Diastolic dysfunction of the left ventricle is an important cause of cardiac morbidity and appears to be one of the earliest detectable abnormalities in a number of disorders.\textsuperscript{1-6} Left ventricular diastolic performance has been described conceptually by two distinct and occasionally discordant parameters—relaxation and compliance.\textsuperscript{7-9} To date, the only definitive methods for assessing these parameters have required direct measurement of intracardiac pressures, which can only be obtained by cardiac catheterization.

Because direct measurements of ventricular function are complex and require invasive data, many have sought noninvasive methods of assessing diastolic function that do not require the use of intracardiac pressure. In general, these methods have used the time course of ventricular filling to infer information about ventricular relaxation and compliance. The ventricular filling pattern was initially obtained from ventricular volumes obtained from radionuclide ventriculograms\textsuperscript{10,11} and M-mode and two-dimensional echocardiograms.\textsuperscript{12,13} These sequential volumes were time-differentiated to yield filling rate throughout diastole.

**Doppler Evaluation of Ventricular Filling**

With the advent of pulsed Doppler echocardiography, it is now possible to examine more directly the pattern of left ventricular filling.\textsuperscript{14,15} Using this technique, the pattern of blood velocity across the mitral valve recorded in diastole is used to calculate the temporal course of ventricular filling (Figure 1A). Several empiric indexes have been derived from the mitral inflow pattern and proposed as markers for ventricular diastolic function, including the peak and integrated velocities of early rapid filling, atrial contraction, and their ratios and the acceleration and deceleration times of the early filling wave. The Doppler method has appeal because it provides a beat-by-beat assessment of ventricular filling without hemodynamic impact and is relatively simple to use. As a result, these Doppler indexes have become so widely used that it is often forgotten that they are only indirect measures of diastolic function, providing no direct assessment of either ventricular relaxation or compliance.

Historically, the noninvasive pattern considered typical of diastolic dysfunction was delayed and reduced early filling of the ventricle, manifest as reduced peak filling rate on the radionuclide ventriculogram or a shift in the Doppler profile to a lower E wave and higher atrial contribution to filling (Figure 1B). Indeed, the E wave-to-A wave ratio (E/A ratio) became the principal Doppler index of diastolic function used to assess hemodynamic impairment in a number of disorders\textsuperscript{16-21} and even to assess the effectiveness of medical therapy.\textsuperscript{22-24}

One of the earliest studies to challenge this simple equating of diastolic filling with function used intravenous nitroglycerin to lower left atrial pressure acutely, resulting in a marked decline in peak E velocity with relative sparing of the A velocity.\textsuperscript{25} Thus, the E/A ratio frequently fell below 1:1, indicating diastolic dysfunction, whereas the simultaneously measured isovolumic relaxation time constant (τ) fell, indicating improved relaxation. Subsequently, other clinical and experimental studies have demonstrated a very complex relation between mitral filling indexes and ventricular preload,\textsuperscript{26-28} afterload,\textsuperscript{26,27} heart rate,\textsuperscript{29,30} and atrioventricular conduction interval\textsuperscript{31} as well as various hemodynamic parameters of relaxation\textsuperscript{26,27,32,33} and compliance.\textsuperscript{34}

In addition, recent reports have described a Doppler pattern of diastolic dysfunction quite different from the classic E/A reversal. This second pattern is characterized by a short isovolumic relaxation time, a tall, narrow E wave with high peak velocity and steep deceleration, and a small A wave (Figure 1C). This pattern has been observed in situations with low ventricular compliance such as constrictive pericarditis,\textsuperscript{35} restrictive cardiomyopathy,\textsuperscript{36} and acute severe aortic insufficiency.\textsuperscript{37}
Thus, diastolic dysfunction may produce opposite effects on the mitral filling pattern, and certain loading conditions may lead to abnormal patterns in the setting of normal relaxation and compliance. It is clear that intelligent interpretation of these indexes requires a more sophisticated theoretical construct within which to analyze them.

Understanding Doppler inflow patterns is in fact a two-step process. First, one must understand how blood velocity relates to its physical determinants. These include the atrioventricular pressure difference, the impeding characteristics of the mitral valve, and the instantaneous compliance of the atrium and the ventricle. Second, one must relate these physical variables to parameters of physiological importance, such as the relaxation time constant, the global characteristics of the ventricular pressure–volume curve, and atrial pressure. In this discussion, we examine both the physical and the physiological bases for the mitral velocity pattern, concentrating on the early filling wave (E wave). Although our understanding of these topics is not complete enough to establish a one-to-one correspondence between Doppler indexes and diastolic function, an appreciation of these factors will help explain the complex and sometimes contradictory data relating ventricular filling and diastolic performance.

### Mathematical Simulation of Ventricular Filling

One difficulty that arises in experimental studies of the Doppler assessment of diastolic dysfunction is that changing one physiological variable may alter other variables in unforeseen and uncontrollable ways. Thus, raising left atrial pressure may alter atrial compliance and enhance ventricular contractility. In such a case, it is unclear whether any observed change in Doppler indexes results from the primary intervention or the secondary effects. To circumvent this problem, we developed a mathematical model of left ventricular filling that allows us to adjust the various physical and physiological parameters independently and to observe the effect on the rapid filling wave.38–40

Similar lumped parameter modeling approaches have been described27,41–47 as well as two-dimensional48–51 and preliminary three-dimensional52,53 approximations to ventricular filling. Each of these models uses a limited number of adjustable parameters to explore the determinants of diastolic filling. The purpose of such modeling is not to duplicate the full anatomic situation but rather to strike a balance between fidelity of the simulation and understandability of the parameter manipulations.

For example, Figure 2 shows computer simulation of our mathematical model, displaying the diastolic ventricular pressure–volume curves along with the Doppler
velocity pattern resulting from alterations in left atrial pressure, \( \tau \), ventricular compliance, and ventricular end-systolic volume. Also shown are several noninvasive indexes calculated from these curves: peak velocity (E, cm/sec), maximal acceleration rate (A, m/sec\(^2\)), and deceleration rate (D, m/sec\(^2\)), and the velocity time integral of the E wave (VTI, cm). The short, vertical line at the start of mitral velocity represents the isovolumic relaxation time (IVRT, msec). The middle curve in each graph displays the same data, whereas the other two curves show a decrease and increase in the parameter of interest. A more detailed explanation of such a display has recently appeared\(^{40}\) in which the predictions of the model were compared with previous results from in vivo experimentation.\(^{26}\) Similar families of curves have been described by several previous investigators.\(^{41,43-45}\) (Space limitations prevent a full description of these studies, but they are recommended.)

**Influence of Atrial Pressure**

In Figures 2A and 2B, increasing atrial pressure leads to a shortening of the IVRT, increased acceleration rate, and a significantly increased peak velocity and VTI. On the pressure-volume relation, this increased filling is manifest as a larger end-diastolic volume. Note that to minimize the adjustable parameters, we assume that the atrium and pulmonary veins empty as a common chamber. One consequence of this is that the calculated velocity curves fall directly to zero rather than displaying the “tail” seen at the end of the E waves in Figure 1 that result from secondary flow from the pulmonary veins.

**Influence of Ventricular Relaxation**

Figures 2C and 2D display changes in the IVRT constant. The most striking effect is a delay in filling
with little actual limitation in total filling. The peak velocity is slightly depressed with lower acceleration and deceleration rates; the IVRT is markedly prolonged. The pressure–volume loops do not differ greatly; at \( \tau = 60 \) msec, the ventricle reaches the fully relaxed curve only at the end of the E wave. However, with further prolongation in \( \tau \), relaxation may remain incomplete and stroke volume would be more markedly reduced.

**Influence of Intrinsic Myocardial Stiffness**

Figure 2E shows three different ventricular pressure–volume curves in which the fundamental chamber elasticity is varied. The numbers shown (left ventricular volume constant \( V_{40} \)) represent the volume addition necessary to raise the ventricular pressure by a factor of \( e = 2.71828 \). The characteristic of these exponential curves is that their slope (which by definition is the instantaneous stiffness, \( dp/dV \)) is given by chamber pressure divided by this volume constant. Thus, the 40-cm\(^3\) curve is the stiffest at all pressures, and this leads to a markedly stunted E wave in Figure 2F.

**Influence of Ventricular Systolic Function**

The curves in Figures 2G and 2H demonstrate the effect that systolic performance has on diastolic filling. Each curve is based on the same diastolic ventricular pressure–volume curve and relaxation rate. All that is varied is the end-systolic ventricular volume (produced either by changes in inotropic state or variation in afterload with the same end-systolic pressure–volume relation). The overall effect on the E wave is similar to those seen in Figures 2E and 2F because higher end-systolic volume causes the ventricle to fill at a steeper portion of its pressure–volume curve.

**Physical Factors Governing Mitral Velocity**

The simulations in Figure 2 demonstrate the global effect that changes in individual physiological parameters have on the Doppler E wave. It is instructive to consider separately the physical factors that govern mitral velocity as well as the physiological determinants of these physical forces. Because different physical forces are responsible for acceleration and deceleration of mitral flow, we will consider these phases of the E wave separately.

**Acceleration of Mitral Flow**

At the time of mitral valve opening, the blood within the mitral apparatus is stationary. As left ventricular pressure drops (with progressive active relaxation), this blood is subjected to a growing force because of the atrioventricular pressure difference \( (\Delta p) \), which causes the blood within the valve to accelerate. Newton's second law of motion states that this acceleration rate \( (a, \text{ the change in velocity with time, } dv/dt) \) is equal to force \( (F) \) divided by mass \( (m) \). The force on the blood shortly after mitral opening is \( \Delta p \) multiplied by the mitral valve area \( (A) \) because pressure is by definition force divided by area. The mass term in this case, however, may not be obvious. One may think of it as the mass of blood being accelerated within the mitral apparatus, given by the area of the valve multiplied by the density of blood \( (\rho) \) multiplied by the effective length of blood column \( (L) \) subject to acceleration. In vitro experiments have demonstrated that this length is approximately proportional to the diameter of the mitral valve.\(^{54}\) Thus, we may write the acceleration rate from Newton's law as:

\[
a = \frac{dv}{dt} = \frac{F}{m} = \frac{A\Delta p}{\rho AL} \frac{\Delta p}{\rho L}
\]

Note that because area cancels out of this expression and blood density is constant \( (1.05 \text{ g/cm}^3) \), the key mitral inertial term (mitral iner tance) is the effective length of the blood column within the mitral valve. Yellin\(^{55}\) has previously identified this inertance as a key parameter determining the acceleration of blood through the mitral valve. Thus, if the blood within the mitral valve were subject to an instantaneously applied pressure difference, mitral velocity would rise linearly at a rate given by \( \Delta p/\rho L \) (initial portions of Figures 3A and 3B).\(^*\) In the physiological situation, the pressure

\*To express acceleration as \( \text{cm/sec}^2 \), the pressure gradient must likewise be written in metric units, with 1 mm Hg = 1,333 dyne/cm\(^2\).
FIGURE 3. Computer simulations demonstrating independent influence of atrioventricular pressure difference and inertial blood mass on velocity acceleration. Panel A: Pressure differentials of 2, 3, and 4 mm Hg are applied suddenly to a column of blood 6 cm long leading to a linear rise in velocity with acceleration proportional to the applied gradient and final velocities proportional to the square root of the gradient (by the Bernoulli equation). Panel B: The same 3 mm Hg pressure difference is applied to three different blood columns with lengths 4, 6, and 8 cm. Again, velocity rises linearly with acceleration inversely proportional to the blood inertance; the final velocity is unaffected by changes in inertance. Panels C and D show the more physiological situation where the pressure difference is applied gradually. In panel C, pressure changes of 20, 30, and 40 mm Hg/sec act on a 6-cm blood column, causing velocity to rise initially with a parabolic shape before eventually tracking the square root of the pressure difference. In panel D, a 30 mm Hg/sec gradient rise acts on blood columns 4, 6, and 8 cm in length, again with a resulting parabolic initial velocity rise whose slope is inversely related to the blood inertance; with time this inertial effect becomes less and less. Each of these graphs models the system as purely inertial with energy conservation, neglecting how chamber stiffness leads to a fall in the pressure difference.

gradient is not abruptly applied but rather increases gradually with ventricular relaxation; for a linearly rising gradient, the initial part of the mitral velocity curve is roughly parabolic, with acceleration increased for more rapidly falling ventricular pressure and retarded for a longer acceleration length (approximately the first 100 msec of Figures 3C and 3D). Such parabolic mitral acceleration curves have been demonstrated in vivo, and the critical role of blood inertance in connecting intracardiac gradients to flow acceleration have recently been reviewed.

Conservation of energy limits peak velocity. As shown in Figure 3, this acceleration decreases with time because the maximal velocity generated by a pressure difference is limited by conservation of energy (expressed in the Bernoulli equation). Within the heart, energy in the blood takes on three principal forms: pressure, kinetic energy, and heat; the total energy in the system must remain constant. In the left atrium, where blood velocity is low, most of the energy is in the form of pressure, but as it moves toward the mitral valve, its velocity rises and it acquires a kinetic energy \( \frac{1}{2} \rho v^2 \), which causes the local blood pressure to fall. In equilibrium, pressure difference and velocity are related by the simplified Bernoulli relation \( \Delta p = \frac{1}{2} \rho v^2 \), which becomes roughly \( \Delta p = 4v^2 \) when pressure is measured in millimeters of mercury and velocity in meters per second. Thus, in Figure 3A, the velocity approaches 71, 86, and 100 cm/sec asymptotically for applied gradients of 2, 3, and 4 mm Hg, respectively. Figure 3B shows that varying mitral inertance does not affect the final velocity, only the rapidity with which this velocity is approached. Figures 3C and 3D show that

\*The effect of pressure gradient and mitral inertance on the velocity rise is given analytically by \( \dot{v}(t) = v_m \tanh \left( \frac{v_{mt}}{2L} \right) \), where \( v_m \) is the hyperbolic tangent function and \( v_{mt} \) is the peak velocity, \( (2 \Delta \rho/\mu)^{1/2} \).
for a gradually rising pressure differential, velocity eventually rises as the square root of time because velocity is proportional to the square root of pressure.

**Pressure recovery within the left ventricle.** As blood emerges from the mitral valve, it slows down as the flow stream expands to fill the left ventricle. This slowing is associated with a decrease in kinetic energy that must lead either to a recovery of pressure or an increase in heat.* When the mitral valve is at all restrictive (e.g., mitral stenosis or prosthetic valves), pressure recovery does not occur, the kinetic energy being dispersed in turbulent eddies downstream from the valve. For normal mitral valves, there may be some pressure recovery, although the magnitude of this is unclear. Thus, the Doppler velocity pattern appears to closely reflect the atrial-to-ventricular pressure difference although it rigorously applies only to the pressure relation between the atrium and the mitral valve.

The analysis in this section has neglected the effect of atrial and ventricular compliance that causes the atrioventricular pressure difference to fall with time. Neglecting compliance in analyzing acceleration is reasonable because at mitral valve opening there is no flow between the atrium and ventricle. This impact of compliance will be considered next in analyzing deceleration.

### Deceleration of Mitral Flow

To understand the effects of chamber compliance or its reciprocal stiffness on velocity deceleration, it may be helpful to first examine a simple example shown in the descending portion of the velocity curve in Figure 4. At the point of interest \( t = 78 \text{ msec} \), the atrioventricular pressure difference is 4 mm Hg, leading to a transmitral velocity of 100 cm/sec. If the effective mitral valve area is 2 cm², the flow rate is 200 cm³/sec. In the next 10 msec, a total of 2 cm³ leaves the left atrium and enters the ventricle, lowering the pressure in the atrium and raising it in the ventricle as determined by the instantaneous chamber stiffness (the reciprocal of compliance). Assuming that the atrial stiffness \( (S_A) \) is 0.1 mm Hg/cm³ and ventricular stiffness \( (S_V) \) is 0.2 mm Hg/cm³, the transfer of 2 cm³ of blood from atrium to ventricle lowers atrial pressure by \( 2 \times 0.1 \) or 0.2 mm Hg while raising ventricular pressure by 0.4 mm Hg, thus lowering the atrioventricular pressure difference by 0.6–3.4 mm Hg. However, a pressure difference of 3.4 mm Hg will not support a velocity of 100 cm/sec but will support one of 92 cm/sec. This fall in velocity of 8 cm/sec in 10 msec indicates a deceleration rate of 800 cm/sec².

### Deceleration is directly related to the product of effective valve area and net chamber stiffness. It is possible to derive a simple analytical expression for this deceleration rate. Recall that chamber stiffness \( (S) \) is the change in chamber pressure caused by a small change in volume: \( S = \frac{dp}{dV} \), defined similarly for the atrium and the ventricle. For mitral valve flow, the critical stiffness parameter combines the atrial and ventricular stiffnesses and represents the change in atrioventricular gradient for an amount of volume passing through the mitral valve; this net stiffness is the sum of the atrial and ventricular stiffness, \( S_n = S_A + S_V \), and is defined as \( S_n = \frac{d\Delta p}{dV} \).

Equivalently, we may consider \( S_n \) as the rate of change in gradient \( (d\Delta p/dt) \) divided by the rate of change of volume \( (dV/dt) \). But \( dV/dt \) is simply the flow rate \( (Q) \) through the mitral valve, given by the mitral velocity multiplied by the effective valve area, \(-vA\) (negative because forward flow through the valve reduces the gradient). If we make one other substitution, replacing \( \Delta p \) with the simplified Bernoulli equivalent, \( \frac{1}{2}pv^2 \), then, by the laws of differentiation, \( d\Delta p/dt = \frac{d}{dt}(\frac{1}{2}pv^2)/dV/dt = \rho v(dv/dt) \). Taken together, these substitutions yield:

\[
\begin{align*}
S_n &= \frac{d\Delta p/dt}{dV/dt} = \frac{d(\frac{1}{2}pv^2)/dt}{dV/dt} = -\frac{\rho v(dv/dt)}{vA} = -\frac{\rho dv/dt}{A}
\end{align*}
\]

Rearranging to solve for the deceleration rate \(-dv/dt\) yields:

\[
-dv/dt = AS_n/\rho
\]

Thus, the rate of fall in velocity is directly proportional to the mitral valve area and the net atrial and ventricular stiffness and is independent of the pressure difference across the valve. Note that this formulation could have been made in terms of chamber compliance, \( dV/dp \) (i.e., \( C_A, C_V, \) and \( C_n \)), which is reciprocal to stiffness*: \(-dv/dt = A/(\rho C_n)\). The quantitative predictions of Equation 2 have been verified in vitro and in canine experiments with mitral stenosis.

Two important facts emerge from this analysis. One is that when the net stiffness (or compliance) is constant during diastolic filling, then the mitral velocity decay will have a constant slope; that is, the decay will be a straight line. Such linear decay is commonly observed in mitral stenosis, implying that whatever changes in atrial and ventricular stiffness may occur during diastole, they must be roughly equal and opposite to keep net stiffness constant. The second observation is that the mitral velocity curve can give no unique information about individual chamber pressures or compliance, only the pressure difference and the net compliance.

### Nonstenotic mitral valves. For nonstenotic mitral valves, the relation is not quite as simple as Equation 2 because the blood velocity does not mirror the instantaneous pressure difference resulting from inertial effects (i.e., the complete Bernoulli equation

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*How much heat? Blood moving through the mitral valve at 200 cm/sec has a kinetic energy of about 20,000 ergs/cm³. If all of this energy were converted to heat \((4.2 \times 10^4 \text{ ergs/kcal})\), blood temperature would increase by about 0.0005°C.

*However, while the stiffness of two connected chambers is the sum of the component stiffnesses, when atrial and ventricular compliance are combined into net compliance, the relation is \( C_n = (1/C_A + 1/C_V)^{-1} = C_A C_V/(C_A + C_V) \), smaller than either \( C_A \) or \( C_V \).
must be used rather than the simplified one). However, the qualitative effect should be the same, and as shown in Figure 2, we expect the deceleration rate for flow through normal valves to be directly related to valve area and net chamber stiffness.

Physiological Factors Governing Mitral Velocity

The discussion above has identified the physical factors that govern the acceleration and deceleration of the mitral velocity curve. We now examine the physiological basis for these physical variables to connect Doppler mitral indexes to parameters of clinical interest.

Acceleration

As shown above, the acceleration rate is directly related to the development of the atrioventricular pressure difference and inversely related to the iner-
tance of blood within the mitral valve. If we make the assumption that atrial pressure is steady at the time of mitral valve opening, we see that the growth of the pressure difference is precisely the rate of ventricular pressure drop that results from active relaxation. Isovolumic relaxation has been described by an exponential decay function: \( p_v(t) = p_{v0}e^{-\frac{t}{\tau}} \), where \( \tau \) is the isovolumic relaxation time constant and \( p_{v0} \) is the left ventricular pressure at peak \( -dp/dt \). The rate of pressure decline for such a function \( (dp_v/dt) \) is given by \( -p_{v0}e^{-t/\tau} = -p_v(t)/\tau \). At the time of mitral valve opening, \( p_v(t) \) is equal to left atrial pressure \( (p_{a0}) \); therefore, the initial rate of growth of the atrioventricular pressure difference is given by \( p_{a0}/\tau \). Thus, the magnitude of the initial impulse given to the blood within the mitral valve is inversely related to \( \tau \) and directly related to initial atrial pressure (see Figure 5).

Physiological basis of mitral iner-
tance. The second physical determinant of mitral velocity acceleration, the mitral iner-
tance, has not been defined in vivo, but in vitro experiments have shown it to be on the order of twice the valve diameter.\(^{54}\) Thus, a stenotic valve will have a small iner-
tance and the velocity will track

Figure 4. Schematic diagram demonstrating how atrial and ventricular chamber stiffness leads to a predictable fall in the pressure difference and hence to velocity deceleration. Panel A shows the time course of chamber pressure and mitral velocity for flow through a 2-cm\(^2\) mitral orifice connecting atrium and ventricle with chamber stiffness of 0.1 and 0.2 mm Hg/cm\(^2\), respectively. Panel B shows an expanded view around the time when mitral velocity is 100 cm/sec (corresponding to a pressure difference of 4 mm Hg). In the shaded 10 msec, about 2 cm\(^3\) cross the mitral valve, lowering atrial pressure by 0.2 mm Hg and raising ventricular pressure by 0.4 mm Hg for a net fall in the gradient to 3.4 mm Hg, which (by the simplified Bernoulli equation) will only support a velocity of 92 cm/sec, leading to a deceleration rate of approximately 800 cm/sec\(^2\). Deceleration rate is directly proportional to the effective mitral area and to the net atrioventricular chamber stiffness, here 0.3 mm Hg/cm\(^3\) (400 dyne/cm\(^2\) in metric units). In this simulation, inertial effects are ignored.
Deceleration

As noted above, the deceleration rate is approximately proportional to the product of effective mitral valve area and net atrioventricular stiffness. The effective valve area is related to the anatomic area in a fairly straightforward way by the coefficient of discharge, typically between 0.6 and 0.9. The physiological basis for net chamber stiffness is more complex. It combines the pressure–volume curve for each chamber along with the instantaneous location on the curve where the chamber is operating. For the ventricle, there is the added complication of active relaxation that may be incomplete at the time of interest.

Mathematical descriptions of atrial and ventricular pressure–volume relations. The ventricular pressure–volume curves in Figure 2 are exponential in shape; similar curves were used to model the atrium and pulmonary veins. Since chamber stiffness is equal to the slope of these curves, stiffness rises with chamber pressure and volume. It was observed above that mitral velocity deceleration is more rapid for high stiffness situations. It is clear from Figure 2 that this may arise either from a material change in the pressure–volume curve (steepening the curve at all pressures, a true change in the diastolic properties of the ventricle, Figure 2E) or from a shift to higher volumes and thus to steeper portions of the same curve (as might result from systolic dysfunction leading to a higher end-systolic ventricular volume, Figure 2G). A number of differently shaped curves have been proposed to model the ventricular pressure–volume relation including simple exponential,\textsuperscript{62} polynomial,\textsuperscript{63,64} power-law,\textsuperscript{65} logarithmic,\textsuperscript{66} and shifted-exponential\textsuperscript{67} functions. These curves differ in their global shape but within the region of physiological interest they are all similar, being concave upward, causing stiffness to increase with volume.

During the course of diastolic filling, the atrium becomes smaller in volume, thus moving to a flatter, more compliant portion of its pressure–volume curve. By contrast, the ventricle (ignoring for the moment active relaxation) becomes less compliant with filling. These are opposite trends and thus must at least partially cancel each other. As noted above, it is the net stiffness that determines the slope of the velocity decay; when constant, this leads to a linear velocity decay.

Dynamic change in ventricular compliance. The additional factor of active ventricular relaxation complicates the situation somewhat. There are two features of relaxation that must be considered. First is the simple fall in ventricular pressure, shown to be approximately exponential during isovolumic relaxation.\textsuperscript{60} The second aspect of relaxation is a dynamic shift in stiffness from the very steep slope at the end of systole to the much flatter diastolic curve. It has been shown in papillary muscles\textsuperscript{68} and isolated ventricles\textsuperscript{69} that stiffness is proportional to pressure throughout the cardiac cycle. Alternatively, this dynamic stiffness has been modeled as a sum of active and passive processes to yield the measured left ventricular pressure, with stiffness derived from the instantaneous slope of this curve.\textsuperscript{70} The two models are not mutually exclusive, and the consequence is that as the ventricle fills, it moves to steeper portions of progressively flatter pressure–volume curves, two trends that partially offset each other. Figure 6 shows how these factors interact; graphs in panels A–D display left ventricular pressure at four points in time where we see three versions of the course of ventricular pressure. The lower arrow in each graph shows the fall in pressure if only active relaxation were occurring (i.e., as if the ventricle were suddenly held isovolumic). The upper arrow shows the pressure change if mitral flow continued but active relaxation stopped abruptly (i.e., the filling proceeds along the current ventricular pressure–volume curve). In between is the net result of these two processes. The overall effect of relaxation on the descending phase of the E wave is complex: When $\tau$ is very short, relaxation is essentially complete by the time of the peak of the E wave and small changes in $\tau$ have little effect on deceleration; on the other hand, if $\tau$ is significantly longer, the relaxation remains an impor-
D W

\[ \text{Determinants of the Mitral A Wave} \]

\[ \text{Physical determinants.} \] The physical determinants of the A wave are essentially the same as those for the E wave: Velocity acceleration is determined by the growing atrioventricular pressure difference with atrial contraction (modified by the mass of blood within the mitral apparatus), whereas deceleration reflects equilibration of this gradient resulting from either the transfer of blood from atrium to ventricle or the end of atrial contraction.

\[ \text{Physiological determinants.} \] The physiology of atrial contraction, however, is considerably more complex than the passive phase of ventricular filling, and atrial function has been studied much less extensively than the ventricular. A few observations may be made, however. It has been shown that the strength of atrial contraction, like the ventricle, is a direct function of preload\(^5\) and that atrial emptying is limited by the afterload against which it ejects. Thus, a high left atrial pressure at the time of atrial contraction (resulting, for example, from delayed relaxation in the
ventricle, tachycardia, or first-degree atrioventricular block) would cause a larger A wave; however, if the ventricle is extremely stiff (e.g., constrictive pericarditis), little atrial volume will be transported across the mitral valve regardless of the strength of contraction (especially since there is a more favorable egress available through the pulmonary veins) and the A wave will be blunted. A final critical issue is the systolic performance of the atrium per se. It has been shown that after cardioversion from atrial fibrillation, atrial mechanical function may take several weeks to return to normal. In the wide spectrum of disease encountered in evaluating ventricular diastolic function, atrial mechanical function likely ranges from severely depressed to hyperdynamic. Although atrial systolic function is difficult to measure and is rarely considered in interpreting mitral velocity patterns, it is likely the most important determinant of the magnitude of the A wave. The recording of pulmonary venous velocity by transesophageal echocardiography has recently been described. It may be that analysis of the reversal of velocity with atrial systole may help assess intrinsic atrial function.

It is worth noting that several previous investigators have included atrial systole in their mathematical models of ventricular filling. Lau and Sagawa provided a detailed analysis of the effect of right atrial systolic function and systemic venous impedance on right ventricular filling. Yellin and colleagues have studied the impact of atrioventricular conduction interval and analyzed these with lumped parameter and distributed models. Beyar and Sideman have used descriptions of fiber contractility and orientation to predict atrial function.

**Characteristics of Mitral Velocity Patterns**

A great number of studies have examined mitral velocity patterns in a wide variety of physiological and pathological conditions. Overall, two very distinct patterns have been described for situations with ventricular diastolic dysfunction.

**Pattern of Delayed Relaxation**

The first pattern (Figure 1B) is characterized by a prolonged IVRT, slowed acceleration and deceleration, low peak velocity, and a low E/A ratio regarding both the peak velocity and the VTI. Such a pattern has been described in normal aging, hypertrophic cardiomyopathy, secondary hypertrophy, myocardial infarction, acute ischemia resulting from increased myocardial oxygen demand and transient coronary occlusion. Unfortunately, while group means of the Doppler indexes differed from normal in these studies, there was a great deal of overlap so that the patterns were less predictable in individual patients.

**Pattern of Increased Stiffness**

The second general pattern (Figure 1C) is quite opposite from the first with a shortened IVRT, increased peak E velocity with rapid acceleration and deceleration, and a small A wave leading to an increase in the E/A ratio. This pattern has been reported in patients with heart transplant rejection, in constrictive and restrictive processes, and in acute severe aortic regurgitation. It has been suggested that patients may shift from pattern 1 to pattern 2 as the severity of amyloid cardiomyopathy progresses.

**Mechanisms of Abnormal Filling Patterns**

Examination of Figure 2 discloses some possible mechanisms for these two patterns of mitral filling. The delayed E wave with blunted acceleration and deceleration of pattern 1 could result from either prolonged or low atrial pressure, findings confirmed in animal and clinical experiments. An increased A wave in this setting would be most consistent with delayed relaxation, causing atrial pressure to be elevated at the time of atrial contraction, although the possibility of hyperdynamic atrial systolic function must also be considered.

The second Doppler pattern (short IVRT; tall, narrow E wave; and small A wave) would be seen if low ventricular compliance were accompanied by a compensatory rise in atrial pressure in an effort to preserve ventricular filling. The very steep deceleration indicates that net chamber (most likely ventricular) stiffness is high because of a primary change in the diastolic property of the ventricle or from systolic dysfunction causing the ventricle to fill along a steep portion of its pressure–volume curve. Note, however, that in Figures 2F and 2H, low ventricular compliance by itself should be associated with a lower than normal peak E wave velocity. An elevated E wave in the presence of reduced compliance can only be explained by atrial hypertension, an observation recently described clinically and theoretically. A low A wave in the presence of elevated atrial pressure indicates either a very high afterload (stiff ventricle) or atrial systolic dysfunction.

**Discussion**

Figure 7 summarizes the physical and physiological determinants of the Doppler E wave. The plus and minus signs indicate whether there is a direct positive or inverse negative relation between the determinant and the factor immediately to its left. Thus, acceleration rate varies directly with Δp/dt and inversely with mitral inerterance, whereas Δp/dt varies directly with atrial pressure and inversely with . Deceleration is increased directly by mitral valve area and net chamber stiffness. Net stiffness is the sum of atrial and ventricular stiffness and as shown is determined by a large number of physiological factors, including the material properties of the myocardium and ventricular systolic function. The effect of on deceleration is complex. If relaxation is incomplete (i.e., ventricular relaxation stops prematurely), then left ventricular stiffness during the descending phase of the E wave will be elevated and deceleration will be increased. By contrast, if relaxation is merely delayed
**Figure 7. Schematic diagram of the physical and physiological determinants of E wave acceleration and deceleration.** The plus and minus signs indicate whether the given factor is directly (+) or inversely (−) related to the item immediately to its left. dΔP/dt, Rate of growth of atrioventricular pressure difference at mitral valve (MV) opening; τ, relaxation time constant; LA V₁ (LV V₁), left atrial (ventricular) volume constants, the volume of blood necessary to raise the pressure in the chamber by a factor of e, 2.71828. Instantaneous chamber stiffness is given by chamber pressure divided by this number. LV ESV, left ventricular end-systolic volume.

(by still ongoing), then stiffness will decrease during this time and deceleration will be slower. The determinants of the A wave are incompletely understood, but in general the A wave will be increased by high left atrial pressure and decreased by a stiff ventricle, with atrial systolic function playing an important but poorly characterized role.

**Inferences From Clinical Doppler Patterns**

Despite the many factors influencing ventricular filling, there are several patterns that point to specific kinds of diastolic dysfunction. A pattern like Figure 1B, with a low, delayed E wave and an accentuated A wave, is generally indicative of delayed relaxation provided that left atrial pressure is normal or increased. Atrial pressure may be available on patients in the intensive care unit; even without direct measurement, whether this pressure is high or low can often be estimated based on the patient’s physical signs or symptoms.

The other major pattern of abnormal filling (Figure 1C) has a very tall, brief E wave and a blunted A wave. This seems to be characterized by the combination of reduced ventricular compliance with elevated left atrial pressure. Such an interpretation could likely be made with more confidence if a large velocity reversal were seen in the pulmonary veins at the time of atrial contraction.

The pattern in Figure 1A is most often associated with normal diastolic function. Unfortunately, however, it does not rule out significant diastolic dysfunction. Note that if a continuum were drawn between the patterns in Figures 1B and 1C, the curve in Figure 1A would lie approximately in the middle. It is therefore possible to see this pattern in situations of reduced compliance or delayed relaxation with mildly elevated atrial pressure. Certainly the details of the curve shape would differ and careful analysis of the filling pattern along with ancillary data (such as the IVRT<sub>90</sub>) may distinguish normal from abnormal function even for a curve like the one in Figure 1A.

**Conclusions**

The pattern of left ventricular filling contains a tremendous amount of physiological information, and Doppler echocardiography, with high temporal, spatial, and velocity resolution, seems the optimal modality for assessing this filling. With current analytical approaches, important clinical observations concerning ventricular diastolic function can be made about a number of Doppler filling patterns. However, it must be remembered that diastolic filling is not equivalent to diastolic function: The mitral valve and left atrium play important roles that are not yet completely characterized in determining transmitral flow. This complex interplay of factors suggests that more sophisticated analysis of Doppler filling patterns is needed to uniquely determine the important physiological aspects of ventricular diastolic function. It is clear, however, that a great deal of fundamental research remains to be done to achieve this goal, in particular to understand how the various physiological parameters of diastolic function affect each other and to better assess left atrial function. An improved understanding of the physical and physiological basis for Doppler filling curves should allow a more intelligent interpretation and an improvement in the noninvasive assessment of ventricular diastolic function.

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**KEY WORDS** • compliance • relaxation • mathematical modeling • mitral valves
Echocardiographic Doppler evaluation of left ventricular diastolic function. Physics and physiology.
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Circulation. 1991;84:977-990
doi: 10.1161/01.CIR.84.3.977
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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