Disorders of Cardiac Diastolic Function

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Introduction

Attention has traditionally been focused on the systolic or contractile function of the heart. However, it has become increasingly apparent that abnormalities of cardiac diastolic function play a critical role in a variety of clinical conditions.

The goals of this discussion are (1) to review the mechanical description of diastolic phenomena, (2) to examine the physiologic and biochemical factors which play a role in relaxation, (3) to relate this basic knowledge to common clinical conditions, and (4) to examine approaches to the diagnosis and management of patients with abnormalities of cardiac diastolic function.

Historical Perspectives

In order to understand the evolution of our present concepts of diastolic function, it is important to consider the efforts of a number of key individuals, both physicists and physicians.

One of the first people to investigate the strength and resistance of materials to stress was Galileo (1). In 1638 he described aspects of the strength of materials in his Dialogues Concerning the Two New Sciences. The exact nature of the relationship between force and displacement was first described by Robert Hooke in 1678 when he noted "Ut tensio sic vis" or that "The power of any spring is in the same proportion with the Tension thereof." In other words, for what has been described as "Hookian" materials, the force exerted by a material is proportional to the degree of extension.

The next major development in the study of the response of materials to deformation was made by the famous physicist, physician, and Egyptologist, Thomas Young. In addition to caring for patients and deciphering the Rosetta Stone, Young defined the effects of a force against a material in terms of a linear relation between the force per unit area (or stress) and the extension per unit length (or strain).

The interest of physicians in diastole and cardiac relaxation also has a long and interesting history. In fact, it was Galen (2) who first suggested that the active dilitation of the right ventricle might contribute to the transfer of blood from the vena cava to the heart. Roughly 1500 years later, Harvey, in de Mortu Cordis, suggested that most of ventricular filling occurred during atrial systole and that active diastolic suction was not responsible for ventricular filling. Subsequently, Frank reached the opposite conclusion, i.e. that most filling occurred early in diastole. Henderson was the first to divide diastole into three periods: a period of early rapid filling, a period of little change, and atrial systole. Subsequently, Wiggers and Katz then established that the extent of filling occurring during atrial systole varied depending upon the strength and timing of atrial contraction.

Interestingly, application of this knowledge regarding diastolic function to the clinical arena has been slow. This may in part be related to two factors. First, as noted in the introduction, there has been an emphasis in cardiology in characterizing cardiac performance in terms of pumping efficiency and systolic function. In fact, the initial description of blood flow by Harvey emphasized the pulsatile nature of blood flow and the analysis of systolic events. More recently, when Frank and Starling analyzed cardiac function, they also tended to emphasize the nature of the systolic performance of the heart (3). Subsequently, the development of cardiac catheterization again emphasized the measurement of pressures and placed an emphasis on systolic function (4).

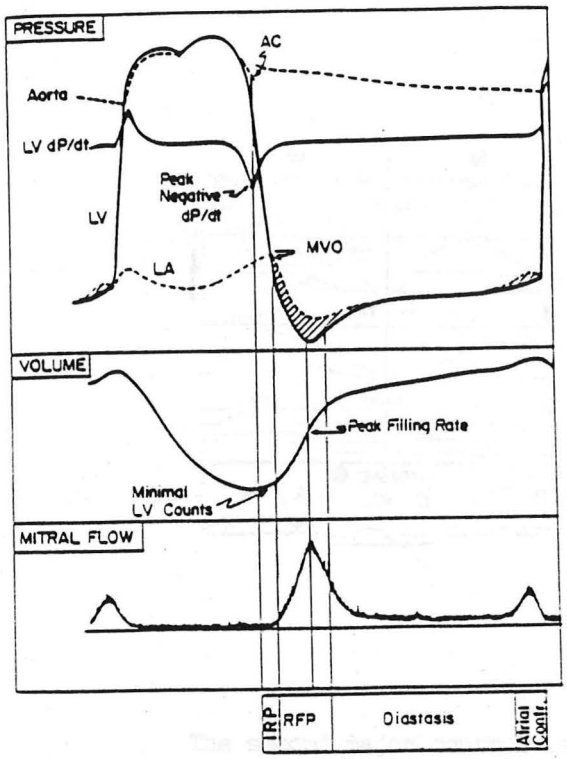
Second, as will be presented, the accurate measurement of changes in cardiac volume are important in the understanding of diastolic phenomena. It is only relatively recently that convenient, reliable methods have been developed for the measurement of cardiac volume and flows.

With the recognition of the importance of diastole and the development of appropriate tools there has been a gradual but substantial increase in our knowledge of diastolic properties of the heart (5) which will be the subject of this review.

Basic Considerations

A variety of approaches have been used in the discussion of diastolic function. The choice of an approach has been frequently dominated by the particular technique used to assess diastolic function and the model under evaluation. In the discussion to follow I have chosen to take a sequential approach: that is, to march sequentially through the events of diastole because that is the manner in which I believe we generally approach it as clinicians. Hence, the discussion will be broadly divided into mechanisms involved during early diastole during rapid filling and mechanisms involved in the latter portion of diastole (6).

It is first relevant to examine the mechanical events which occur durir diastole. As shown in Figure 1A, diastole is classically defined as beginn at the time of the closure of the aortic valve and ending with the beginning of systole and closure of the mitral valve. Hence, in essence the duration of diastole is classically defined in terms of systolic events. Diastole is then typically divided into four phases: the isovolumic relaxationperiod, the rapid filling period, diastasis and atrial systole. During isovolumic relaxation the aortic and mitral valves are closed and there is little change in ventricular volume. However, pressure rapidly falls until it is below left atrial pressure at which point the mitral valve opens and filling of the ventricle begins.



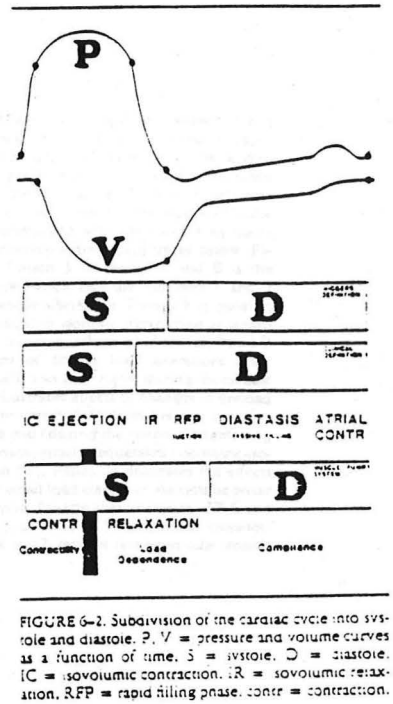


FIGURE 6-2. Subdivision of the cardiac cycle into systole and diastole. P, V = pressure and volume curves as a function of time. S = systole. D = diastole. IC = isovolumic contraction. IR = isovolumic relaxation. RFP = rapid filling phase. contr = contraction.

Figure 1

Now from a mechanistic viewpoint three events occur during diastole: active myocardial relaxation, passive filling related to myocardial distensibilty, and atrial contraction. Unfortunately, there is not a one-to-one correlation between the clinically defined mechanical events and the mechanisms involved. This discrepancy has lead some authors (7) to suggest that the diastolic intervals be redefined to reflect the underlying mechanisms (Figure 1B).

Early diastolic filling

Myocardial relaxation is determined by three major factors: (1) the load on the heart muscle, (2) inactivation, and (3) the nonuniform distribution of load and inactivation in space and time (7,9). It is important to consider each of these factors in some detail.

The idea of load dependence has been derived from experiments in isolated cardiac muscle. If one alters the load (preload or afterload) on muscle during the first two-thirds of contraction, there is change in relaxation (Figure 2). As the preload or afterload is raised, the onset of relaxation is delayed (8). If, however, the load is applied in the final third of contraction or during relaxation, the duration of relaxation is markedly shortened. Hence, there is transition zone approximately two-thirds of the way through systole at which the loading response dramatically changes; it has been suggested that this transition zone plays a major role in the control of diastolic performance in the intact heart.

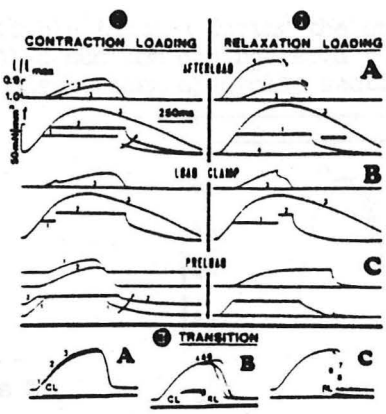


FIGURE 6-1. Effects of changes in contraction and relaxation loading on relaxation in isolated cat papillary muscle. This figure shows some of the experiments that have given us insight into load dependence of relaxation in cardiac muscle [7]. In all panels, several twitches obtained in isolated cat papillary muscle have been superimposed with the shortening traces above and the corresponding force traces below. Panels I and II. Twitch 3 in panels A and B is the isometric control twitch and the numbers 1 and 2 refer to comparable afterloads. Twitch 4 in panel A (right) is a freeloaded isotonic contraction at length lmax. Panel A illustrates effects of afterload. Panel B illustrates effects of abrupt load alterations (load clamps) early (left) and late (right) during the cardiac cycle. Panel C illustrates effects of changes in preload either before the twitch (left, from preload 1 to preload 2) or at the end (during the isotonic lengthening phase) of a physiologically sequenced (isometric-isotonic) relaxation [8]. Panel III illustrates the effects on relaxation of small load clamps in the systolic phase of the cardiac cycle. Muscle characteristics (29° C and 12/min): length at lmax, 7.5 mm; mean cross-sectional area, 0.84 mm2; ratio of resting to total tension at lmax, 8.%.

Figure 2

The second major control is via inactivation. Fundamentally, relaxation is governed by the processes that lead to the detachment of cross-bridges. Hence, the sensitivity of relaxation to loading conditions is diminished when the reuptake of cytosolic calcium is decreased (9,10). However, it appears that at low concentrations of myoplasmic calcium the effects of load predominate over the effects of the altered calcium concentration. As discussed below, the removal of intracellular calcium is an energy dependent process. In addition, the sensitivity of the myofibrills to the calcium concentration can be altered by intracellular acidosis.

The third factor in the control of relaxation relates to the nonuniformity of the loading of individual cells. The general analysis of loading and inactivation effects has been done in isolated muscle preparations. Clearly, in the intact heart there are differences in the sequence of contraction which lead to varying load dependence. This is potentially even of more importance in the setting of ischemia and infarction.

Now, when one attempts to apply these ideas to relaxation in the intact heart, the situation becomes more complex. If one first considers the effects of loading, these can again be divided into those occurring during the first two thirds of contraction and those occurring late in contraction and during relaxation.

First, with increases in volume or pressure loading early in the first two-thirds of systole there a prolongation in isovolumic pressure decline indicating slower relaxation (11,12,13). Again, this is analogous to the effects of increased preload and afterload in isolated muscle. Second, multiple factors alter the loading of the left ventricle late in systole and into diastole. These factors include deformation during contraction, impedance alterations in the vasculature late in ejection, filling of the coronary reservoir during isovolumic relaxation, and the Laplace relationship after mitral valve opening (9). The effect of the timing of loading on relaxation in the intact heart is shown in Figure 3. It is this loading due

to multiple factors during the end of systole that leads to the phenomenon of diastolic suction during rapid filling. If relaxation is made load independent, then diastolic suction does not occur (9).

Figure 3

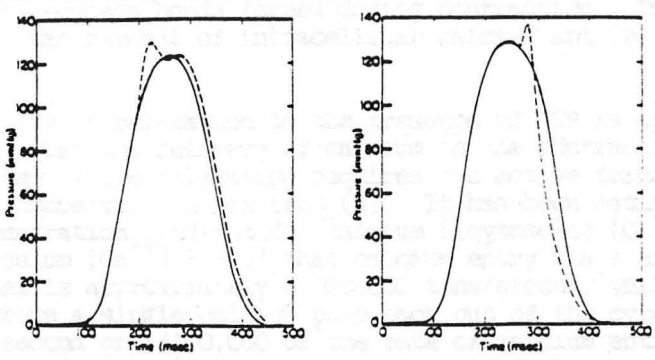


FIGURE 7-8. The effect of an abrupt volume increment on the time course of left ventricular pressure. The solid lines are control isovolumic beats, and the broken lines are intervention (quick-stretch) beats. In the panel on the left, the volume increment is given early in the contraction; in the panel on the right, the volume increment is given late in the contraction. In both experiments, 6 ml of warm blood were infused within 15 msec. The early volume infusion caused an abrupt increase in pressure, followed by a steep decline, and then a plateau before pressure begins to drop toward the diastolic level. The onset of pressure decline was 12 msec later in the early intervention experiment. By comparison, the same volume increment given in late systole produces a quite different result. Here the pressure decline is earlier and much more rapid; peak negative dP/dt increased from 1742 mmHg/sec in the control beat to 3005 mm Hg/sec in the intervention beat.

The fact that the response to loading varies depending upon the time during contraction at which it is applied means that relatively minor shifts in the timing of loading can lead to significant effects on relaxation. Shifts of loading from late to early in ejection will delay relaxation while shifts from late to early ejection will tend to speed relaxation. This type of change in loading can be induced by changes in arterial impedance due to drugs or alterations in vascular tone, by alterations in contractility, and by changes in the nonuniformity of the distribution of the load (14).

Given the effects of systolic loading on relaxation, Brutsaert (9) (Figure 1) has suggested that from a conceptual point of view it may be useful to consider the rapid filling phase to be part of "systole" in the sense that it is an integral part of cardiac muscle relaxation. In this conceptual structure, systole consists of a contraction and a relaxation phase. The contraction phase consists of isovolumic contraction and the first half of ejection. The relaxation phase consists of the final portion of ejection, isovolumic relaxation, and the rapid filling phase and reflects the load dependence of this portion of classical diastole. True diastole would then consist of passive filling and atrial contraction. This approach, in a sense, divides the cardiac cycle into an active "systolic" phase involving the active aspects of both contraction and relaxation and a "diastolic" phase which is truly passive.

Active Relaxation

Fundamentally, the ability of the heart to relax is dependent on the release of the actin-myosin bonds formed during contraction. This release is dependent upon (1) the removal of intracellular calcium and (2) the presence of ATP.

The sensitivity of relaxation to the presence of ATP is apparent if one considers the fact that the delivery of calcium to the contractile mechanism is a passive process, while relaxation requires the active transport of calcium against a concentration gradient (4). It has been estimated on the basis of the concentration gradient for calcium [(cytosolic [Ca^{++}] = 0.1 μM, sarcoplasmic reticulum [Ca^{++}] = mM)] that calcium entry via a single sarcolemmal channel is approximately 3,000,000 ions/second, while the ATP dependent flux across a single calcium pump back out of the cytosol is on the order of 30 ions/second or 1/100,000 of the rate of calcium entry. As shown in Figure 4, this difference in speed is compensated for, to a degree, by increasing the number of pump sites in the sarcoplasmic reticulum. However, by depending upon this large number pumps to relax the tissue, the relaxation mechanism becomes energy dependent. It is this difference in the ability to move calcium that appears to make the active relaxation of the myocardium vulnerable to small changes in ATP concentration. Smith (4) has suggested that the fact that a small decrease in ATP concentration impairs active relaxation suggests that ATP may play an allosteric role in stimulating the calcium pump. With more severe falls in ATP to levels below that required to maintain the transport of calcium, one would then have contracture.

TABLE 1. *Balances between Ca^{2+} fluxes during activation and relaxation in the myocardium*

A. Surface areas of membranes in the myocardium (16) ($\mu m^2/\mu m^3$)	
Sarcolemma + t tubules (SL)	~0.3
Sarcoplasmic reticulum (SR)	~1.2
B. Densities of Ca^{2+} channels and Ca^{2+}-pump sites (sites/μm^2)	
Ca^{2+} channels in the cardiac SL (17,18)	1–5
Ca^{2+}-pump proteins in cardiac SR (11,19)	6,000
C. Number of sites/μm^3 [A × B]	
Sarcolemma + t tubules	~1
Sarcoplasmic reticulum	~7,000
D. Rates of Ca^{2+} fluxes involved in activation and relaxation (ions/sec)	
Activation (flux through a Ca^{2+} channel) (14)	~3,000,000
Relaxation (flux by a Ca^{2+}-pump site) (15)	~30
E. "Ca^{2+} flux reserve capacity" (ions/sec · μm^3) [C × D]	
Activation	~3,000,000
Relaxation	~210,000

Figure 4

Other factors may significantly modify active relaxation. Clearly, increased sympathetic tone leads to more rapid relaxation and it is a major factor in the time course of relaxation. This mechanism appears to play an important role in allowing the heart to fill with increasing heart rate. In addition, there is the suggestion that rates of relaxation may be altered with changes in myosin isoforms.

It also appears that acidosis may alter the effect of ischemia on diastolic function. Recently, Grossman, Ingwall and colleagues (15) have compared the effect of myocardial ischemia due to increased oxygen demand in the presence of significant coronary stenosis with ischemia of comparable duration due to total coronary occlusion. They found that diastolic dysfunction was prominent in the setting of ischemia caused by increased oxygen demand but was minimal during ischemia due to total coronary occlusion. They found no significant change in ATP concentration in either group over the period of ischemia. They concluded that the protection against diastolic dysfunction in the setting of total occlusion may reflect the effects of hydrogen ion accumulation, loss of coronary vascular turgor, and repeated systolic stretch (15).

Additional studies by the same group (16) suggest that the rapid development of intracellular acidosis in the setting of total occlusion decreases myofibrillar calcium sensitivity leading to a decrease in calcium activated diastolic tension.

Another interesting observation has been made by Bittl and Ingwall (17) (Figure 4). They examined the flux through the creatine kinase reaction by means of phosphorus-31 NMR saturation transfer. In this method one can take advantage of the fact that exchange of the gamma phosphate of ATP with phosphocreatine occurs rapidly on the NMR time scale. Hence, the NMR method allows one to measure the unidirectional flux between phosphocreatine and ATP. Using this technique they found that there was a linear relationship between flux and the degree of stretching. Hence, the turnover of ATP increases in the setting of increased distension.

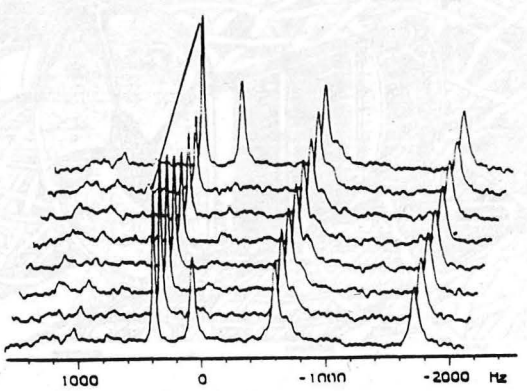
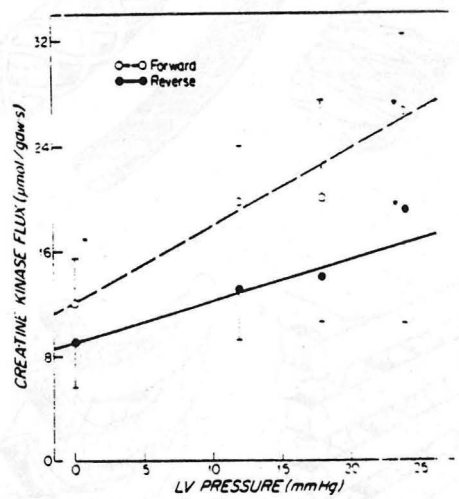


Figure 5



*Creatine kinase flux. The product of the forward or reverse rate constant and the intracellular content of either CrP or [γ-P]ATP, respectively, yielded the value for chemical flux for the creatine kinase reaction at four levels of left ventricular pressure. * $P < 0.05$ indicates the first value for chemical flux that demonstrates a difference from baseline. The slopes for the two linear regressions are statistically different ($P < 0.05$).*

In man, the studies of the biochemical correlates of diastolic function have been limited. Bashore (18) examined the correlation between a number of indices of systolic and diastolic function and measurements of ATP from left ventricular biopsy specimens obtained at the time of pressure-volume studies. They found weak linear correlation between the adenosine triphosphate to protein ratio to peak negative dP/dt (r=-0.74) and peak filling rate (r=0.76).

Diastolic Suction

As was briefly mentioned in the introduction, there has been considerable controversy as to whether the phenomenon of "diastolic suction" occurs during rapid filling. The details of cardiac structure are beyond the goals of this discussion. However, it is evident that there are aspects of the organization of the heart which allow it to store energy during contraction that is then used to aid in relaxation. This idea of storing energy is termed "elastic recoil" and is comparable to the energy stored in a spring when it is compressed to less than its resting length. Connective tissue in the heart forms a weave of struts which tether muscle cells together (19,20). Strands twisted around each cell similar to a hammock (Figure 6) appear to act to prevent overstretching along one diagonal during filling and to prevent over contraction along the other diagonal during contraction. This stretching would store energy tending to reextend the muscle. Similarly, there are struts of connective tissue that tether the individual cells together again forming a hammock like network that can be use to store energy during contraction. Interestingly, hearts in amphibians do not have this connective tissue web and do not have as active ventricular filling as mammalian hearts.

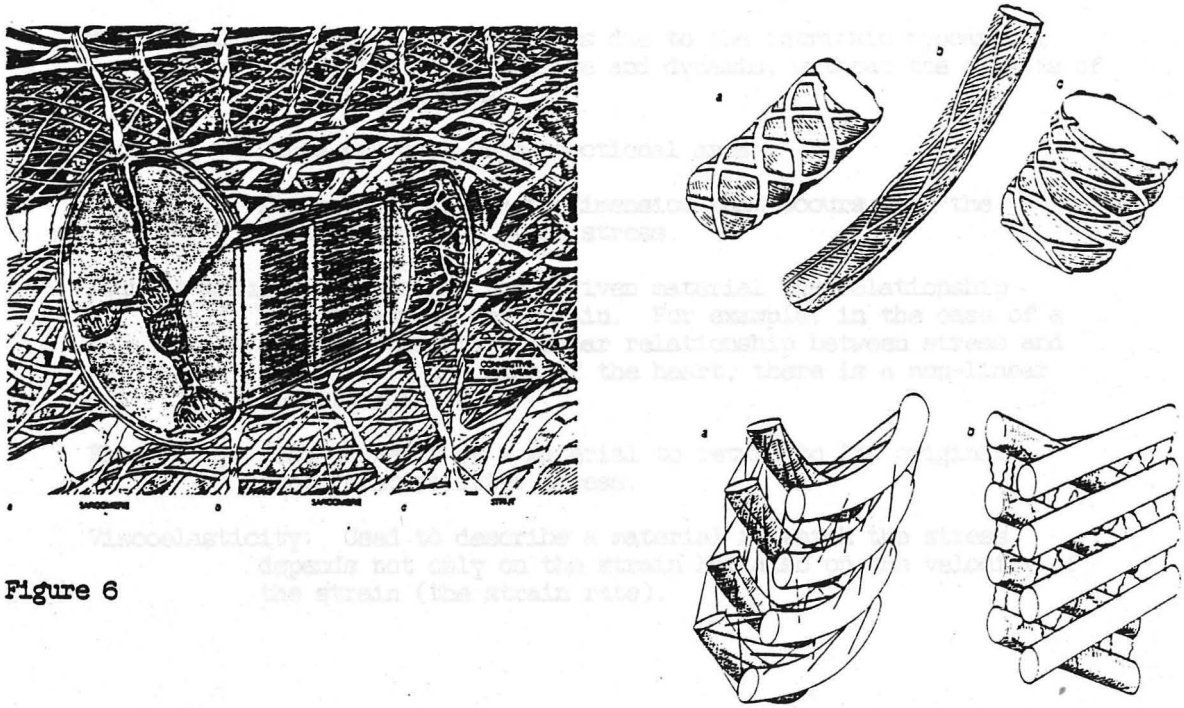


Figure 6

Mid-to-late diastole

With the end of active relaxation and rapid filling, one can then turn to the evaluation of passive physical properties of the relaxed myocardium. Clearly, slowing of active relaxation can influence measurement of the passive physical properties of the ventricle.

A wide variety of terms have been used in the description of the diastolic properties of the heart. Hence, it is important to use a common set of terms (21,22,23,24) to minimize confusion:

Distensibility: The change in volume with a change in pressure. Mathematically, this is written as dV/dP. This is also referred to by some authors as compliance: A much used and much abused term. A dangerous term in that it is dependent on the volume of the chamber and hence should not be used to compare the distensibility of two hearts that are at widely different volumes.

Stiffness: The change in pressure with a change in volume or dP/dV. This is the reciprocal of distensibility or compliance.

Left ventricular chamber stiffness: The stiffness of the entire left ventricle as it interacts with surrounding structures. Hence, it is altered by physical properties of the left ventricular myocardium, intrinsic dynamic factors in the myocardium, and factors extrinsic to the left ventricle, including the pericardium and right ventricle.

Myocardial stiffness: The stiffness due to the intrinsic myocardial properties, both passive and dynamic, without the effects of extrinsic factors.

Stress: Force per unit cross sectional area.

Strain: The percent change in dimension that occurs with the application of a given stress.

Young's modulus: Describes for a given material the relationship between stress and strain. For example, in the case of a spring, there is a linear relationship between stress and strain. In the case of the heart, there is a non-linear relationship.

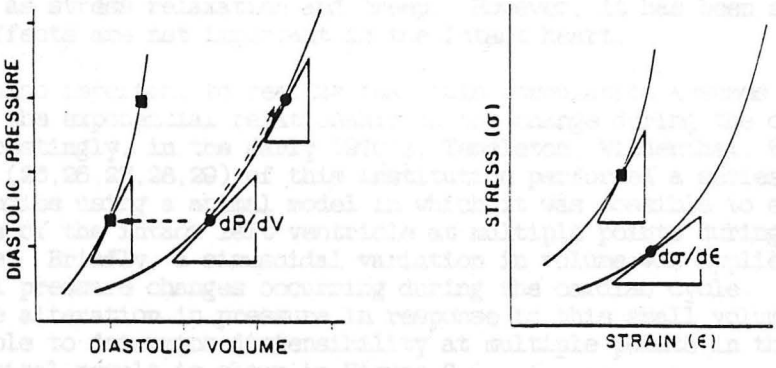
Elasticity: The property of a material to return to its original configuration after stress.

Viscoelasticity: Used to describe a material in which the stress depends not only on the strain but also on the velocity of the strain (the strain rate).

Left ventricular chamber stiffness is determined by examining the change in pressure associated with a given change in volume via a pressure-volume curve. This point is illustrated in Figure 7. Note that because of the curvilinear nature of the relation between diastolic pressure and volume, the rate of change, dP/dV, varies with volume. Now if there is an exponential relationship between pressure and volume, then the change of dP/dV with pressure can be expressed in terms of a single exponential constant which is termed the chamber stiffness constant. If one examines this relationship in different ventricles, one finds different curves describing the left ventricular chamber stiffness (and its reciprocal, the left ventricular chamber distensibility or compliance).

To obtain a measure of the stiffness of the myocardial wall one need to examine the stress-strain relationship. Here the stress is calculated by converting the pressure to force per unit area and strain is calculated from the volume on the basis of known aspects of the geometry. (For a more detailed discussion of these points the reader is refered to references 1,21, and 22). Again we find that the relationship is non-linear and can be well described with an exponential constant which is termed the elastic stiffness or myocardial stiffness constant. The use of terms stress, strain, and elastic stiffness allow for comparison of the stiffness and elasticity of structures of different sizes and shapes.

Figure 7



Now given that one can describe the stiffness of the left ventricular chamber in terms the stiffness constant, it is important to note that two changes can take place. First, there can be a change in the slope of the curve as discussed, but second, there can also be a displacement or movement of the entire curve with or without a change in slope (Figure 7). Hence, one can have the situation where there is displacement of the curve down but an increase in the slope (this type of response can occur in patients given nitroprusside). Therefore, simple reporting of the chamber stiffness constant alone is not adequate and displacement must also be noted.

The diastolic pressure volume relationship can be altered by a variety of factors both extrinsic and intrinsic to the heart. As noted by Grossman (6), changes in factor extrinsic to the left ventricle can lead to significant parallel shifts without changes in curvature. This behavior can be seen in constrictive pericarditis, pericardial tamponade, or in the setting of tumor in the pericardial space. Similarly, increases in right ventricular volume in the setting of a taut pericardium can lead to extrinsic compromise of left ventricular filling. This can be seen in the setting of acute right ventricular infarction.

An additional effect has been suggested related to coronary vascular turgor (the so-called erectile effect). The large amount of blood flow through the myocardium may play a role in wall stiffness, particularly when pressure and flow fall in the setting of coronary occlusion with poor collateral flow. This effect may explain, in part, the increase in distensibility that can occur in the setting of coronary occlusion.

In the absence of extrinsic factors, a variety of intrinsic factors may cause this measure of chamber stiffness to change. These include changes in the true passive elasticity of the wall, such as the thickness of the wall and its composition (i.e., proportion of muscle, fibrosis, or infiltrating process), in the setting of hypothermia, or changes in osmolality. In addition, changes in the myocardium related to residual cross-bridging can occur not only in early diastole as described above, but also be carried into mid and late systole.

It is important to note that this type of analysis assumes that the relationship between diastolic pressure and volume is exponential. Such an analysis ignores effects of viscous and inertial drag, and viscoelastic effects such as stress relaxation and creep. However, it has been suggested that these effects are not important in the intact heart.

It is also important to realize that this formulation assumes that the constants in the exponential relationship do not change during the cardiac cycle. Interestingly, in the early 1970's, Templeton, Wildenthal, Willerson, and Mitchell (25,26,27,28,29) of this institution performed a series of important studies using a animal model in which it was possible to evaluate the stiffness of the intact left ventricle at multiple points during the cardiac cycle. Briefly, a simusoidal variation in volume was applied on top of the normal pressure changes occurring during the cardiac cycle. By measuring the alteration in pressure in response to this small volume change it was possible to determine distensibility at multiple points in the cardiac cycle. A typical result is shown in Figure 8.

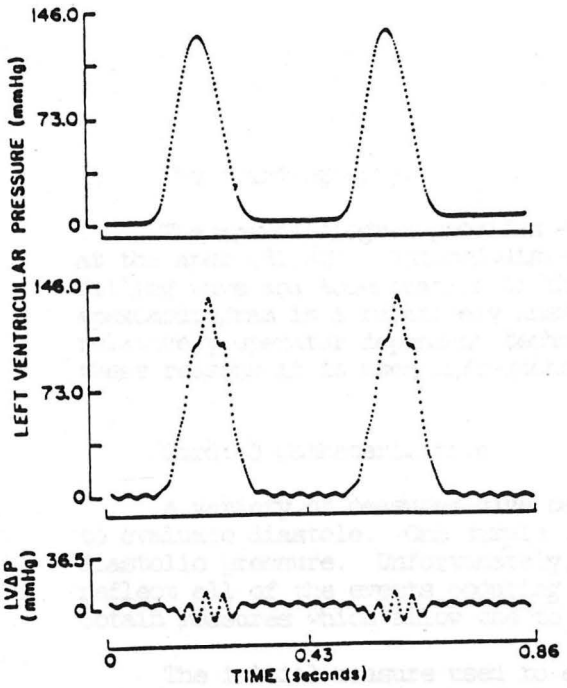


FIG. 33. Averaged ventricular pressure waveforms showing unperturbed ventricular pressure (*top*), perturbed ventricular pressure (*middle*), and the difference between them (*bottom*), which is the change in pressure due to the volume perturbations. [From Templeton et al. (150), with permission of the Authors and the Editor of *Cardiovascular Research*.]

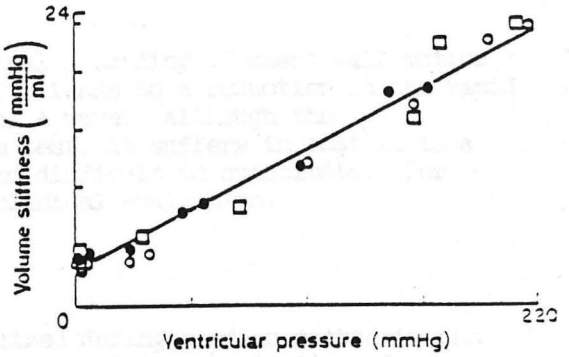


FIG. 34. Volume stiffness-pressure relations during control, ●, norepinephrine infusion, ○, and after an increase in ventricular volume, □. [From Templeton et al. (150), with permission of the Authors and the Editor of *Cardiovascular Research*.]

Figure 8

Clinical Assessments of Diastolic Function

A variety of invasive and non-invasive techniques have been utilized in an attempt to assess diastolic function in man (30). As discussed above, one is interested in a measure of the change in pressure associated with a change in volume at multiple points in time. Hence, it is desirable to measure all of these factors simultaneously. Unfortunately, this is generally difficult in that invasive pressure measurements are required. For this reason, these techniques have attempted to approach the problem from the standpoint of measuring only one of the pertinent variables, i.e., pressure or volume, with respect to time. Thus it is evident that fundamentally they all have significant limitations. In general, it is reasonable to expect volume derived indices to provide a better characterization of relaxation than pressure or interval derived measures (Brutsaert). However, it is possible to obtain some useful clinical information using these techniques. In particular, each of these methods have certain advantages and disadvantages for the clinician from the standpoint of patient risks, costs, and utility of the data obtained.

Phonocardiography

The apexcardiogram provides a graphical recording of chest wall motion at the apex (31,32). Reduced distensibility leads to a reduction in the rapid filling wave and accentuation of the apical A wave. Although the apexcardiogram is a relatively inexpensive test, it suffers in that it is a relatively operator dependent technique and difficult to quantitate. For these reasons it is used infrequently in clinical evaluation.

Cardiac Catheterization

A variety of measures have been utilized during cardiac cathterization to evaluate diastole. One simple measure is the left ventricular end diastolic pressure. Unfortunately, it provides only one point in time to reflect all of the events occuring during diastole. It would be desireable to obtain measures which allow one to separate early and late diastolic events.

The initial measure used to evaluate cardiac relaxation during cardiac catheterization has been the maximum rate of left ventricular pressure fall, or the peak negative dP/dt (33). This measure has significant limitations. First, it is extremely dependent on loading conditions, in particular the peak pressure; i.e., if the level of peak pressure in higher then the value of peak negative dP/dt will be higher. Hence, a rise in peak negative dP/dt could be due to an increase in the rate of relaxation of an increase in the peak pressure. However, if a change in pressure can be excluded, then this measure may be quite useful.

Because the rate of fall is dependent on the initial loading condition, subsequent studies have used an exponential rate constant to describe the rate of left ventricular pressure fall (34). The fall in pressure with respect to time can written in the form:

$$P(t) = P_o e^{-t/T} + P_B$$

where $P(t)$ = pressure at time t,

T or tau = the exponential time constant for the decay in pressure

P_o = the initial pressure

P_B = the pressure as t goes to infinity.

This formulation allows the pressure to decay to some resting value during long diastoles. Studies in animals and in man (35,36) have demonstrated that the fall in pressure is approximated remarkably well by the exponential function. (This finding may reflect the fact that the calcium uptake by the sarcoplasmic reticulum is an exponential process). Typical values for these variables are shown in Table I. It is important to realize that this time constant is shortened by catecholamines.

TABLE 20-4. *Evaluation of Left Ventricular Diastolic Performance: Normal Values for Some Indices of Relaxation and Filling*

	Normal Values	Reference
Peak $-dP/dt$	2660 ± 700 mmHg/sec	7
	2922 ± 730 mmHg/sec	67
	1864 ± 390 mmHg/sec	68
	1825 ± 261 mmHg/sec	69
T (logarithmic method, equation 7)	38 ± 7 msec	67
	33 ± 8 msec	68
	31 ± 3 msec	69
T (derivative method, equations 8 and 9)	55 ± 12 msec	69
P_a (derivative method, equations 8 and 9)	−25 ± 9 mmHg	69
PFR	3.3 ± 0.6 EDV/sec	63
Time to PFR	136 ± 23 msec	63
Peak $-dh/dt$ (posterior wall)	3.4 ± 3.0 cm/sec	64
	3.2 ± 3.7 cm/sec	66

Peak $-dP/dt$ = maximum rate of LV isovolumic pressure decline; T = time constant of LV isovolumic relaxation, calculated assuming both zero pressure intercept (equation 7) and variable pressure (P_a) intercept (equations 8 and 9); PFR = LV peak filling rate, from radionuclide ventriculography, normalized to end-diastolic volumes (EDV/sec; Peak $-dh/dt$ = maximum rate of posterior wall thinning, measured by echo.

Table I

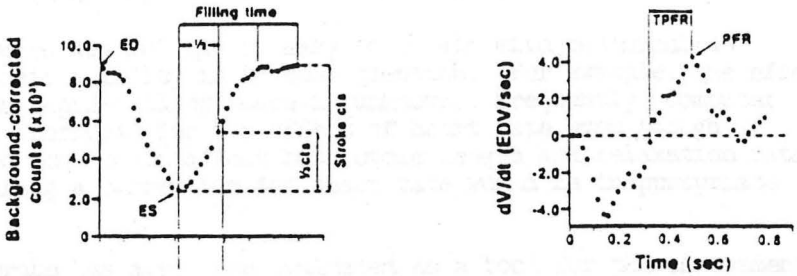
The complete pressure-volume loop, as previously discussed, provides the information really necessary to evaluate changes in distensibility. In the case of cardiac catheterization, the volume information has been obtained through ventriculography with the attendant injection of iodinated contrast material. Repeated measurements were complicated by the known effects of dye on relaxation (37,38). Recently, radionuclide ventriculography and echocardiography have been have been utilized in combination with invasive pressure measurements to obtain pressure-volume loops.

Using the pressure-volume loop one can look for displacements suggesting the presence of external factors influencing distensibility and changes in the slope suggesting changes in intrinsic factors. Examples of pressure volume loops in several conditions associated with abnormal left ventricular distensibility are shown in Figure 10.

Radionuclide Ventriculography

Radionuclide ventriculography (RVG) potentially provides a means of assessing volume changes during different portions of diastole (39,40,41,42,43). In radionuclide ventriculography the blood pool is tagged with a radiopharmaceutical and images are taken at multiple points in the cardiac cycle, generally every 30 to 50 milliseconds. The radioactive counts over a region of interest over the heart is then measured to obtain a blood pool radioactivity time curve (Figure 9).

Figure 9



Although this method is attractive from a theoretical standpoint it has a number of technical limitations. First,as pointed out by Bonow (41), the accurate determination of peak LV filling rate requires a higher temporal resolution than is typically used for the measurement of ejection fraction by radionuclide ventriculography. Framing rates of greater than 40 frames per second are typically required (<25 msec per image). Because of the short sampling time, the number of counts acquired with each cycle is small, meaning that many cycles need to be averaged to obtain adequate counts for each frame. The first derivative of this curve gives a measure of the rate of filling of the left ventricle (44) (Figure 9).

The low number of counts makes the data noisy. Hence, several methods have been suggested to smooth or fit the data to a defined curve. There is considerable difference of opinion in the nuclear cardiology literature with regard to the best method for performing this filtering. Of importance is the fact that the measures of diastolic function obtained are heavily dependent on the curve fitting or smoothing approach used, making it difficult to compare results from different investigators.

Second, since the approach is fundamentally dependent on the number of counts reaching the camera reflecting the number of counts in the ventricle, attenuation of counts can lead to errors in the determination of the rate of change. Third, because gated multiple cardiac cycles must be used to acquire the data, arhythmias can alter the shape of the filling curve.

A less complicated measure is the first third (of diastole) filling fraction. This is calculated as the percentage of the end-diastolic counts reached during the first third of diastole. This value should reflect active left ventricular relaxation more closely than measures that include a larger portion of diastole.

As an additional comment, although some of the initial work using radionuclide ventriculography to evaluate diastolic function was done using a

first pass technique (45), there are arguments against the use of this method (46) and equilibrium gated approach is to be preferred.

Although measures are relatively easy to obtain with radionuclide ventriculography, their validity is in some question. For example, the effect of heart rate on the rapid-filling phase is unknown. Frequently, computer software is used to "correct" for the effect of heart rate even though changing sympathetic tone could affect both cycle length and relaxation rate at the same time making a correction for heart rate would be inappropriate (4).

The nuclear probe has also been evaluated as a tool for the assessment of diastolic function (47,48).

Echocardiography (M-mode and two dimensional)

As compared with catheterization, echocardiography is fundamentally a technique that measures distances. Hence, M-mode echocardiography can be used to make a single linear measurement of the ventricular dimension which is used to reflect changes in ventricular size during diastole (49).

A second approach is to calculate the rate of increase in left ventricular dimension during diastole. A typical example is shown in Figure 10. Measurements are made at multiple points during relaxation and the velocity (or, in other words, the rate of change of distance, dD/dt) at each point in time is calculated. As shown in Figure 10, this measure is often indexed to the dimension. This approach assumes a uniform ventricular geometry and thus is of limited use in the setting of regional wall motion abnormalities.

Figure 10

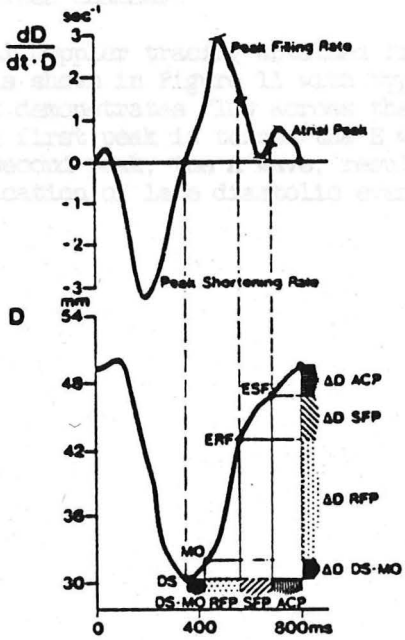


FIG. 2. Left ventricular dimension–time curve and its first derivative as obtained by echocardiographic analysis of left ventricular wall motion showing different phases of left ventricular filling and emptying. Abbreviations: ACP, filling due to atrial systole; *D*, dimension; DS, end-systolic dimension; ERF, end of phase of rapid filling; ESF, end of phase of slow filling; MO, mitral valve opening; RFP, rapid-filling phase; SFP, slow-filling phase; *t*, time. (From ref. 42, with permission.)

A third approach is to evaluate the rate of posterior wall thinning, dh/dt. Lastly, a wide variety of M-mode derived intervals,such as the rapid-filling period, slow filling period, and total diastolic filling periods, have been used to evaluate diastolic function (50). The isovolumic relaxation time can be used to assess early diastole and is measured by simultaneous echo and phonocardiography. One measures the time from aortic valve closure to mitral valve opening. The relaxation time index (time from the minimum left ventricular dimension to mitral valve opening) is similar but does not require the use of the phonocardiogram to establish time of aortic valve closure. It tends to underestimate the true isovolumic relaxation time. The rapid filling time is defined as the time between mitral valve opening and the point at which the normalized rate of lengthening has fallen to 50% of its peak value (51). An additional index of diastolic function is the left atrial size. Smith (89) has demonstrated that there is a significant difference in atrial size between patients with hypertension and altered diastolic function and normal controls.

An important limitation of echocardiography in the assessment of diastolic function relates to the difficulty in obtaining an adequate study in a significant number of older patients.

Doppler Echocardiography

More recently Doppler echocardiography as emerged as an important tool in the evaluation of diastolic function (52). Doppler echocardiography is quite different than M-mode or two dimensional echocardiography in that it measures the velocity of blood motion and not the structural dimension of the chamber. Because of the fact that the flow velocity between regions is related to the pressure differences between those two regions, Doppler flow velocities can be used to make statements regarding the relative pressure difference between chambers.

A typical Doppler tracing obtained from the left ventricle near the mitral valve is shown in Figure 11 with typical values given in the table to the right. It demonstrates flow across the mitral valve during early and late diastole. The first peak is termed the E wave and reflects early diastolic events. The second peak, the A wave, results from atrial contraction and can give some indication of late diastolic events.

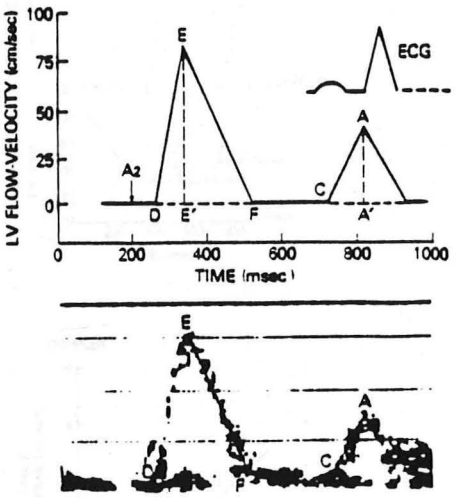


Table 1. Normal Values for Variables Describing Left Ventricular Diastolic Flow Velocity Profile, Obtained With Doppler Echocardiography in 29 Normal Subjects*

	A_2–D (ms)	D–F (ms)	Slope (m/s²)	E–E' A–A'
Mean	75 ± 11	214 ± 26	5.0 ± 1.0	2.5 ± 0.9
Range	53 to 100	162 to 266	3.5 to 6.5	1.1 to 5.1
95% confidence limits†	≤94	≤258	≥3.3	≥1.0

*These subjects were previously studied in our laboratory (5) but are not part of the present study group.
†Upper or lower 95% confidence limits of normal, whichever was most appropriate for each variable. A_2 = the descending portion of the early diastolic flow velocity peak. A_2–D = time interval from the aortic closing component of the second heart sound to the onset of the early diastolic flow velocity peak. D–F = duration of early diastolic flow velocity peak. E–E' A–A' = ratio between heights of early and late diastolic flow velocity peaks.

Figure 11

Hence, Doppler offers potential advantages over measurement-based M-mode or two dimensional echo techniques. First, it is to a significant degree less constrained by the geometric assumptions involved in the M-mode techniques. Second, it does not require the calculation of a derivative. Third, in the absence of regurgitation, a change in left ventricular volume is related to the flow across the mitral valve. Rokey (53) calculated the volume of flow across the mitral valve on the basis of mitral valve area and the velocity of flow across the mitral valve and showed a good correlation with cineangiography.

Subsequently, Spirito (54) examined several Doppler measurements and found a good correlation between Doppler and radionuclide measurements of diastolic function. In particular, he found that the time interval from the aortic closure component of the second heart sound to the end of the early diastolic flow velocity E peak correlated well with the time interval from end-systole to the end of rapid filling as assessed by radionuclide ventriculography (r=0.83). The descent of the Doppler early diastolic flow velocity peak correlated well with the radionuclide peak filling rate (r=0.79). Also, the E to A ratio (ratio of the peak filling velocity early in diastole to the peak filling velocity late in diastole) correlated with the ratio of left ventricular filling during rapid filling and during atrial systole (r=0.76).

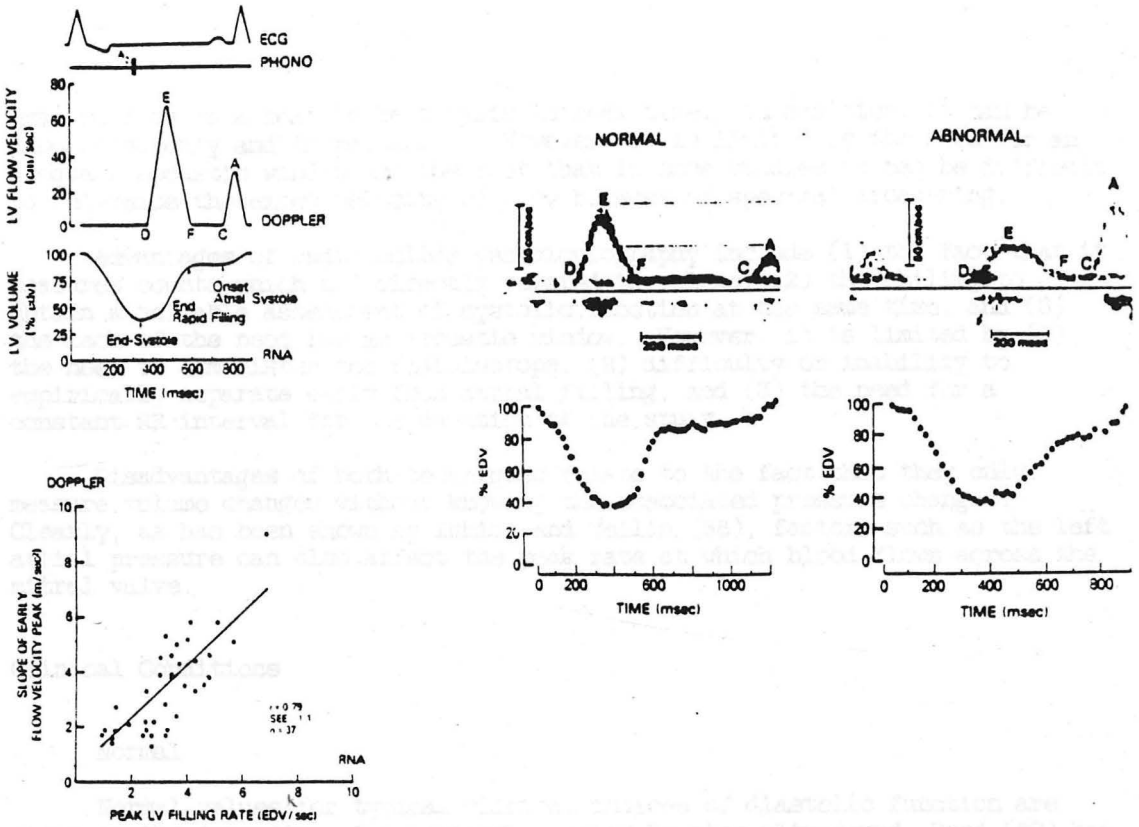


Figure 12

Friedman (55) also examined the correlation between Doppler and radionuclide ventriculography and found the agreement to be good if identical variables were compared (Figure 12). Comparisons with M-mode assessments have also shown a good correlation (56).

Nuclear Magnetic Resonance Imaging

Although there have been no reports of the use of nuclear magnetic resonance imaging in the evaluation of diastolic function, it has been used in the assessment of systolic function (57). It could potentially be used in the assessment of diastolic function in a manner similar to radionuclide ventriculography if high framing rates can be obtained.

Comparison of Radionuclide Ventriculography and Doppler Echocardiography

In summary, in comparing Doppler with radionuclide ventriculography each method appears to provide reasonable, clinically useful information if performed carefully. As outlined by Friedman, each method has significant advantages and disadvantages. Advantages of Doppler include: (1) the ability to easily compare relative filling early and late in diastole, (2) the excellent temporal resolution (typically, 5 msec) and (3) the ability to

examine flow on a beat by beat basis in real time. In addition, it can be done repeatedly and is portable. However, it is limited by the need for an adequate acoustic window and the fact that in some studies it may be difficult to determine the exact velocity of flow because of spectral broadening.

Advantages of radionuclide ventriculography include (1) the fact that it measures counts which are directly related to volume, (2) the ability to obtain a reliable assessment of systolic function at the same time, and (3) the lack of the need for an acoustic window. However, it is limited by (1) the need to administer the radioisotope, (2) difficulty or inability to empirically separate early from atrial filling, and (3) the need for a constant RR interval for the duration of the study.

Disadvantages of both techniques relate to the fact that they only measure volume changes without knowing the associated pressure changes. Clearly, as has been shown by Ishida and Yellin (58), factors such as the left atrial pressure can also affect the peak rate at which blood flows across the mitral valve.

Clinical Conditions

Normal

Normal values for typical clinical indices of diastolic function are shown in the Appendix. Interestingly, using Doppler ultrasound, Reed (59) has demonstrated that the fetal heart in utero is less compliant than in newborns or adults. This finding is consistent with studies in fetal lambs (60) and may be related to differences in the relative distribution of contractile and non-contractile elements in the fetal myocardium as compared with the adult heart. Left ventricular filling has been examined in neonates (61) using Doppler echocardiography. Interestingly, there was no difference in peak early diastolic filling velocity between neonates and adults. However, there was a difference in peak early diastolic filling rate (peak early diastolic filling velocity X Mitral valve area) which correlated with the left ventricular volume. These data were felt to suggest that the relationship between peak early diastoic filling rate and left ventricular size was due to differences in mitral valve size and not differences in peak mitral flow velocity.

Effects of aging

It is now well established that ventricular compliance alters with increasing age (62,63,64). Using echocardiography, Manyari and colleagues examined elderly individuals without evidence of organic heart disease or abnormal systolic function. They found significant decreases in peak and average filling rate, increases in the duration of the rapid filling phase and the time to peak filling rate, and an increase in the atrial contribution to ventricular filling. These changes with age occurred independent of other pathologic processes such as ischemic heart disease or hypertension and were unrelated to differences in heart rate or systolic performance.

Miller used radionuclide ventriculography and correlation analysis to examine factors influencing left ventricular filling and found that there was a strong negative correlation between peak diastolic filling rate and age ($r=-0.82$, $p<0.0001$) (Figure 13). In addition, they found a correlation between increasing heart rate and peak flow rate ($r=0.61$). The figures illustrate that the effects of age and heart rate on peak flow rate are significant and need to be taken into account in studies of pathologic conditions.

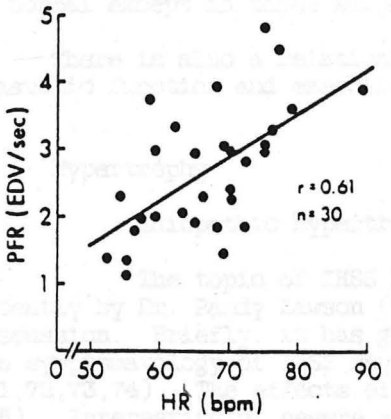


FIGURE 2. The large increase in peak filling rate (PFR) with heart rate (HR) in the 30 normal subjects. EDV/sec = end-diastolic volumes/second.

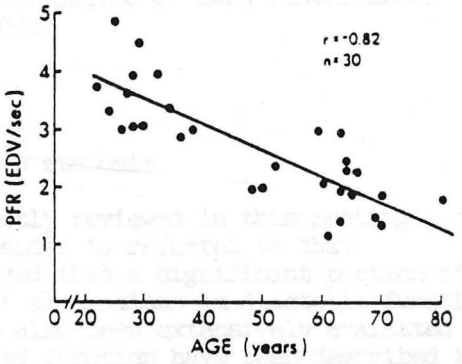


FIGURE 1. The large decline in peak filling rate (PFR) with age in the 30 normal subjects. EDV/sec = end-diastolic volumes/second.

Figure 13

Athlete's heart

It has also been noted that endurance athletes demonstrate alterations in rapid ventricular filling consistent with a change in diastolic function (65,66,67). Colan examined elite athletes with and without evidence of hypertrophy by echocardiography. He found that the peak rate of left ventricular dimension increase was greater in swimmers and power lifters than in control subjects. When the peak rate of dimension increase was normalized for end-diastolic dimension and systolic function, diastolic function was normal. Interestingly, Douglas examined a group of endurance athletes without increased chamber size who also showed better than normal diastolic function in terms of early to late left ventricular inflow velocities. Hence, it appears that the diastolic abnormalities in patients with pathologic hypertrophy are unrelated to differences in wall thickness alone and that there seems to be a difference between the hypertrophy seen with athletic training and that occurring with pressure or volume overload in disease states.

Finkelhor used Doppler echocardiography to compare normal controls with endurance athletes. He found the peak velocity of diastolic filling and the rapid filling time to be similar in the two groups. However, they did find

that the A to E ratio and the percent contribution of atrial systole to diastolic filling was lower in the trained group. These data are in contradistinction to the results seen in patients with hypertension (see below). The authors suggested that because the total diastolic filling time was significantly longer in the athletes (due to slower heart rates) that there was more complete atrial emptying prior to atrial contraction so that the atrial component was less.

Alterations in filling has also been described in weight lifters (68). Pearson examined weight lifters and found a significant increase in myocardial mass. However, similar to endurance athletes, diastolic function appeared to be normal except in those subjects who had used anabolic steroids heavily.

There is also a relationship between the degree of left ventricular diastolic function and exercise tolerance (69).

Hypertrophy

Idiopathic hypertrophic subaortic stenosis

The topic of IHSS has been expertly reviewed in this meeting recently by Dr. Randy Lawson (70) and the reader is referred to that discussion. Briefly, it has gradually emerged that a significant portion of the symptomatology of IHSS may be related to alterations in diastolic function (71,72,73,74). The effects of therapy have also been extensively evaluated (75). Interestingly, severe abnormalities of function have been described in patients with limited mild left ventricular hypertrophy (76).

Aortic Stenosis

Another group of considerable interest with pathologic hypertrophy is patients with aortic stenosis. Fifer (77) studied children and adults with and without aortic stenosis using echocardiography. He found that early diastolic filling and wall thinning rates were significantly depressed in both children and adults with aortic stenosis. In addition, the effect on diastolic function appeared to be related to age and increases in systolic pressure. However, there was no relationship to systolic performance, ie, children with normal or supranormal systolic performance and adults with depressed systolic performance all showed a depressed diastolic function. The authors concluded that hypertrophy itself was the major determinant of the change in ventricular filling.

There are several possible reasons that hypertrophy itself could lead to abnormal diastolic function. First, considering the active portion of relaxation, it is known that in models of cardiac hypertrophy the duration of intracellular calcium transport and diastolic tension decay are prolonged (78). Second, there is evidence that subendocardial ischemia is present in these patients which would also alter active relaxation. Third, from the standpoint of both active and passive relaxation, patchy fibrosis has been noted in patients with aortic stenosis. This fibrosis could alter recoil during both portions of relaxation. Evidence of increased fibrosis has been noted in the hearts of spontaneously hypertensive rats (79). Interestingly, Hess (80)performed left ventricular biopsies in patients before and after

surgery for aortic valve disease and found that there was significant fibrosis present both pre and post surgery, and, in fact, the relative degree of fibrosis increased following surgery associated with a decline in left ventricular mass. In addition, there was an increase in myocardial stiffness following surgery, paralleling the rise in relative interstitial fibrosis.

Two additional points regarding studies in patients with aortic stenosis are of note. Oldershaw (81) [using echocardiography] examined diastolic function during exercise in patients following aortic valve replacement. He found that although systolic function was normal at rest and with exercise and the left ventricular filling time was normal at rest, the filling time failed to show the normal drop with exercise, suggesting a residual abnormality of diastolic filling. Also, Hess (82) [using catheterization] examined the role of diastolic function in pulsus alternans in patients with aortic stenosis and found that alterations in diastolic function did not appear to play a role.

Systemic hypertension

The effects of hypertension on left ventricular relaxation has been extensively evaluated (83,84,85). Fouad was one of the first to recognize that there was abnormal ventricular relaxation in hypertensive patients (86) (Figure 14). There appears to be in most studies a correlation between the increase in myocardial mass and the degree of dysfunction (87,88,89). Alterations in diastolic function have been demonstrated by doppler echocardiography in even mild hypertension (90). Smith (93) found that in patients with hypertension without an increased myocardial mass that there was evidence of abnormal diastolic function in terms of a prolonged isovolumic relaxation time. It has also been shown that there is an improvement in filling that occurs with the reduction of mass with therapy of essential hypertension (91).

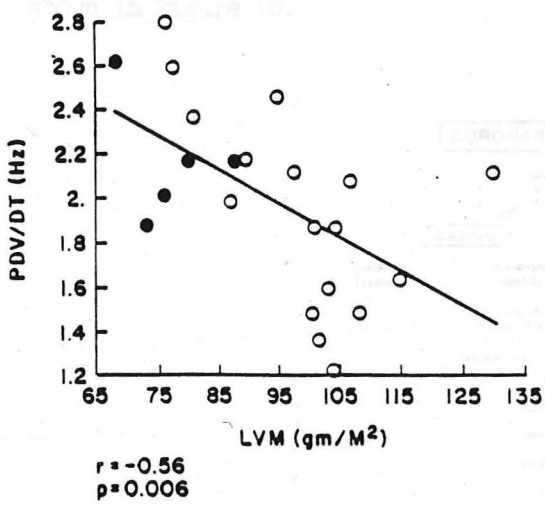


FIGURE 1. Negative correlation between echocardiographically (M mode) determined left ventricular mass (LVM, normalized for body surface area, M^2) and the maximum rate of left ventricular filling (PdV/dt).

Figure 14

This effect in the elderly with hypertension has been specifically described (92). However, this raises a significant concern. It has been clearly demonstrated (as noted above) that there is a strong correlation between alterations in diastolic function and age. Many early studies of diastolic function in hypertension did not include appropriate age-matched controls, making it difficult to be certain that the effects seen were not due to age alone. In fact, in mild hypertension using age corrected data, Gadin was unable to demonstrate a significant difference in peak mitral flow velocity early in diastole as compared to controls. He found only the transmitral late diastolic flow velocity integral to be correlated with left ventricular mass. With age matched controls it was possible to demonstrate differences as a diminished rate of deceleration of early diastolic transmitral flow and an increased early diastolic deceleration time and late diastolic flow time.

This effect has also been noted in children with systemic hypertension (93) using Doppler echocardiography before the appearance of the development of systolic function abnormalities of left ventricular hypertrophy. The fact that these changes can be detected in young patients suggests that they are changes with hypertension independent of age, heart rate systolic function, or left ventricular loading conditions.

Coronary Heart Disease

Ischemia and Infarction

The fact that early relaxation is an energy requiring process would suggest that diastolic function would be sensitive to the presence of ischemia. It has long been appreciated that alterations in relaxation occur early in the setting of ischemia and precede the appearance of abnormalities of contraction (94,95,96,97,98). The potential mechanisms in ischemia are shown in Figure 15.

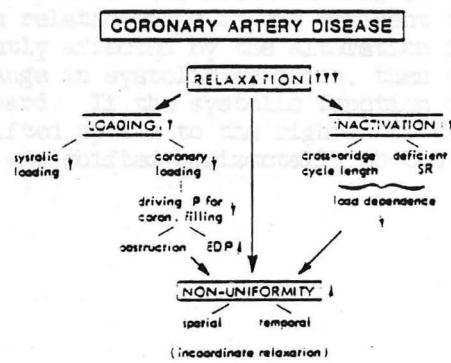


Figure 15

First, in hypoxia there is inhibition of the uptake of calcium by the sarcoplasmic reticulum and impaired detachment of force generating sites between actin and myosin. The delayed inactivation would diminish load dependence.

It has been demonstrated that ischemia due to total occlusion and that due to partial occlusion have different effects on diastolic function (99) (Figure 19). Myocardial ischemia associated with partial occlusion and increased oxygen demand demonstrated an upward shift in the pressure-segment length relationship which was associated with an increase in the stiffness in the ischemic region. In the setting of total occlusion, the pressure-segment length relationship was either unaltered or shifted down.

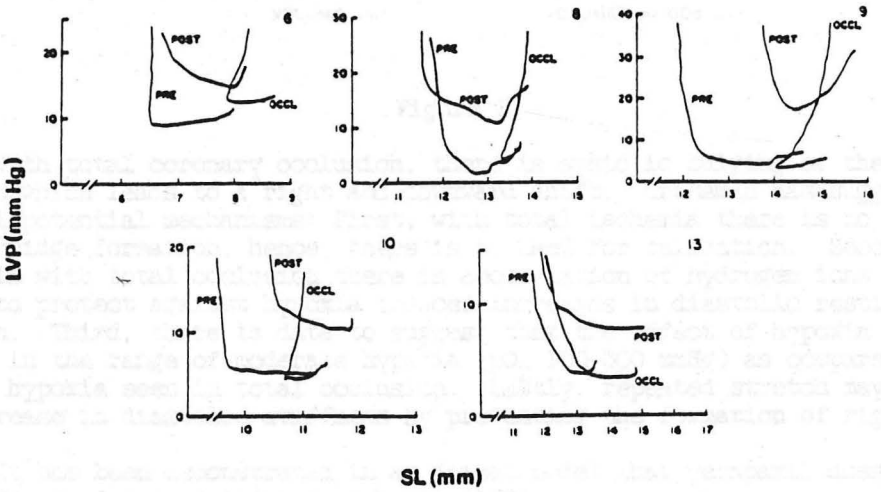


FIGURE 5. *Diastolic left ventricular pressure-segment length relationship (in LAD region) PRE = pre-pacing with stenoses. POST = immediately post-pacing, OCCL = at 3 minutes of LAD occlusion. In general, the diastolic pressure-segment length relation shifted upward after pacing tachycardia. However with coronary occlusion ischemia, an upward shift was not seen.*

Several additional points were noted in this study. In examining the pressure-segment length relationships it was apparent that the diastolic function was significantly affected by the alteration in systolic function. If there was little change in systolic function, then the diastolic function curve was displaced upward. If the systolic function deteriorated, the diastolic curve was shifted up and to the right. If there was severe systolic dysfunction, the curve was shifted horizontally to the right

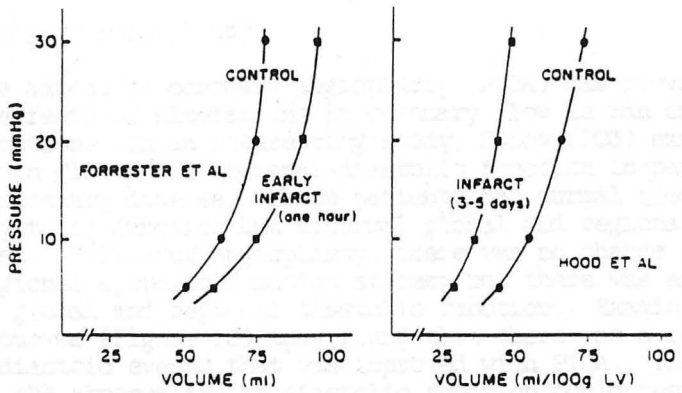


Figure 17

With total coronary occlusion, there is systolic bulging of the ischemic segment which leads to a right and downward shift. Grossman has suggested several potential mechanisms: First, with total ischemia there is no systolic cross bridge formation, hence, there is no need for relaxation. Second, in ischemia with total occlusion there is accumulation of hydrogen ions which is known to protect against hypoxia induced increases in diastolic resting tension. Third, there is data to suggest that the effect of hypoxia is most severe in the range of moderate hypoxia (pO_2 100-300 mmHg) as compared to the severe hypoxia seen in total occlusion. Lastly, repeated stretch may prevent an increase in diastolic stiffness by preventing the formation of rigor bonds.

It has been demonstrated in an animal model that verapamil does alter the effects of pacing induced ischemia (100).

In an interesting study Fujibayashi (101) examined the effects of very brief coronary occlusion (1-2 minutes) on systolic and diastolic function. After occlusion, systolic function returned to normal in 5 to 10 minutes following 1 minute of occlusion and 20 to 30 minutes following 2 minutes of occlusion. Interestingly, the recovery times for diastolic function were considerably longer: 60-75 minutes following a 1 minute occlusion and 90-105 minutes following a 2 minute occlusion. Nifedipine administered during the period of occlusion reduced the time for recovery of diastolic function to 10-15 minutes. When nifedipine was begun prior to occlusion the subsequent recovery was very rapid, i.e., 1-2 minutes.

The reasons for the very rapid improvement with preocclusion administration of nifedipine are unclear. It is possible that nifedipine leads to a reduction of calcium accumulation in the cell during the period of occlusion and reperfusion.

In addition, Cannon (102) has described a group of patients with normal epicardial coronary arteries but with abnormal vasodilator reserve and demonstrated impaired left ventricular filling at rest similar to some patients with coronary artery disease and normal left ventricular function.

Coronary angioplasty

The advent of coronary angioplasty (PTCA) has provided a means for examining the effects of alterations in coronary flow in man on left ventricular function. In an interesting study, Bonow (103) examined the effect of PTCA on global and regional diastolic function in patients with single vessel coronary disease. These patients had normal ejection fractions and regional systolic function but abnormal global and regional diastolic function at rest. Following angioplasty, there was no change in ejection fraction or regional systolic function at rest but there was an immediate improvement in global and regional diastolic function. Examining the regional time activity curves (Figure 18) they found that there was a regional asynchrony in diastoic events that was improved with PTCA. The authors suggested that the abnormality in diastolic function could result from the asynchrony of regional diastolic function as a result of ischemia and, hence, was rapidly reversible.

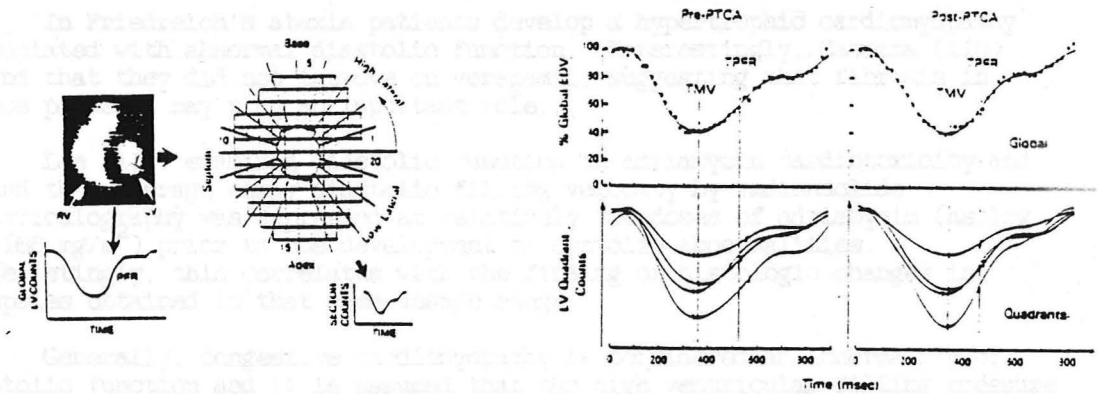


Figure 18

Wijns and colleagues (104) have examined the effects of acute coronary occlusion during PTCA on left ventricular stiffness. They found that transient abrupt coronary occlusion of 20 or more seconds caused significant increase in regional chamber stiffness. In addition, there was a rise in global stiffness in those patients in whom the left anterior descending coronary artery was occluded, probably reflecting the extent of the ischemic bed. When measurements were repeated 12 minutes following the occlusion, the measures of regional diastolic function were still abnormal, while measures of global function were still slightly elevated.

In addition, Lewis (105) has described an improvement in diastolic function during exercise following PTCA.

Post bypass surgery

Revascularization has been reported to improve indices of diastolic function (106). However, in some patients persistent elevations of end diastolic pressure and decrease in passive distensibility remained consistent with presumed fibrosis or other chronic structural changes.

Other conditions

As might be predicted, measures of diastolic function have been found to be abnormal in a variety of conditions associated with infiltration of the myocardium. It appears that abnormalities of diastolic function appear early in the course of amyloidosis and can be quite severe before evidence of systolic dysfunction is present (107). Chagas disease leads to regional edema, inflammatory infiltration, destruction of fibers, and eventual fibrosis, which leads to alterations of diastolic function early in the course of the disease (108,109).

In Friedreich's ataxia patients develop a hypertrophic cardiomyopathy associated with abnormal diastolic function. Interestingly, Casazza (110) found that they did not improve on verapamil, suggesting that fibrosis in these patients may play an important role.

Lee (111) examined diastolic function in adriamycin cardiotoxicity and found that average early diastolic filling velocity by radionuclide ventriculography was depressed at relatively low doses of adriamycin (as low as 166 mg/m^2) prior to the development of systolic abnormalities. Interestingly, this correlates with the finding of histologic changes in biopsies obtained in that same dosage range.

Generally, congestive cardiomyopathy is considered an abnormality of systolic function and it is assumed that the high ventricular filling pressure is a consequence of impaired ejection of blood leading to an increase in end diastolic volume, dilation of the chamber, and a rise in pulmonary venous pressure. Clearly, there are concomitant alterations in diastolic function in these patients and that the systolic and diastolic abnormalities are "coupled" (112,113,114,115,116).

Management

The management of abnormalities of diastolic function should reasonably be based on an understanding of the underlying pathologic process. Hence, if there is an abnormality in loading, then an alteration in the loading conditions should improve the hemodynamics. If there is primarily an abnormality in inactivation, then interventions to reduce calcium loading or the energy status of the cell may prove to be useful. Finally, if there is a structural alteration of the heart with scar or loss of the mechanical basis of elasticity, then there is presently no intervention available for our use.

Calcium-Entry Blockade

Clearly, many pharmacologic interventions have effects on multiple aspects of the mechanism. In particular, calcium antagonists alter calcium loading but also lead to alterations in loading conditions, non-uniformity of relaxation, and coronary flow which may interact in a complex and unpredictable way in different patients.

Walsh (117) has recently reviewed the multiple effects of calcium-entry blockade on diastolic function. It is known that a reduction in cytosolic calcium can lead to an increased calcium-troponin binding in the myofilaments (118) and that cytosolic ionized calcium is necessary for the sarcoplasmic membrane calcium ATPase believed necessary for calcium sequestration and load-independent inactivation of contraction (119,119). Hence, one would suspect that calcium-entry blockade would reduce cytosolic calcium and diminish both inactivation-dependent relaxation and contraction. In the intact animal the effect on the time constant of left ventricular pressure decay has been demonstrated for each of the major clinical calcium-entry blockers (Figure 19).

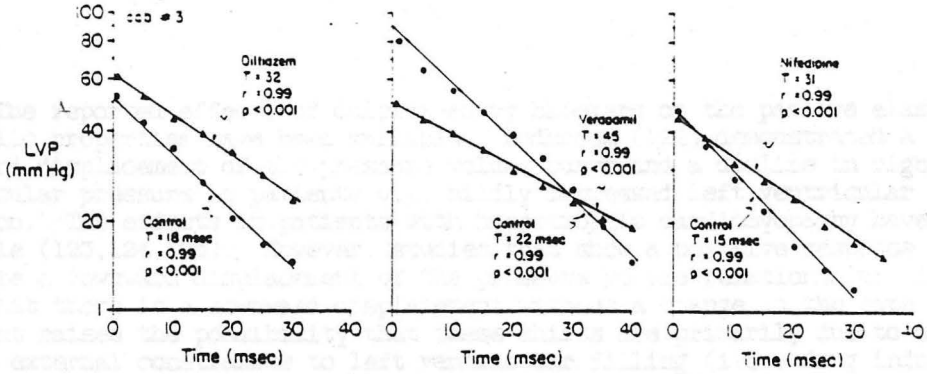


Figure 19

When the agents are given in equidepressant doses there is impaired relaxation as shown. On the other hand, equihypotensive infusions lead to augmented relaxation with nifedipine and little change with diltiazem and verapamil. Interestingly, the effect of nifedipine could be blocked by nonselective beta blockade. Hence, it appears that calcium-entry blockade may directly impair normal left ventricular relaxation. However, the impaired rate of relaxation produced by the calcium blockers in normal tissue can be reversed by the reflex sympathetic stimulation and afterload reduction associated with the use of these agents.

In the setting of ischemia, the results are mixed (120). In different in vitro models different effects are seen (119). Lorell (121) found that nifedipine improved measures of diastolic compliance in patients with pacing induced angina. Hence, multiple effects may be playing a role, as shown in Table 2.

Table 2

Potential effects of calcium-entry blockade on ventricular relaxation

Direct effects
Normal myocardium — impair[31]
Hypoxic myocardium — impair[36]
Ischemic myocardium — augment in vitro,[38] in vivo unclear[39]
Hypertrophied myocardium — unclear
Hypertrophic cardiomyopathy — unclear[43, 44]
Indirect effects[31]
Improved systolic loading — augment
Reflex sympathetic stimulation — augment
Improved coronary blood flow — augment

The reported effects of calcium-entry blockers on the passive elastic diastolic properties have been variable. Ludbrook (122) demonstrated a downward displacement of the pressure volume curve and a decline in right ventricular pressure in patients with mildly depressed left ventricular function. The effects in patients with hypertrophic cardiomyopathy have been variable (123,124,125). However, studies that show a positive response indicate a downward displacement of the pressure volume relationship. The fact that there is a downward displacement without a change in the rate constant raises the possibility that these shifts are primarily due to changes in the external constraints to left ventricular filling (i.e., drug induced changes in right ventricular filling in the presence of the pericardium) and not intrinsic changes in the muscle elasticity.

Inotropic agents

The effects of inotropic agents on diastolic function have been investigated by a number of groups. Carroll (126) examined the effects of dopamine and dobutamine and found that these agents enhanced early diastolic distensibility by accelerating relaxation, augmenting filling, and reducing end-systolic chamber size, but in some cases actually caused a rise in end diastolic pressure. Nitroprusside, in comparison, led to a fall in in left ventricular end diastolic pressure without a consistent change in relaxation.

In a study of patients treated with milrinone (127), there were clear changes in diastolic function which could not be accounted for on the basis of changes in peak left ventricular pressure or changes in pulmonary capillary wedge pressure. In animal models there is preliminary evidence that milrinone shortens the duration of tension and increases the concentration of cyclic-

AMP, leading to a failure of sarcoplasmic reticulum calcium uptake. However, a recent study using a similar phosphodiesterase inhibitor, enoximone (128), showed no difference from the pressure volume relationships seen with nitroprusside. The pressure volume curve was displaced downward in the case of each drug, suggesting that the change resulted in part from a reduction in external factors and not intrinsic changes in myocardial stiffness.

Conclusion

Medicine has made significant strides in the management of abnormalities of systolic function of the heart. Advances in our understanding of ventricular loading and the development of new unloading and inotropic agents have allowed us to substantially improve patient care. However, with the improvement of our management of abnormalities of systolic function has come a greater recognition of the importance of diastolic phenomena in many clinical conditions. As the tools to evaluate diastolic function in man improve, the challenge will be to devise interventions which can correct these abnormalities of diastolic function.

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