value in patients with atrial fibrillation. A ratio >11 corresponds to left ventricular end-diastolic pressure ≥15 mm Hg. To ensure accuracy, several beats must be measured because of the heart rate variability.

### Table 7.5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Constrictive Pericarditis</th>
<th>Restrictive Cardiomyopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume</td>
<td>Dilated (usually normal) ≥1.5</td>
<td>Dilated Normal to mildly reduced ≥1.5</td>
</tr>
<tr>
<td>LV contractility</td>
<td>E/A ratio</td>
<td>Minimal respiratory change &lt; 20</td>
</tr>
<tr>
<td>Response to Valvular Disease (L/min)</td>
<td>E-wave ≥25% &gt;80</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>e’ (septal vs. lateral)</td>
<td>Septal &gt; lateral</td>
<td>Septal &gt; lateral</td>
</tr>
<tr>
<td>Hepatic vein flow</td>
<td>Expiratory diastolic normal</td>
<td>Inspiratory diastolic normal</td>
</tr>
</tbody>
</table>

LA, left atrium; LV, left ventricle.
Prognostic Significance of Echo-Doppler Parameters in Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Study Parameter</th>
<th>Population</th>
<th>CutOff Value</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glower et al., 1996</td>
<td>DT</td>
<td>508 pts, low EF</td>
<td>125 ms</td>
</tr>
<tr>
<td>Poult et al., 1997</td>
<td>Mitrail inflow pattern</td>
<td>173 pts, CHF, low EF</td>
<td>Response to A loading</td>
</tr>
<tr>
<td>Hansen et al., 2001</td>
<td>Mitrail inflow pattern</td>
<td>35 pts, CM</td>
<td>RF pattern vs. all others</td>
</tr>
<tr>
<td>Hioki et al., 2004</td>
<td>E/e′</td>
<td>258 pts, elderly</td>
<td>183 ms, EF &lt;50%</td>
</tr>
<tr>
<td>Wang et al., 2005</td>
<td>E′</td>
<td>150 pts, CM</td>
<td>3/5 sec/cm</td>
</tr>
<tr>
<td>Díaz et al., 2009</td>
<td>DT and AR-A</td>
<td>145 pts, CM</td>
<td>DT &lt; 130 ms, AR &gt; 10 ms</td>
</tr>
<tr>
<td>Okura et al., 2006</td>
<td>E/e′</td>
<td>230 pts, nonvalular AF</td>
<td>15</td>
</tr>
<tr>
<td>Brach et al., 2007</td>
<td>E′/E″</td>
<td>370 pts, CM and MR</td>
<td>15</td>
</tr>
<tr>
<td>Takemoto et al., 2005</td>
<td>LA volume index</td>
<td>1,375 elderly pts, normal EF</td>
<td>&lt;28, 28-37, &gt;37 ml/m²</td>
</tr>
</tbody>
</table>


AF, atrial fibrillation; CM, congestive heart failure; CMR, cardiovascular MRI; DT, deceleration time; EF, ejection fraction; HF, heart failure; LA, left atrium; MR, myxomatous infarction; MI, initial reperfusion; RF, restrictive filling pattern.

### Hemodynamics

- Harru...
Chapter 7 Evaluation of Left Ventricular Diastolic Function

Stress Testing


Techniques and Methodology


