Determinants of Left Ventricular Filling and of the Diastolic Pressure-Volume Relation

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Until the 1970s, the left ventricle was considered an isolated shell in which the left ventricular diastolic pressure-volume relation depended on the myocardium's material properties and the left ventricle's wall thickness and geometry. According to this view, the relation between diastolic pressure and volume could change only in response to chronic changes in the cardiac muscle's material properties, such as scarring due to infarction, or changes in cardiac geometry due to hypertrophy. As a consequence, the diastolic pressure-volume relation was considered unique over the short term. A practical application of this assumed uniqueness was that left ventricular diastolic pressure was used as a surrogate for volume in evaluating systolic function.

However, in the early 1970s, studies of patients with coronary artery disease contradicted this simplistic view of the diastolic pressure-volume relation. In these patients, the left ventricular diastolic pressure-volume curve shifted upward temporarily immediately after cardiac pacing–induced angina and then returned to prepacing values. Later, other investigators observed that vasodilator and vasoconstrictor drugs, which change the vascular loading conditions of the left ventricle, also produced acute reversible shifts in the left ventricular diastolic pressure-volume curve. In the process of explaining these clinical observations, we have learned that many factors can affect left ventricular filling and the diastolic pressure-volume relation acutely.

The original concept that the pressure within the left ventricle is determined by the balance between the forces due to pressures within the ventricular cavity that expand the ventricle and forces due to elasticity of the myocardium that resist this expansion remains the centerpiece of our understanding of the diastolic pressure-volume relation. However, it is now clear that changes in active relaxation of the myocardium, mechanical interaction between the ventricles, the pericardium, so-called diastolic suction, pulmonary-cardiac contact pressure, myocardial viscoelasticity, and engorgement of the coronary vasculature all play some role in determining the left ventricular pressure-volume relation during diastole (Figure 1). The questions are, how large an effect does each of these factors have on the left ventricular diastolic pressure-volume relation, and when during diastole do each of them act? The answers are that during early diastole the rate of relaxation and diastolic suction are important. During late diastole (and at end-diastole) the extent of relaxation and ventricular interaction modulated by the pericardium are important. The other factors—pulmonary-cardiac contact pressure, viscoelasticity of the myocardium, and engorgement of the coronary vasculature—are less important in determining the left ventricular diastolic pressure-volume relation.

We will first review the pressure-volume relation itself and show how it depends on the relation between left ventricular wall stress, pressure, and geometry. We will then review the evidence for the roles that the various factors play in shifting the left ventricular diastolic pressure-volume relation, consider problems in measuring some of these factors, explore the mechanisms of some factors, and assess the implication of each factor for systolic function.

Geometry, Muscle Elasticity, and the Basic Pressure-Volume Relation

The diastolic pressure-volume relation results from forces acting both on and within the myocardium. The forces acting on the myocardium, in turn, result from the pressure within the left ventricle and the other cardiac chambers and from the constraining forces exerted on the epicardium by the pericardium and the lungs. The forces acting within the myocardium result from the fact that the myocardium is an elastic material so that the muscle itself develops a resisting force as it extends. The physical relations that govern these forces provide the framework in which we will discuss the factors that affect the diastolic pressure-volume relation.
To understand many of the factors that affect the left ventricular diastolic pressure-volume relation, the left ventricle can be modeled as a simple, pressurized, spherical shell. Three simplifying assumptions permit us to derive an equation, the Laplace Law, which relates wall stress to pressure and geometry (i.e., radius and wall thickness). (Stress, $\sigma$, is the force per cross-sectional area of a material such as the muscle.) The assumptions are that 1) the left ventricle is a sphere with uniform wall thickness, $h$, and inside radius, $r$; 2) the left ventricle is in static equilibrium (i.e., nothing is moving); and 3) the wall is thin, so that the stress may be considered constant through the wall. To begin, the sphere is cut through its center to expose the internal forces (Figure 2A). The total force tending to push the lower hemisphere away from the upper hemisphere is equal to the pressure within the sphere, $p$, times the internal cross-sectional area, $\pi r^2$. The total force in the wall holding the two halves together equals the wall stress, $\sigma$, times the cross-sectional area of the wall. These two forces must balance

$$p(\pi r^2) = \sigma(\pi (r + h)^2 - \pi r^2)$$  

which simplifies to

$$pr = \sigma h (2 + h/r)$$  

Since we assumed a thin wall, the ratio of the thickness to the internal radius is much smaller than 2, so we can neglect $h/r$. Solving Equation 2 for the stress yields

$$\sigma = pr / 2h$$  

Equation 3, the Laplace Law for a thin-walled sphere, relates the pressure in the left ventricle and its geometry (i.e., radius and wall thickness) to the wall stress. According to the Laplace Law, the wall stress in a sphere increases in direct proportion to the internal pressure and radius and decreases in inverse proportion to the wall thickness.

Equation 3 provides a good approximation of the mean left ventricular stress for a given diastolic pressure despite the fact that the left ventricle is not "thin." "Thin" in an engineering sense usually means that $h/r < 0.1$. Although $h/r$ is in the range 0.3-0.5 at end-diastole, Equation 3 still provides accurate estimates of relative changes in wall stress and can be used to gain semiquantitative insight into physiological processes.

The Laplace Law and the elastic properties of the myocardium can be used to derive the ventricular pressure-volume relation. The Laplace Law shows...
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Determinants of Diastole

Strain

FIGURE 2. The elastic component of the diastolic pressure-volume curve is determined by the balance of the force (pressure) in the ventricular chamber tending to push the chamber apart and force (stress) in the wall holding it together (A), combined with the relation between stress and strain (distension) of the myocardium (B). These elements are combined to derive the pressure-volume relation for the left ventricle shown by the solid line in panel C (Equation 5 in the text). The relation expressed in panel C (and Equation 4) provides a good description of the left ventricle's pressure-volume characteristics above the equilibrium volume, \( V_0 \), but not below \( V_0 \), when the myocardial wall is in compression and storing elastic energy (dashed line). The ability of the myocardium to store elastic energy in compression when the end-systolic volume is below the equilibrium volume gives rise to the phenomenon of so-called diastolic suction, a, stress; p, pressure; r, radius of curvature (to the endocardium); h, wall thickness; \( \alpha \) and \( \beta \), elasticity parameters; \( e \), Lagrangian strain.

that as the ventricular pressure increases, the wall stress increases, extending the muscle and thus increasing the ventricle’s radius. In our assumed spherical ventricle, the radius is related directly to ventricular volume (\( V=4/3\pi r^3 \)). The next step is to relate the wall stress to ventricular volume.

The relation between wall stress and ventricular volume depends on the elastic properties of the myocardium. As in most biological materials, muscle becomes stiffer as it is extended; that is, it requires greater increments of force to produce each additional increment of length. The elastic properties of the total myocardium are very difficult to measure, but the elastic properties of a one-dimensional strip of muscle is much easier. Using one-dimensional strips of papillary muscle, the elasticity of the myocardium can be represented as a one-dimensional stress-strain relation. Strain, \( e \), is a normalized, dimensionless measure of the deformation of a solid such as the myocardium. The most common way of defining strain is Lagrangian strain, which is defined as extension from equilibrium length divided by the equilibrium length, \( e=(l-l_0)/l_0 \). The equilibrium length is the length that a specimen of material exhibits when subjected to no external forces. This equilibrium length is usually used as the reference length for computing strains.

The elastic properties of the myocardium have been described by an exponential relation between stress \( \sigma \) and strain \( e \) [Equation 4]:

\[
\sigma = \alpha (\epsilon^{\beta} - 1)
\]  

In a purely elastic material, the stresses depend only on the strain (deformation), \( e \). The parameters \( \alpha \) and \( \beta \) in Equation 4 are constants and determine the precise nature of this relation, which is shown by the curve in Figure 2B and described by Equation 4; thus, \( \alpha \) and \( \beta \) are called elastic constants.

This one-dimensional stress-strain relation can now be extended to a pressure-volume relation by using the spherical ventricular geometry and the Laplace Law for a sphere. In addition, the concept of an equilibrium length, described above, can be generalized to an equilibrium volume, \( V_0 \), the volume that a shell (such as the left ventricle) exhibits when subjected to no transmural pressure. Glantz and Kernoff combined the Laplace Law with Equation 4 for the elastic properties of the myocardium to obtain an equation for the pressure-volume relation of the left ventricle:

\[
p = \alpha \eta (2+\eta) \left[ (e^{2+\eta} V_{0}^{2/3} - V_0 - 1) \right],
\]  

where

\[\eta = h/r = hV/(4\pi/3V)\]

Equation 5 reveals that the pressure-volume relation depends on three things: the elastic properties of the myocardium (\( \alpha \) and \( \beta \)), the wall thickness (\( h \)), and the left ventricle’s equilibrium volume (\( V_0 \)). Glantz and Kernoff validated Equation 5 by comparing the muscle stiffness estimated from pressure-volume data obtained by inflating dog left ventricles with the stiffness measured directly from muscle strips removed from those hearts.

Equation 5, however, is not a good description of the pressure-volume characteristics of the left ventricle below its equilibrium volume, \( V_0 \). As the dashed curve in Figure 2C shows, the actual ventricular pressure drops rapidly as chamber volume falls below \( V_0 \), whereas Equation 5 predicts little change in pressure (dark curve in Figure 2C). This difference is probably due to two factors: First, the assumption of a “thin” wall is drastically violated at small volumes. Second, Equation 4 is probably not a good description of the elastic properties of the myocardium in compression. The mechanics of the heart at volumes below \( V_0 \) is just beginning to be studied. The rapid drop in pressure that occurs for ventricular volumes below \( V_0 \) (Figure 2C) is important for understanding so-called diastolic suction.
Effects of Hypertrophy

When the left ventricle is subjected to a chronic volume or pressure overload, it grows. The Laplace Law provides the theoretical framework for understanding the mechanical stimulus for the changes that take place. In addition, while the changes that accompany hypertrophy often have beneficial effects in terms of helping the left ventricle maintain systolic function in the face of increased loading, this is often accomplished at the expense of increases in diastolic pressure that can eventually lead to circulatory congestion and congestive heart failure because of increases in end-diastolic pressure necessary to maintain a given end-diastolic volume.

When the left ventricle is first subjected to a volume overload, the myocardium is strained more than usual during diastole because the difference between the volume and equilibrium volume, \( V_0 \), is increased. As a result of this increased strain, diastolic wall stress and end-diastolic pressure increase. Over time, cardiac myocytes respond by elongating and thickening in a way that effectively increases \( V_0 \) with little or no increase in wall thickness. This increase in \( V_0 \) means that the larger volume now corresponds to a lower strain, and so leads to correspondingly lower wall stress and diastolic pressure. The left ventricle appears to stop growing when it has increased \( V_0 \) to the point that end-diastolic wall stress has returned to values present before imposition of the volume overload.

This so-called eccentric hypertrophy also occurs in response to physical training and in people with aortic or mitral insufficiency. The changes that accompany volume overload seem to be primarily those associated with changing size of the heart (and the related changes in equilibrium volume) rather than intrinsic changes in the elastic properties of the myocardium.

This situation contrasts with that observed during pressure overload. In pressure overloads, the stress that the myocardium must develop during systole is increased because of the increased afterload. The left ventricle responds by developing so-called concentric hypertrophy in which there is an increase in wall thickness with little or no change in chamber radius, presumably because of the addition of new sarcomeres in parallel with existing ones. This increase in wall thickness allows the left ventricle to generate increased systolic pressure at a lower level of average wall stress (i.e., force development in individual sarcomeres) than would occur in the absence of hypertrophy. In addition to these purely geometric effects, the structure of the cardiac interstitium changes to increase the amount of collagen present and thus increase the elastic stiffness.

The net effect of these changes is to lead to higher diastolic pressure at any given volume. This upward shift in the diastolic pressure-volume relation accounts in part for the increase in diastolic pressure that accompanies pressure overload and the potential for patients with pressure overload to develop congestive heart failure.

The analysis thus far has presumed that stress in the wall is determined principally by ventricular geometry and myocardial elasticity. Although this is true late in diastole when the heart is fully relaxed, it is not true during early diastole, while the muscle is relaxing from the previous beat and is rapidly expanding, or during atrial systole. During early diastole, wall stress is composed of components due to the relaxation from the previous systole as well as the muscle’s passive elastic properties. Fortunately, the Laplace Law can still be used to understand the effects of these stresses because it simply relates ventricular pressure, radius, and wall stress and thus intrinsically incorporates the state of the myocardium. Moreover, the relation between left ventricular size, left ventricular wall thickness, and the elasticity of the myocardium is the single most important determinant of the diastolic pressure-volume relation.

Relaxation

The rate and extent of relaxation are two different quantities, each of which influences the left ventricular diastolic pressure-volume relation. The extent of relaxation is the end state of the muscle after relaxation has completed and is the more important of the two because it determines the myocardium’s equilibrium length, which, in turn, determines the left ventricle’s equilibrium volume. Impaired extent of relaxation means smaller than normal equilibrium volumes, which lead to larger strains and higher diastolic pressures at a given end-diastolic volume. Higher pressures at the same volume result in an upward shift in the diastolic pressure-volume relation. Thus, the extent of relaxation is important at the end of diastole. The rate of relaxation affects the diastolic pressure-volume relation early in diastole because it affects the atrioventricular pressure gradient and therefore affects filling rate during the rapid filling phase of diastole. The rate of relaxation generally does not influence end-diastolic directly because the relaxation process is over by the time diastole ends.

Estimating Relaxation Rate

One must be able to quantify changes in left ventricular relaxation to study how it affects diastolic pressure. The rate of relaxation can be quantified using the exponential relation Weiss et al proposed. They quantified left ventricular relaxation rate by fitting the time course of the isovolumic pressure fall beginning at the time of \( dP/dt_{min} \) and lasting through the mitral valve opening with the exponential function of time:

\[
p(t) = p_0 e^{-\frac{t}{T}}
\]

where \( p_0 \) is pressure at time of \( dP/dt_{min} \), \( t \) is time after \( dP/dt_{min} \), and \( T \) is time constant of isovolumic pressure fall. Ventricular relaxation rate is thus
quantified by a single number, T, the relaxation time constant. (The time constant equals the time required for the pressure to decay to $e^{-1} = 0.37$ of its original value.) This formulation also has the benefit of being easy to compute; taking the natural logarithm of both sides of Equation 6 yields a linear relation between $\ln(p)$ and t, with a slope of $1/T$.

The major problem with Equation 6 is the implicit assumption that if the left ventricle were allowed to relax fully without filling (as $t \rightarrow \infty$), the pressure would fall asymptotically to zero. Zero pressure asymptote means that the isovolumic ventricle would have zero wall stress when it is fully relaxed (Equation 3). However, as shown in Figure 2C, the total ventricular wall stress is zero only if the left ventricle is at its equilibrium volume, $V_o$, and the end-systolic and equilibrium volumes are not necessarily the same.28-31

Equation 6 can be modified to take into account the effect of unequal end-systolic and equilibrium volumes by incorporating the term, $p_o$, which is the pressure to which ventricle would relax if the ventricle were held at its end-systolic volume and allowed to relax completely:

$$p(t) = (p_o - p_e) e^{-t/T} + p_e \quad (7)$$

One cannot observe $p_e$ directly in situ because the mitral valve opens and the left ventricle begins filling before the muscle fully relaxes from the previous systole. However, Yellin et al.31 observed pressures as low as $-13$ mm Hg in dog left ventricles by preventing filling and allowing the ventricles to relax completely while being held at their end-systolic volumes. This observation of negative pressures validated the hypothesis that the left ventricular end-systolic volume was smaller than the equilibrium volume in these dogs.

Although incorporation of $p_e$ in Equation 7 improves the accuracy with which it can describe relaxation, the presence of $p_e$ in Equation 7 complicates calculation of T from data collected during isovolumic relaxation because the natural logarithm of both sides of Equation 7 no longer yields a linear relation between pressure and time as it did for Equation 6. Other methods for determination of T have been proposed such as those using the time derivative of both sides of Equation 7,32 solving Equation 7 without assuming anything about $p_e$ and without using the time derivative,33 or using a polynomial fit to the isovolumic pressure fall,34,35 but none of these methods has proven completely satisfactory.

The problem of assuming a zero pressure asymptote ($p_e=0$) when calculating the relaxation time constant, T, has been put in perspective by comparing three different ways of calculating T (Figure 3). Yellin et al.31 computed T: 1) by using the true $p_e$ which they obtained experimentally by occluding the mitral valve during systole to prevent filling during subsequent beats (Figure 3); 2) by letting the pressure asymptote float and determining it, together with T, from the best fit analysis to the data from a normal isovolumic relaxation period; and 3) by assuming $p_e=0$, as originally proposed by Weiss et al.27 Figure 3 shows pressure versus time curves as a result by computing T using each of these three approaches. Curve 1 shows the actual time course of the relaxation in a left ventricle after occluding the mitral valve to prevent filling. In this case, the end-systolic volume was less than the left ventricle’s equilibrium volume, and the ventricle relaxed to a pressure of $-9.2$ mm Hg. Using this value for $p_e$ in Equation 7 yields a value for the relaxation time constant, T, of 34 msec. This is the true value. Curve 2 shows the result obtained by using data from the normal period of isovolumic relaxation (from time 0 to time t_s) and using a best-fit analysis to estimate both $p_e$ and T in Equation 7. This procedure yielded an unrealistically low value of $p_e$ of $-19.7$ mm Hg and an unrealistically high value of
T of 55 msec. Curve 3 shows the result obtained by assuming \( p_r = 0 \) in Equation 7 (i.e., using Equation 6) and estimating \( T \) using the data from the normal period of isovolumic relaxation. The resulting estimate of \( T \) is 33 msec, which is surprisingly close to the true value of 34 msec. Indeed, an important result of the Yellin et al\(^{31} \) study was that although the value of \( T \) calculated by assuming \( p_r = 0 \), systematically underestimates the true value of \( T \), that is, calculated using the true pressure asymptote measured experimentally, it underestimates the true value by only about 10%. Therefore, although using Weiss et al\(^{27} \) original monoexponential formulation to determine \( T \) (Equation 6) systematically underestimates the true time constant, \( T \) determined in this manner can still be used as a reasonable measure of how quickly the ventricle relaxes.

**Effects of Ischemia on the Extent of Relaxation**

As noted in the introduction, slowed calcium uptake by the sarcoplasmic reticulum in response to ischemia has been proposed to explain the shifts in the diastolic pressure-volume curve after cardiac pacing-induced angina in patients with ischemic heart disease. This hypothesis led several investigators to measure the rate of relaxation in patients following production of ischemia.\(^{4-36-42} \) Unfortunately, although people routinely observed slowed relaxation (i.e., a larger value of \( T \)), the reduction in relaxation rate secondary to ischemia was not large enough to produce the shifts in the diastolic pressure-volume curve that had been observed at end-diastole. Moreover, animal studies of the effects of global ischemia and hypoxia on myocardial stiffness failed to demonstrate that ischemia can cause changes in myocardial stiffness.

However, a new experimental preparation that more closely modeled the situation that existed in the clinical studies, clarified the link between ischemia and shifts in the diastolic pressure-volume curve.\(^{45-47} \) In this preparation, occluders were placed on the circumflex and left anterior descending coronary arteries of open-chest, open-pericardium dogs and then tightened until flow in these two arteries was reduced by approximately 50%. The left ventricular diastolic pressure-volume curve was not affected by this decrease in flow. The hearts were then paced at approximately twice the resting heart rate. Immediately after pacing was stopped, the pressure-volume curve shifted upward but returned to normal within 1 minute. Thus, in contrast to previous animal studies, reversible shifts in the diastolic pressure-volume relation were produced that mimicked the shifts observed in patients with coronary artery disease.

These reversible shifts in the left ventricular diastolic pressure-volume relation do appear to be associated with the myocyte's ability to move calcium in and out of the cytosol, but the principal effect of impaired calcium handling ability should be on the extent of relaxation rather than on the rate. Although there is some slowing of relaxation (reflected by an increase in \( T \)) due to a reduction in the ability of the sarcoplasmic reticulum to sequester cytosolic calcium, the primary effect seems to be accumulation of calcium within the cytosol which, in turn, leads to an increase in the number of active cross bridges during diastole. The increased number of cross-bridges remaining at the end of diastole alters the extent of relaxation by causing the myofilaments (and therefore the equilibrium length) to be shorter than during normal cardiac function (or during demand-induced ischemia). The shorter equilibrium length is manifested globally as a smaller equilibrium volume (\( V_0 \)). The smaller equilibrium volume means that the strain, wall stress, and chamber pressure increase at any given volume even if the stress-strain characteristics of the muscle (\( \alpha \) and \( \beta \) in Equations 4 and 5) do not change.

Differences from previous experimental studies led Serizawa et al\(^{45,46} \) to propose that there are actually two types of ischemia in the intact heart: "supply-induced" and "demand-induced." During supply-induced ischemia the normally beating heart is underperfused (or perfused with a deoxygenated perfusate), which reduces systolic work, oxygen demand, and the amount of metabolic waste products produced. This is the situation that prevailed during the earlier animal studies. Under these conditions, a low coronary flow is sufficient both to supply oxygen and to remove metabolites, and, consequently, there are little or no changes in the diastolic properties of the myocardium. In contrast, during "demand-induced" ischemia, such as that during pacing after coronary artery occlusion, myocardial metabolic demands increase while the supply of oxygen and the capacity to remove waste products are limited by the occlusion. As a result, the sarcoplasmic reticulum takes up calcium more slowly, and more actin-myosin cross bridges remain intact at the end of relaxation.\(^{40-48-50} \) When an excess of \( Ca^{2+} \) remains in the cytosol after a contraction, an excess of cross-bridges remains attached and the equilibrium length of the muscle is shorter than normal. Thus, inadequate supply of ATP, \( Ca^{2+} \) overload, leakage of \( Ca^{2+} \) from the sarcoplasmic reticulum, or perhaps even the failure of the cell to return \( Ca^{2+} \) to the extracellular space are all possible mechanisms that could cause the upward shift in the diastolic pressure-volume relation that accompanies ischemia.

Although the distinction between supply-induced and demand-induced ischemia provides an appealing explanation for the differences observed in different experimental models of cardiac ischemia, it does not completely explain the mechanism for upward shifts in the diastolic pressure-volume curve in people with coronary artery disease. The hypothesized mechanism of the shifts observed during pacing in these patients is that the tachycardia increases the demand for oxygen without permitting a concomitant increase in supply. Conversely, dur-
ing coronary artery occlusion, the reduced blood flow supposedly results in reduced oxygen demand because systolic function is depressed. Although the evidence for this hypothesis is quite consistent and convincing in otherwise healthy experimental animals, this situation does not hold in humans with coronary artery disease. The situation with pacing-induced angina is a clear example of demand-induced ischemia. With the advent of percutaneous transluminal coronary angioplasty, the clinical analogue of experiments in which a coronary artery was transiently occluded became possible. Serruys et al51 performed a detailed study of systolic and diastolic function in patients with coronary artery disease during angioplasty. Heart rate and systolic pressure remained essentially constant during the period of balloon occlusion, but the left ventricular diastolic pressure-volume curve shifted upward during the occlusion, then moved back toward preoclusion values after the occlusion ended. The precise mechanisms for these shifts remain to be defined, but these results do indicate that the situation in sick people is more complex than that which is achieved in acute animal models of transient ischemia.

The clearest evidence that impaired Ca\(^{2+}\) uptake by the sarcoplasmic reticulum in the presence of hypoxia impairs myocardial relaxation is provided by studies of the load-dependence of relaxation in isolated muscle taken from different animal species.52,53 In these studies, cat, rat, and frog papillary muscles were investigated because each species has a different amount of sarcoplasmic reticulum and therefore relaxes differently in response to changing mechanical loading conditions. Cat myocytes are rich in sarcoplasmic reticulum and are thus sensitive to ischemia, which alters calcium energetics within the cell, whereas frog myocytes have relatively little sarcoplasmic reticulum. Rat myocytes have an intermediate amount. At various times during isotonic contraction, the afterloads were increased incrementally. In the cat papillary muscle, the time course of relaxation changed when the load increased, implying that relaxation was sensitive to loading conditions. In contrast, frog heart muscle relaxation was largely independent of load. Rat heart muscle was in between. Thus, cardiac muscle relaxation appears to depend on load and the ability of the sarcoplasmic reticulum to sequester Ca\(^{2+}\) and hence release actin-myosin cross-bridges.

Chuck et al54 demonstrated that hypoxia made cat papillary muscle less sensitive to load. Hypoxia suppresses the re-uptake of calcium by the sarcoplasmic reticulum,55,56 and this action would prolong activation because it would prolong the period during which calcium remains in the vicinity of the actomyosin cross-bridges. This could explain the observed diminution of load sensitivity. Hypoxia plus caffeine (which tends to make the sarcoplasmic reticulum permeable to calcium) made cat papillary muscle completely insensitive to load, and the force-deflection traces for the cat muscle were similar to those for frog papillary muscle. Thus, by making the cat papillary muscle hypoxic and adding caffeine, the cat muscle was effectively converted to frog heart muscle, which has little sarcoplasmic reticulum. This means that the ability of the sarcoplasmic reticulum to sequester cytosolic Ca\(^{2+}\) is probably the rate-limiting step of load-dependent relaxation. Moreover, since hypoxia (or ischemia) results in more calcium remaining in the cytosol at end-diastole, the equilibrium length would also decrease because a greater number of intact cross bridges would result in shorter muscle fibers at end-diastole due to the lack of complete relaxation. Thus, hypoxia or ischemia would cause a lessening of the extent of relaxation.

Factors That Affect the Relaxation Rate

A number of factors affect the relaxation rate but do not shift the entire diastolic pressure-volume relation because none of the changes in relaxation rate is large enough to affect the ventricular pressure at end diastole. Changes in relaxation rate do, however, affect the atrioventricular pressure gradient and thus affect the left ventricular filling rate during early diastole.

Several factors do not affect the time constant of isovolumic relaxation, T. For instance, T is independent of changes in ventricular volume, end-diastolic pressure, peak left ventricular pressure, stroke volume, end-systolic fiber length, and heart rate in isolated, isovolumically contracting dog hearts57,58 and in isolated ejecting left ventricles with the heart on right heart bypass.59

On the other hand, several factors do affect relaxation rate, as quantified by T. The extent of systolic shortening and interventions thought to influence calcium dynamics at a cellular level, such as ischemia, exogenous calcium, and norepinephrine, affect T.27,58 The time required for pressure to fall to 50% of its peak value (which equals 0.692T) increased by about 20% during reperfusion after regional ischemia but was unaffected by nitroprusside or by the ischemia itself.59 T changed by 12% to 18% while rapidly increasing or decreasing left ventricular afterload in open-chest anesthetized dog hearts.60 T also decreased after administration of isoproterenol and increased after administration of propranolol, suggesting that contractility affects T. T increased by 58% as both end-diastolic pressure and mean aortic systolic pressure increased during volume loading of intact hearts in anesthetized dogs.32 Finally, T increased by 45% after administration of phenylephrine to increase afterload in anesthetized dogs.61 The duration of relaxation is also increased (i.e., relaxation is slowed) in filling versus nonfilling left ventricles.14

Although in all of the cases just listed the changes in relaxation rate were large, they were not large enough to change end-diastolic pressure, because relaxation was always complete before end diastole.
at normal heart rates (Figure 4). Ventricular relaxation is considered complete approximately 3.5T after dP/dt_{min} because the ventricular pressure falls to 3% of its value at dP/dt_{min} after 3.5 time constants. Since T is typically about 40 msec in dogs and humans, the effect of relaxation is essentially over 140 msec after dP/dt_{min}. This means that relaxation from the previous systole will not have any effect on end-diastolic pressure at heart rates below approximately 150 to 160 beats/min (assuming that diastole occupies 40% of the R-R interval). [Weisfeldt, 1980]. At very high heart rates, it is possible that relaxation may not be complete before the next systole begins.

**Hypertrophy and Relaxation**

Whereas so-called physiological hypertrophy, which accompanies increased physical activity, and volume-overload hypertrophy do not appear to affect left ventricular relaxation, pressure-overload hypertrophy and hypertrophic cardiomyopathy reduce the rate and extent of relaxation. The reduced rate and extent of relaxation combine to reduce significantly the rate of left ventricular filling during early diastole. These changes in relaxation appear to be due to changes in the way the sarcoplasmic reticulum handles calcium; the whole process slows in the presence of pressure-overload hypertrophy or hypertrophic cardiomyopathy.

Myocardial ischemia also plays a role in modulating left ventricular relaxation in the presence of pressure-overload hypertrophy, even in the absence of coronary artery disease. Pressure-overload hypertrophy is associated with a substantial decrease in capillary density and coronary vasodilator reserve. Thus, in dogs with pressure-overload hypertrophy, pacing tachycardia (which increases myocardial oxygen demand) can reduce subendocardial perfusion and produce metabolic evidence of ischemia. Studies of patients with aortic stenosis also reveal hemodynamic and metabolic evidence of ischemia in response to increased demands on the heart, as well as histological evidence of interstitial fibrosis compatible with ischemic injury.

The mechanics of pressure-overload hypertrophy also aggravate the problems associated with ensuring adequate perfusion of the subendocardium. In thick walled shells, the stress is highest on the inside wall, and the gradient of stresses across the wall increases as the wall thickens. Thus, as the myocardium thickens to reduce the average stress in the wall, the stress near the endocardium may increase, putting additional demands on the cells located near the endocardium. The reduction of capillary density and coronary reserve in this region that accompanies pressure-overload hypertrophy further reduces the capacity to deliver oxygen and remove waste products in this region, particularly when wall stresses increase in response to increased demands put on the heart as a whole.

In sum, it appears that pressure-overload hypertrophy and hypertrophic cardiomyopathy affect relaxation in two ways. First, the function of the sarcoplasmic reticulum itself is depressed, slowing the uptake (and possibly the release) of calcium. This slowing of calcium uptake results in a slower relaxation and may allow changes in the resting level of calcium within the sarcomeres and so affect the extent of relaxation as well. Second, these forms of hypertrophy appear to be associated with at least transient subendocardial ischemia, and the ischemia itself affects rate and extent of relaxation.

**Implications for Systolic Function**

The original clinical studies of pacing-induced angina documented the effects on the diastolic pressure-volume relation of the entire left ventricle and led to the search for relaxation abnormalities as the cause of these effects. However, coronary artery disease is a regional disease, in which the regions of the heart that are served by obstructed vessels are affected while the regions served by unobstructed vessels are not affected. Thus, if the mechanism for shifts in the left ventricular diastolic pressure-volume curve during ischemia is a reduction in the equilibrium length of the ischemic muscle because of changes in the extent of relaxation, it should be
possible to show stiffening of the muscle in regions served by obstructed arteries and normal diastolic properties in the regions perfused by patent arteries. Angiographic studies of regional wall motion in patients who had coronary artery disease have demonstrated this point. In regions served by an obstructed coronary artery, the diastolic pressure-segment length curve shifted upward after pacing-induced angina. In parts of the heart perfused by normal coronary arteries, the resulting increase in diastolic pressure led to higher stresses and therefore greater strain (extension) of the normal myocardi-um. This condition stores elastic energy in the muscle, which is released during relaxation, resulting in an elastic recoil of the ventricle. Under some experimental conditions, negative ventricular pressures can be observed as evidence for this elastic recoil and, because a negative ventricular pressure during diastole would tend to suck blood into the ventricle from the atrium, the condition is often called ventricular diastolic suction.

Ventricular Diastolic Suction

Normally at end-systole the muscle fibers are compressed to lengths shorter than their equilibrium length, resulting in a left ventricular end- systolic volume smaller than the equilibrium volume. This condition stores elastic energy in the muscle, which is released during relaxation, resulting in an elastic recoil of the ventricle. Under some experimental conditions, negative ventricular pressures can be observed as evidence for this elastic recoil, and, because a negative ventricular pressure during diastole would tend to suck blood into the ventricle from the atrium, the condition is often called ventricular diastolic suction.

When left ventricular end-systolic volume is smaller than equilibrium volume, the muscle fibers are compressed to lengths shorter than their equi-
librium lengths, resulting in the phenomenon of ventricular diastolic suction. The term “ventricular diastolic suction” is unfortunate because it implies that a distinct property of the left ventricle generates negative pressures and “sucks” blood in from the atrium. Actually, so-called diastolic suction is merely a manifestation of the ventricle’s elastic properties when the end-systolic volume is less than the equilibrium volume. The forces generated during systole compress the muscle fibers to a length shorter than their equilibrium length and in so doing store energy in the muscle fibers and the surrounding collagen matrix as in a compressed spring. As in a spring, the more the muscle is compressed (i.e., the smaller the end-systolic volume), the more potential energy is stored in the muscle and the larger the recoil forces. The muscle does not need to be compressed very much to generate large recoil forces because the pressure-volume curve for the left ventricle bends down sharply at negative strains during compression (Figure 2C). These forces decrease the pressure in the left ventricle during early diastole and therefore increase the atrioventricular pressure gradient, which in turn increases left ventricular filling rate.

Therefore, experimental studies have provided the best evidence that negative pressures occur in relaxed left ventricles when end-systolic volume is less than equilibrium volume. Brecher et al. observed negative left ventricular pressures after squeezing arrested dog hearts to a small volume and then releasing them. Tyberg et al. used isolated dog hearts to show that ventricular pressures as low as −10 mm Hg could be measured by rapidly occluding the ventricular inflow tract during ventricular systole in a manner that did not displace any volume or otherwise disturb the system. Suga et al. observed diastolic suction by removing the left atrium and mitral valve from the heart and allowed it to beat in a pool of blood; blood filled the ventricle even though there was no atrial pressure driving it. Yellin and colleagues conducted the most elegant experiments demonstrating diastolic suction. They implanted a modified Star-Edwards prosthetic valve in the mitral orifice of dogs, which allowed them to prevent left ventricular filling by rapidly occluding the mitral orifice during systole. They recorded pressures as low as −13 mm Hg in the first beat after occlusion and −28 mm Hg during subsequent beats.

Clinical studies seldom directly demonstrate diastolic suction by revealing negative diastolic pressures because when the left ventricular pressure falls below the left atrial pressure, the mitral valve opens and blood flows into the ventricle. This filling causes the left ventricular volume to increase above V₀, so the condition that allows negative pressures to be observed is eliminated. However, the manifestations of a smaller end-systolic than equilibrium volume are observed occasionally in humans, particularly when partial occlusion of the mitral orifice impairs normal filling. Such partial occlusion occurs in patients with mitral stenosis, and negative diastolic pressures as low as −7 mm Hg have been observed in these patients. If mitral flow had been prevented altogether (as it can be in experimental animals), even more-negative pressures could probably be observed. Thus, partial mitral occlusion is an intermediate condition between the two experimental cases explained above and provides indirect evidence of diastolic suction.

Diastolic suction helps the heart respond to increased demands when contractility increases. Increasing contractility leads to smaller end-systolic
volumes, stronger recoil forces, and thus, a larger atrioventricular pressure gradient and more rapid early diastolic filling. This increase in filling rate maintains or even increases end-diastolic volume and so maintains end-diastolic sarcomere stretch and, therefore, systolic function.

Ventricular Interaction

The chambers of the heart interact mechanically with each other, particularly during diastole, when the pressures (and, hence, wall stresses) are low. Acute increases in right ventricular volume cause increases in left ventricular diastolic pressure. Similarly, increases in left ventricular volume increase right ventricular diastolic pressure. Thus, in addition to ischemia, which alters relaxation, ventricular interaction also shifts the left ventricular diastolic pressure-volume curve in response to changes in the vascular loading conditions the left ventricle faces. The degree of direct ventricular interaction and its importance to the left ventricular diastolic pressure-volume relation and the overall function of the heart depend on the mechanical forces (stresses) to which the muscle is subject and on the elasticity of the myocardium. The pericardium, which encloses the entire heart, strengths mechanical ventricular interaction. (Pericardial effects will be discussed in detail in the next section.)

The stresses in the intraventricular septum are particularly important in ventricular interaction, since the position of the septum depends on the transseptal pressure gradient and its material properties. Shifting of the septum is an important element in mediating ventricular interaction. When the left ventricular diastolic volume is held constant and right ventricular volume is increased, the left ventricular anterior-posterior dimension increases and the septum becomes flatter and moves toward the left ventricle.

Ventricular interaction has been observed in patients given drugs that alter ventricular loading conditions and shift the diastolic pressure-volume relation upward or downward. For example, ventricular interaction can explain the acute shifts upward or downward in the pressure-volume relation in patients given a vasoconstrictor angiotensin or the vasodilator nitroprusside. This observation, confirmed by others, was particularly important because it was the first evidence that hemodynamic changes other than ischemia alter the diastolic pressure-volume relation.

Evidence for the hypothesis that ventricular interaction was responsible for the shifts in the diastolic pressure-volume relation after giving vasodilating or vasoconstricting drugs was provided by a study in which patients were given nitroglycerine or amyl nitrate. The left ventricular pressure-volume curve shifted downward in the patients given nitroglycerine but did not shift in those patients given amyl nitrate. Both drugs lower systemic arterial pressure, but nitroglycerine also reduces right ventricular filling and volume by lowering venous return. Since nitroglycerine reduced right ventricular size as well as lowering arterial pressure, left ventricular pressure also fell. Therefore, ventricular interaction appeared responsible for the downward shift of the left ventricular pressure-volume curve.

Direct experimental evidence to support the hypothesis that ventricular interaction, modulated by the pericardium, was the mechanism for the shifts in the diastolic pressure-volume curve in response to vasodilation or vasoconstriction has been provided by animal studies. In this study, nitroprusside was administered to conscious dogs instrumented with ultrasonic crystals to determine ventricular dimensions. After giving nitroprusside, the left ventricular pressure-dimension curve shifted downward. These shifts disappeared when the pericardium was removed. Thus, the pericardium plays an important role in modulating the upward and downward shifts in the diastolic pressure-volume relation after acute administration of vasodilators or vasoconstrictors.

Direct Versus Series Interaction

So far we have been discussing so-called direct ventricular interaction, which is a manifestation of the forces transmitted through the septum (and, to a lesser extent, via the pericardium) between the two cardiac ventricles. However, there are two types of ventricular interaction: direct interaction, via mechanical forces across the septum, and series interaction, because right ventricular output becomes left ventricular input after passing through the pulmonary circulation.

The degree of direct ventricular interaction can be determined from isolated heart preparations in which the volume in one ventricle is held constant while the pressure-volume relation of the other ventricle is determined. These experiments, while easy to interpret, require severe disruption of the normal anatomical situation in which right ventricular output becomes left ventricular input and, thus, are of limited value in understanding the normally functioning heart.

Determining the degree of ventricular interaction using intact heart reflects normal physiology and anatomy but the results are difficult to interpret. Studies of ventricular interaction using intact hearts have reported various degrees of direct interaction. This variability is due in large part to the difficulty of determining the relative roles of direct and series ventricular interaction in the intact circulatory system. Using the traditional approach of collecting data in physiological steady state, it is virtually impossible to separate direct from series ventricular interaction in the intact circulatory system.

The problem of determining the relative roles of direct versus series ventricular interaction in the intact circulatory system is underscored by two recent independent studies. Using nearly identical preparations and protocols, both studies dem-
onstrated significant changes in left ventricular shape (particularly in the septal-free wall dimension) when right ventricular volume increased after a pulmonary artery constriction. However, whereas Olsen et al.\textsuperscript{119} interpreted these data to indicate that direct interaction was the less important effect, Visner et al.\textsuperscript{120} reached the opposite conclusion. To resolve this conflict, Slinker and Glantz\textsuperscript{121} used a new approach that took advantage of the time lag between a change in right ventricular output and left ventricular input\textsuperscript{122-124} to separate, empirically, the series (delayed) from the direct (immediate) ventricular interaction. After transiently constricting the pulmonary artery or venae cavae, they measured left and right ventricular volumes and pressures over several seconds and found that direct interaction was about one half as important as series interaction in determining left ventricular end-diastolic size with the pericardium on. Removing the pericardium decreased direct interaction to about one fifth as important as the series effect, supporting the view that the pericardium modulates ventricular interaction.

The relation of direct to series interaction also depends on the stiffness of the ventricular walls. In hypertrophied hearts with thickened ventricular walls (resulting from three months of renal hypertension), direct interaction at end-diastole was only about one tenth as important as series interaction in determining left ventricular size with the pericardium on.\textsuperscript{123} Removing the pericardium had very little effect on the relative importance of direct versus series interaction in these hypertrophied hearts because the thicker myocardium (and particularly the intraventricular septum) carried a relatively greater proportion of the wall stress than the normal hearts.

**Implications for Systolic Function**

Diastolic ventricular interaction is important for maintaining systolic function in response to changes in loading conditions, such as those associated with vasodilation. For instance, the downward shift in the left ventricular diastolic pressure-volume curve, such as that which occurs after acute administration of the vasodilator nitroprusside, is a critical factor in maintaining stroke volume.\textsuperscript{126} Specifically, Figure 7 shows data from a patient before and after nitroprusside administration.\textsuperscript{7} During the control condition, the end-diastolic pressure was 16 mm Hg, and the end-diastolic volume was 194 ml, with a stroke volume of 118 ml. After administering nitroprusside, the diastolic pressure-volume curve shifted downward, so that the end-diastolic pressure fell to 9 mm Hg, but, because the curve shifted, end-diastolic volume fell only slightly, to 176 ml, and stroke volume remained essentially constant at 114 mm Hg. Now, suppose that no ventricular interaction and no pericardium existed, so that the left ventricular diastolic pressure-volume curve moved down a unique pressure-volume curve and the end-diastolic volume fell as end-diastolic pressure fell. If this had happened, then the end-diastolic volume would have dropped to about 94 ml, making it impossible to maintain stroke volume near its original value of 118 ml. But because the entire pressure-volume curve shifted downward, stroke volume was maintained in the presence of a lowered end-diastolic pressure. Thus, ventricular interaction is important for maintaining systolic function.

**The Pericardium**

The pericardium surrounds the heart, reducing friction between the heart and the surrounding tissues and providing a barrier against infection. Its attachments to the mediastinum help restrain the heart from excessive motion within the chest when body position changes. When the heart's volume increases, the heart presses on the pericardium, which, in turn, presses back on the epicardium and constrains the heart's expansion.\textsuperscript{128} Because it constrains the whole heart and is stiffer than the myocardium, the pericardium increases the mechanical interaction between the four cardiac chambers. Thus, an increase in the size of one ventricle causes the pressure-volume relation of the other ventricle to shift upward due to the constraint of the pericardium.

**How the Pericardium Affects the Left Ventricular Diastolic Pressure-Volume Relation**

The pericardium modulates the pressure-volume relation both because it exerts normal stresses.
perpendicular to the epicardium and because it has a steeper stress-strain relation than the myocardium. The effect of the pericardium on the diastolic pressure-volume relation depends on the magnitude of the normal stress exerted by the pericardium on the epicardium, which, in turn, depends on the elastic properties of the pericardium (i.e., its stress-strain relation). At small pericardial volumes, pericardial stress is low and the pericardial stress-strain curve is fairly flat, so that large changes in strain (volume) result in only small changes in stress (pressure). Thus, at small pericardial volumes, the pericardium exerts only small normal stresses on the epicardium and the effect of the pericardium on ventricular diastolic pressure is small. However, when heart volume increases acutely above normal end-diastolic volumes, the pericardium is stretched and is moved up its increasingly steeper stress-strain curve (Figure 8). At steeper portions of the curve, small increases in strain (volume) result in large increases in stress (pressure). Thus, the normal stress exerted on the epicardium is large, and the pericardium contributes substantially to ventricular diastolic pressure. This increased stress means that a higher absolute left ventricular pressure is required to achieve a given left ventricular volume.

The key to assessing how much the pericardium influences the left ventricular diastolic pressure-volume relation under physiological conditions is determining where the pericardium normally operates on its pressure-volume curve. Answering this question is difficult, and it has been the subject of considerable debate. Several investigators have assessed the effect of the pericardium by comparing the left ventricular diastolic pressure-volume relations before and after removing the pericardium. At high left ventricular filling pressures (above about 10 mm Hg) pericardial stiffness clearly increases left ventricular diastolic pressures. This effect becomes more pronounced as left ventricular filling pressure and end-diastolic volume increase. In contrast, Stokland et al reported only a slight (4%) increase in left ventricular myocardial chord lengths after they increased blood volume and opened the pericardium of open-chest dogs, and Tyson et al reported little effect of the pericardium in conscious, chronically instrumented dogs with low diastolic pressures. Therefore, although the constraining effect of the pericardium contributes significantly to the upward shift of the left ventricular pressure-volume curve under the conditions of acute cardiac dilatation, there is at most a minimal effect at normal diastolic pressures.

The Atria

The pericardium increases mechanical coupling not only between the two cardiac ventricles but also between the ventricles and the atria. In a study using postmortem dog hearts in which the mitral and tricuspid valves were removed and the orifices plugged with disks, Maruyama et al found the effect of left atrial pressure was about one fourth that of right ventricular pressure in determining left ventricular pressure with the pericardium around the heart. When the pericardium was removed, neither the right nor the left ventricular diastolic pressure-volume relation was affected by a 22 mm Hg increase in right or left atrial pressure alone (Figure 9). The pericardium's role in strengthening the interaction between the atria and ventricles is not surprising because the atria have thinner walls, are more easily distended, and therefore are more tightly coupled with the pericardium than either of the ventricles. Although the left atrium and ventricle were isolated from one another in the Maruyama et al study, their results can still indicate a tighter coupling between the pericardium and the cardiac chambers even when the atrioventricular valves are open. For example, during diastole, while the mitral valve is open, the left atrium and left ventricle form in essence a single chamber that is influenced by the presence of pericardium. The pericardium surrounding the atria is essential for modulating the mechanical coupling between them and the ventricles.

Measuring Pericardial Pressures

Much of the controversy regarding the role of the pericardium centers on the magnitude of the constraining forces the pericardium exerts on the epicardium. Because these forces are difficult to measure, much of the debate about the importance (or lack of importance) of pericardial constraint revolves around methodological issues relating to the measurement of pericardial pressure.

The most direct way to assess pericardial constraint is to measure the normal stress exerted by the pericardium, the so-called "pericardial pressure" between the pericardium and the epicardium. Under normal conditions, the stresses in the peri-
A) Right Ventricular Pressure-Volume Relationship

B) Left Ventricular Pressure-Volume Relationship

Figure 9. The effect of the pericardium on chamber pressure-volume relations. The ventricular pressure-volume relation of one ventricle is shifted upward when the pressure in one or more of the other chambers is increased. The pericardium causes this interaction to be more forceful. In addition, the direct interaction effect of the right ventricle on the left is greater than the left is on the right, particularly with the pericardium on. The representative right (A) and left (B) ventricular pressure-volume curves from isolated, perfused dog hearts were obtained while holding the other three chambers at various pressures from 5–30 cm H2O (4–22 mm Hg) with and without the pericardium. Curves 1, 2, and 3 in each situation were with the pericardium on [pericard (+)]. Curves 4, 5, and 6 were without the pericardium [pericard (−)]. Prv, right ventricular pressure; Plv, left ventricular pressure; Vrv, right ventricular volume; Vlv, left ventricular volume. (From Maruyama et al130 with permission of the American Heart Association.)

cardium, which cause the ventricles to interact more forcefully, are transmitted directly to the epicardium as normal stresses with the small amount of fluid in the pericardial sac serving as a lubricant. During tamponade, when there is a significant amount of fluid in the pericardial sac, the normal stresses exerted by the pericardium are transmitted to the epicardium as a fluid pressure. There is no physical difference between these two conditions from the point of view of the epicardium because a normal stress and a hydrostatic pressure generate equivalent normal stresses on the epicardium.

The two basic methods for measuring pericardial pressure have been controversial since the 1960s, when Holt et al138 used a thin-walled balloon to measure pericardial pressures and reported pericardial restriction of atrial and ventricular distension, and Wood et al139,140 used open-ended catheters to measure pericardial pressure and reported no such restriction. Although ventricular pressures can be measured accurately and easily with open-ended or manometer-tipped catheters, these instruments yield accurate measurements of pericardial pressure only in very limited situations, namely when there is substantial fluid in the pericardium. When there is a minimal amount of fluid in the pericardial space, the normal stress of the pericardium acts directly on the epicardium, and open-ended or manometer-tipped catheters greatly underestimate the "pressure" (normal stress) the pericardium exerts on the epicardium.

The balloon versus catheter controversy was resolved by comparing pericardial pressure measured in open-chest dogs with flat fluid-filled balloons and open-ended catheters while infusing saline into the pericardium.135,136,141 Above pericardial fluid volumes of 30 ml, the two methods yielded similar results. However, below 30 ml, the open-ended catheter substantially underestimated the pericardial pressure because there was insufficient pericardial fluid to transmit the normal stress (generated by the pericardium) to the pressure transducer (Figure 10). In a different study, Mann et al142 used air-filled balloons to measure pericardial pressure and also concluded that a balloon is the appropriate way to measure pericardial pressure.

Flat balloons always measure the normal stresses the pericardium exerts on the epicardium because the balloon creates a confined region for the fluid to transduce the normal stress into a hydrostatic pressure that can be measured with a pressure transducer inside the balloon. Smiseth et al136 demonstrated this point unequivocally when they used such a balloon to measure pericardial constraint after cutting small slits in the pericardium. Because the slits allowed the pericardial fluid to drain, an open-ended catheter inserted in the pericardium measured no pressure. Even so, the pericardium, now similar to a stiff net, still exerted a normal stress on the heart, which a flat balloon transducer accurately measured. During tamponade, when the pericardial space is filled with fluid, the balloon floats in the pericardial fluid and senses its pressure. Thus, the balloon measures the normal stress the pericardium exerts on the epicardium whether or not there is fluid in the pericardial space. Using flat balloons is essential for accurate measurement of pericardial pressure, unless one can ensure that sufficient fluid exists in the pericardial space to
transmit the stresses between the epicardium and pericardium via the fluid pressure.

**Measurement Artifacts Resulting From Instrumenting the Pericardium**

The experimental manipulation necessary to instrument the pericardium can affect the observed left ventricular diastolic pressure-volume relation. Opening the pericardium to instrument the pericardial space invariably leads to artifacts in measuring pericardial pressures and could account for divergent results among various experimental studies. Gibb and Churchill, Stokland et al, Spadaro et al, and Tyson et al have all demonstrated that reapposing the pericardium with sutures or glue can magnify the pericardial constraint, particularly if long pericardial incisions from base to apex are used. To reduce the possible measurement artifacts due to opening and closing the pericardium, Tyson et al suggest opening the pericardium with an incision across the base of the heart instead of cutting the pericardium along the long axis. They then constrict the venae cavae to reduce heart size, and pop the heart out of the pericardium. This procedure leaves the pericardial sac relatively intact. In addition, the pericardium can be left under and covered by the heart to keep it moist while the heart is instrumented thereby avoiding shrinkage, which has been observed during cardiac surgery. After instrumenting the heart, the process is reversed: the venae cavae are again constricted to reduce heart size and the heart is replaced in the pericardial sac with a minimum of trauma to the pericardium. When the heart is prepared in this way, the effect of pericardial constraint is less than is observed using the older technique with an incision along the long axis of the heart. This procedure has become widely accepted for instrumenting the heart in a way that will minimally disturb the pericardium.

**Assessing Pericardial Constraint in Patients**

Although knowing pericardial pressure is important in assessing pericardial constraint and hence ventricular function during diastole, it is seldom possible to measure pericardial pressure in patients directly. Obviously, measuring pericardial pressures with balloons is too invasive for patients. However, because the right ventricle and atria have thinner walls than the left ventricle and, hence, are more closely coupled with the pericardium, right ventricular or atrial pressure has been proposed as a substitute for direct measurement of pericardial pressure. In a comparative study between patients with tamponade who underwent pericardiocentesis and open-chest dogs with large pericardial effusions, Smiseth et al concluded that right ventricular pressure was a useful approximation of pericardial

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**Figure 10.** The difference between the measured and calculated pericardial pressures as a function of pericardial fluid volume. The pericardial pressure measured using a flat balloon containing a pressure transducer is compared with the pressure measured using an open-ended catheter inserted in the pericardial space. The pericardial pressure was computed as the difference in measured intraventricular pressure with and without the pericardium around the heart at various left ventricular volumes. The open-ended catheter significantly underestimates pericardial pressure unless there is at least 30 ml liquid within the pericardium. Dark, shaded area shows the pericardial fluid volumes at which both methods of measurement fall within the 95% confidence interval of the calculated pressure. The flat balloon, however, approximates the calculated pressure regardless of the volume of fluid in the pericardium. Lightened lines indicate the 95% confidence intervals of the pressure curves. (Modified from Smiseth et al with permission of the American Heart Association.)
pressure. Likewise, Tyberg et al. found that the pericardial pressure was similar in magnitude to the mean right atrial pressure in patients over a wide range of these pressures (-4 to 20 mm Hg). These investigators concluded that in normal hearts during diastole when the right atrioventricular valve is open, right atrial and ventricular pressures can be used to approximate pericardial pressure.

There are clearly limits to approximating pericardial pressure with right atrial or ventricular diastolic pressure. One example is when the right ventricle stiffens as a result of right ventricular hypertrophy. Another example is in patients with cor pulmonale or pulmonary hypertension. In both cases, right atrial pressures may be much higher than pericardial pressures. During pericardial drainage to treat cardiac tamponade, pericardial pressure falls considerably below right atrial pressure. These low pericardial pressures most likely occur because in patients with large chronic pericardial effusions, the pericardium is stretched well above its normal capacity. Thus, removal of the pericardial fluid would result in a very loosely fitting (or even collapsed) pericardium and no pericardial constraint. Under normal conditions, however, the right atrial pressure can probably be used as a reasonable approximation for pericardial pressure during diastole.

**Pericardial Adaptation to Ventricular Hypertrophy**

The pericardium adapts to chronic increases in heart size by increasing its mass (size) and as the pericardium expands over time, its effect on the left ventricular diastolic pressure-volume relation decreases. This changing role of the pericardium was demonstrated by Lewinter and Pavlec who compared left ventricular diastolic pressure-segment relations before and after removing the pericardium in dogs during the early (7-9 days) and late (34-50 days) stages of hypertrophy after imposing a chronic left ventricular overload. Removal of the pericardium early after the volume overload was created reduced the right and left ventricular end-diastolic pressures and increased dimensions at matched levels of left ventricular end-diastolic pressure greater than 10 mm Hg. Hence, shortly after creating the volume overload, the heart had expanded against the pericardium, which led to an increase in diastolic left ventricular pressure. In contrast, after left ventricular mass increased, neither left ventricular end-diastolic dimension nor right ventricular end-diastolic pressure changed when the pericardium was removed, indicating that the pericardium had expanded and was exerting less of a constraining force on the heart. Thus, when the pericardium hypertrophies along with the heart, the pericardium plays a smaller role in determining the left ventricular diastolic pressure-volume relation than in normal hearts. The influence of the pericardium changes because as the heart increases in size the pericardium is stressed chronically. The pericardium responds to this increased stress by increasing its size. When this happens the enlarged pericardium would operate on a flatter portion of its stress-strain curve; the constraining forces are smaller and the influence of the pericardium on the heart is less than its influence before the hypertrophy.

Another effect of myocardial hypertrophy is that the relative importance of the pericardium and of direct ventricular interaction is less when the ventricular wall thickens. For example, in normal dog hearts, Slinker and Glantz found that removing the pericardium decreased the relative importance of direct versus series ventricular interaction in dogs from about one half to one fifth. In hearts that had hypertrophied in response to three months of renal hypertension, the importance of direct interaction was less, becoming only about one tenth as important as series interaction with the pericardium and essentially zero without the pericardium. As the ventricular walls thicken in response to the pressure overload, the thicker walls become less distensible, and more of the ventricular pressure is balanced by the elasticity of the myocardium as opposed to the pericardium.

**Implications for Systolic Function**

By restricting the expansion of the heart, and thus restricting extension of the sarcomeres that make up the myocardium, the pericardium can affect left ventricular systolic function via the Frank-Starling mechanism under certain pathological conditions. For example, right ventricular infarction can precipitate a low cardiac output syndrome. Although a reduction in right ventricular systolic function plays a role by reducing right ventricular output and left ventricular input, ventricular interaction, mediated by the pericardium, is also important. Goldstein et al. produced right ventricular infarction in dogs by infusing mercury into the coronary circulation. Immediately after the infarct, the right ventricle attempted to dilate within the pericardium, increasing pericardial pressure, increasing left ventricular diastolic pressure, and inhibiting filling. The associated lower left ventricular end-diastolic volumes impaired systolic function because of the Frank-Starling mechanism. When the pericardium was opened and the right ventricle was free to dilate without competing with the left ventricle within the pericardium, the left ventricle could expand and increase end-diastolic volume, stroke volume, and cardiac output.

**Pulmonary-Cardiac Contact Pressure**

The observation that blood pressure and cardiac output fell in patients ventilated with positive end-expiratory pressure (PEEP) stimulated interest in the effect of the lungs on cardiac function. Just as the ventricles and the pericardium interact with each other because they are in physical contact, so the heart and lungs interact mechanically.
because they are in physical contact. Like the pericardium, the lungs affect the left ventricle’s diastolic pressure-volume curve by exerting a normal stress on the heart. The contact pressure, which is on the order of a few millimeters of mercury, has little direct mechanical effect during systole. However, during diastole, when pressures are low, inflating the lungs can increase pressure outside the heart and lower the left ventricular transmural pressure at any given absolute left ventricular pressure. This lower transmural pressure can reduce end-diastolic volume and reduce cardiac output because of the Frank-Starling mechanism. This mechanical interaction between the heart and lungs explains the reduction in cardiac output that occurs during PEEP.

Lung hyperinflation or positive pressure ventilation with more than 10 cm H$_2$O (8 mm Hg) PEEP reduces both ventricles’ diastolic size because of the direct compressive force the lungs apply to the heart. Fewell et al.\textsuperscript{164} directly observed the effect of mechanical compression of the heart by hyperinflated lungs by attaching flat balloon pressure transducers to the epicardium of both left and right ventricles of dog hearts. Cardiac transmural pressures were calculated as the difference between ventricular and balloon pressures. They determined transmural pressures during 0 and 12 cm H$_2$O PEEP with the chest open, the chest closed and evacuated, and with the pericardium intact and removed. With the chest closed and the pericardium intact, absolute left and right ventricular end-diastolic pressures increased from 4 to 7 mm Hg and from 3 to 6 mm Hg respectively, when PEEP was increased from zero to 12 cm H$_2$O (Figure 11). In contrast, left and right ventricular end-diastolic transmural pressure and volumes both fell. This difference between absolute and transmural end-diastolic pressure was not due to the pericardial constraint because the pericardium simply transmits the pressure exerted by the lungs and removing it does not alter the effect of pulmonary-cardiac contact pressure. This fact was demonstrated in the open-chest dogs in which the lungs were held away from the heart to prevent the lungs from pressing on the heart. Although end-diastolic volume increased about 11% when the lungs were held away from the heart, there was no change in either cardiac output or ventricular end-diastolic pressure during PEEP. Lung hyperinflation or positive pressure ventilation with more than 10 cm H$_2$O PEEP decreases right and left end-diastolic volumes due to mechanical compression of the heart by the hyperinflated lungs. Heart rate does not change; therefore, cardiac output drops because of the Frank-Starling mechanism. The reduction in cardiac output appears to be primarily a mechanical effect of the lungs pressing on the heart, which occurs independently of changes in myocardial contractility, or neural and humoral effects.

Viscoelastic Properties of the Myocardium

So far we have seen that the primary determinants of left ventricular filling and of the diastolic pressure-volume relation are the myocardium’s intrinsic mechanical characteristics—the geometry...
of the ventricular cavity (particularly wall thickness), the elasticity of the myocardium, and extent and rate of relaxation—and the external forces acting on the left ventricle through ventricular interaction, the pericardium, and pulmonary-cardiac contact pressure. In addition to these major factors, there are two additional factors that make a small contribution to the diastolic pressure: viscoelasticity of the myocardium and coronary vascular engorgement.

Like most biological materials, the myocardium is viscoelastic so that stresses in the heart wall depend on the rate at which it deforms (strain rate, \( \dot{e} \)) as well as on the magnitude of the deformation (strain, \( e \)). This dependence means that the diastolic pressure depends on the filling rate as well as on the ventricular volume and that the diastolic pressure at a given volume increases as filling rate increases. Although there is no doubt that viscous forces contribute to diastolic pressure, particularly during rapid filling and atrial systole, this contribution is probably small.

Because viscous forces increase with filling rate, these forces are greatest during the rapid filling phase in early diastole and atrial systole. However, elastic recoil or restoring forces are also most significant during rapid filling. Therefore, it is difficult to separate changes in the diastolic pressure-volume relation during early diastole due to myocardial viscoelasticity from the changes due to active relaxation.

To demonstrate the effect of myocardial viscoelasticity on the left ventricular diastolic pressure-volume relation, several investigators have shown that during rapid diastolic filling the ventricular pressure exceeds that predicted by a simple elastic model. The most elegant analysis of viscoelastic effects in the intact heart during diastole was done by Rankin et al., who represented myocardial viscoelasticity analytically. They modified the equation for purely elastic myocardium given by the two-element model given by Equation 8 (solid lines). The lower solid line is the purely elastic curve (given by Equation 5) predicted from the dynamic data when the strain rate is zero. Myocardial viscoelasticity causes higher ventricular pressures to be observed than predicted by a purely elastic model during rapid filling and atrial systole. (From Rankin et al., with permission of the American Heart Association.)

\[
\sigma = \alpha (e^\mu - 1) + \gamma \dot{e}
\]

where \( \gamma \) is a viscosity parameter and \( \dot{e} \) is \( \frac{de}{dt} \), and combined this equation with an elliptical model of the left ventricle to compute wall stress from pressure, volume, and wall thickness. They then alternately occluded and released both venae cavae and the aorta of dogs to obtain a variety of left ventricular sizes and filling rates. This experiment allowed them to relate strains (\( \epsilon \)) and strain rates (\( \dot{\epsilon} \)) from measurements of left ventricular diameters obtained from ultrasonic crystals sewn on the epicardium with the computed wall stress. Although computation of strain rates based on ultrasonic crystal dimension measurements of the heart may be problematic, the experimental stress-strain data fell very close to that predicted by Rankin et al.'s viscoelastic model. These data suggested that viscoelastic effects play a substantial role during early diastole and atrial systole, when filling rates are high.

The conclusions that of viscoelastic effects in the whole heart cause increased diastolic pressures when filling rates are high are consistent with the observation that viscoelastic behavior can be elicited by suddenly stretching a strip of isolated muscle and monitoring the resisting force over time in a so-called "stress relaxation experiment." If the muscle was purely elastic, the force would change instantaneously with the length, and then remain constant at the value appropriate for the new length. A three-element model, consisting of two elastic elements (springs) and one viscous element (dashpot) (Figure 13A), best represents the stress relaxation response of isolated muscle. When length is suddenly increased, strain rate is theoretically infinite, so the spring-dashpot combination in parallel cannot extend (because the force in the dashpot becomes infinite) and the series spring model extends. But this extension of the single spring creates a force imbalance between it and the spring-dashpot combination. These forces redistribute themselves over time until the forces in the two springs are equal and the material reaches a new equilibrium at the increased length (Figure 13B). Thus, in response to a suddenly imposed change in length, the force in the three-element model increases asymmetrically and then falls off as the dashpot begins to extend, reducing the total...
force on the strip of muscle and observe the change in length over time in a so-called creep experiment (Figure 13C). (These two terms, which are very often misused in the cardiovascular literature, describe the response [behavior] of a particular viscoelastic material to a specified input, that is, a step increase in length or in force. Stress-relaxation and creep are not mechanisms or material properties.)

In contrast to the model just discussed, Equation 8 represents a two-element viscoelastic model in which a single elastic and viscoelastic element are in parallel (Figure 13A). The stress-relaxation response for this two-element model is different from that previously described for the three-element model; the two-element model predicts that the material will exhibit a theoretically infinite force for the instant immediately after the muscle is stretched, and thereafter assume the constant value appropriate for the new length (Figure 13B). This response is not observed in isolated muscle. Thus, although the fit of data observed by Rankin et al185 is compelling (Figure 12), a theoretical difficulty remains. The two-element model defined by Equation 8 does not exhibit the stress-relaxation and creep behavior that has been observed in isolated cardiac muscle. This contradiction has not yet been resolved.

The fact that viscous forces increase at the same time that filling is greatest during active relaxation (or atrial systole) makes separating viscoelastic from relaxation effects difficult. Pasipoularides et al188 proposed a mathematical method to separate viscoelastic from relaxation effects. They subtracted a component of pressure assumed to be due to relaxation calculated based on the monoexponential model of isovolumic pressure fall (Equation 6) and then examined the residual pressure for evidence of viscoelastic (i.e., rate-dependent) effects. In so doing, they assumed that the isovolumic ventricle would relax to a zero pressure asymptote (p∞=0). Although Pasipoularides et al188 admitted that a nonzero pressure asymptote could alter their results by shifting the passive pressure-volume curve up or down, they argued that this would have a negligible effect on the passive stiffness-stress relation in their model. Using this method to evaluate patients with normal hearts who had undergone cardiac catheterization, they concluded that in hearts in the "basal" state, the strain rate-dependent (viscoelastic) effects were minimal. This conclusion is supported by Fioretti et al,192 who reasoned that viscous effects in early diastole are overshadowed by relaxation effects. The confounding effects of relaxation are not present late in diastole during atrial systole, when the ventricle is fully relaxed. Thus viscoelastic effects probably do play a role in increasing left ventricular pressure during atrial systole (Figure 12).

In summary, whether or not they are measurable, viscous forces increase continuously as a function of filling rate. The difficulty in interpreting these
strain rate–dependent effects is that the strain rates are highest in early diastole, when filling is fastest and when active relaxation from the previous beat is taking place. It is probable that most of the effects that have been attributed to viscoelasticity during rapid filling are due to active relaxation. However, viscous forces make an identifiable contribution to left ventricular pressure during atrial systole.

Coronary Vascular Engorgement

Increasing coronary artery pressure has been hypothesized to stiffen the network of coronary arteries that permeate the myocardium and so stiffen the left ventricular wall, analogous to the way erectile tissue stiffens when it is engorged with blood. This resultant stiffening of the left ventricular wall would be reflected in the diastolic pressure-volume relation just as if the muscle itself became stiffer. The effect of coronary vascular engorgement on ventricular stiffness would be most evident late in diastole, when the coronary arteries are maximally perfused. Although myocardial stiffening as a result of vascular engorgement has been demonstrated in isolated heart preparations, the effect is small, so it does not contribute appreciably to the diastolic pressure-volume relation.

The first reported evidence for a myocardial erectile effect was the finding that the end-diastolic pressure in isovolumically contracting dog left ventricles increased when coronary arterial perfusion pressure increased. Although Salisbury et al did not measure chamber stiffness directly in this study, they nevertheless showed that the left ventricular diastolic pressure increased by as much as 18 mm Hg (to 22 mm Hg) when coronary arterial pressure increased from 35 to 125 mm Hg. They proposed that the mechanism responsible for this behavior was engorgement and stiffening of the matrix of blood vessels in the myocardium. Later, Olsen et al found that the left ventricular pressure-minor axis strain curve shifted upward (indicating increased ventricular stiffness) when they increased coronary perfusion pressure from 40 to 120 mm Hg in potassium-arrested dog hearts. To demonstrate that coronary arterial perfusion pressure alone caused the ventricular stiffening and not coronary blood flow, they performed similar experiments after administering the vasodilator adenosine to increase coronary blood flow. The pressure-minor axis strain relation as a function of coronary arterial perfusion pressure were the same with or without adenosine. Therefore, the left ventricular stiffness depended on coronary arterial perfusion pressure below the autoregulatory range of 80 mm Hg. The effect, however, was small.

If increasing coronary arterial perfusion pressure causes the myocardium to stiffen, then reducing perfusion pressure should have the opposite effect. By reducing coronary arterial perfusion pressure to zero in isovolumic dog hearts, Gaasch et al observed that diastolic wall thickness decreased by 7% and diastolic pressure decreased by 23%. In addition, Gaasch and Bernard found that during reactive hyperemia (after coronary artery ligation and reperfusion), wall thickness was 10% greater than the control (before ligation), indicating a stiffened myocardium.

Other similar studies have not demonstrated changes in chamber stiffness as a function of coronary perfusion pressure. The lack of observed changes in chamber stiffness in these studies may have resulted from either measuring diastolic pressures and flows at a single left ventricular volume or too small a change in the coronary perfusion pressure to obtain much effect.

The main problem encountered in studies designed to determine whether the myocardium stiffens due to coronary vascular engorgement is to decouple metabolic effects (changes in the myocardium due to changes in coronary blood flow or perfusate) from hydraulic (erectile) effects. Many studies have compared how myocardial stiffness changes when coronary flow is stopped (ischemia) with how stiffness changes when the coronary arteries are perfused with a hypoxic perfusate (hypoxia). In both cases, oxygen supply to the heart is reduced, which affects cell metabolism, calcium flux, active relaxation, and, perhaps, myocardial stiffness. Therefore, hypoxia or ischemia would tend to mask a possible erectile effect by the effects of the ischemia or hypoxia. This masking is further complicated by the small nature of the erectile effect itself. For example, Vogel et al perfused isolated rabbit hearts with a variety of normoxic and hypoxic media and found that changes in the diastolic pressure-volume curve were directly related to changes in wall thickness associated with the different perfusates, independent of the effects of ischemia per se.

The problem of decoupling erectile (hydraulic) from metabolic effects was directly addressed by Watters et al and Bouchard et al who used a rapid freeze-clamp method to stop metabolism ten seconds after stopping coronary arterial perfusion and measured left ventricular equatorial cross-sectional area, diastolic wall thickness, developed pressure, and high energy phosphate metabolism in isovolumic rat and hamster hearts. Ten seconds of ischemia was not sufficient to cause measurable changes in metabolism but did reduce left ventricular diastolic wall thickness by 4% and left ventricular epicardial cross-sectional area by 8%. Thus, they demonstrated an erectile effect independent of metabolic effects within the first 10 seconds of ischemia.

Theoretical work has also demonstrated that coronary vascular engorgement has a small effect on left ventricular stiffness. Huyge did a theoretical analysis of the beating left ventricle and intramyocardial coronary circulation using a nonlinear, finite element analysis which showed that diastolic ventricular stiffness increased slightly, by 10%, when coronary perfusion pressure was increased from 45 to 120 mm Hg. Thus, both experimental and theoretical
investigation has shown that increasing coronary perfusion pressure increases the apparent stiffness of the diastolic left ventricle, but the effect is small.

Conclusion

Studies of diastolic function have been a fruitful area of investigation for the last 10 years and our understanding of diastolic function has changed significantly since the last Brief Review on the subject published in Circulation Research. It is now well established that the traditional view of the diastolic left ventricle as an isolated shell in which filling pressure and volume are uniquely related is incorrect: The diastolic pressure-volume relation changes in response to changes in the heart's operating environment. The diastolic pressure-volume relation depends on the balance between the pressure in the left ventricle and the stresses in the myocardium. These stresses, in turn, depend on the size and thickness of the ventricle and the elasticity of the myocardium. Thus, when the left ventricle contracts to a volume smaller than its equilibrium volume, elastic energy is actually stored in the myocardium. This stored energy is manifested as so-called diastolic suction, which increases the atrioventricular pressure gradient and speeds filling during early diastole. In addition to these factors, there are two major categories of factors that can acutely change the diastolic pressure-volume curve.

The first category of factors includes those that alter the extent of relaxation from the previous systole, such as demand-induced ischemia. This type of ischemia impairs active uptake of calcium from the cytosol which yields a higher resting concentration of calcium in the sarcomeres during diastole and a smaller apparent equilibrium volume for the ventricle. This smaller equilibrium volume means that the strains (and, hence, stresses) within the wall of the heart will be higher for any given volume of the left ventricle than before ischemia, so there will be a higher pressure at any given volume.

The second category of factors that alter the diastolic pressure-volume curve includes those that alter the external mechanical environment in which the left ventricle resides, in particular, the other cardiac chambers, the pericardium, and contact pressure with the lungs. Interventions such as vasodilation and vasoconstriction alter the forces that these other components exert on the left ventricle. Since the pressure within the left ventricular cavity represents the net effect of the forces within the myocardium and those outside it, changes in these external forces are reflected in pressure changes within the left ventricle at any given volume, and therefore shift the diastolic pressure-volume curve.

These changes in the diastolic pressure-volume curve have several important implications for systolic function. First, when the end-systolic volume is below the left ventricle's equilibrium volume, the myocardial wall is put into compression and stores elastic energy during systole (just as compressing a spring stores energy). This energy is released when the myocardium relaxes and acts to reduce the ventricular pressure, thus, increasing the atrioventricular pressure gradient during early diastole. Increasing the atrioventricular pressure gradient causes the ventricle to fill more rapidly which helps maintain end-diastolic volume and, via the Frank-Starling mechanism, systolic function. Second, shifts in the diastolic pressure-volume relation in response to vascular loading changes are essential in helping the left ventricle maintain stroke volume during vasodilation because these changes maintain end-diastolic volume even though left ventricular end-diastolic pressure falls during vasodilation. Finally, the fact that filling pressure and volume are not uniquely related means that end-diastolic pressure cannot be used as a surrogate for end-diastolic volume when assessing systolic function.

Acknowledgments

We thank William Parmley, Julian Hoffman, David Teitel, Bryan Slinker, Chester Boltwood, Robert Appleyard, Mimi Zeiger, and the referees for their helpful criticisms of this manuscript.

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**KEY WORDS**: cardiac mechanics, relaxation, ischemia, diastolic suction, viscoelasticity, ventricular interaction, pericardium, cardiopulmonary interaction, left ventricle, cardiac filling, coronary vascular engorgement
Determinants of left ventricular filling and of the diastolic pressure-volume relation.

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_Circ Res._ 1989;64:827-852
doi: 10.1161/01.RES.64.5.827

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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http://circres.ahajournals.org/content/64/5/827.citation

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