Myocardial relaxation and passive diastolic properties in man

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ABSTRACT We have developed a model for assessing the influence of the decaying contractile systolic tension on diastolic wall dynamics and the passive properties of left ventricular muscle. Total measured left ventricular diastolic pressure and stress (σT) are determined by two overlapping processes: (1) the decay of actively developed pressure and stress (σX) and (2) the buildup of passive filling pressure and stress (σ*). The decaying contractile stress σX is formulated in terms of a relaxation pressure with a time constant (T) assessed during the isovolumic relaxation interval. By subtracting the contribution of σX from σT we obtain σ*. With micromanometry, echocardiography, and cineangiography, total and passive stress-strain relations and strain rates were evaluated over the entire filling period in six normal control subjects and in seven patients with aortic stenosis. Elastic stiffness constants (k), the slopes of the linear passive stiffness vs σ* relations, did not differ in the two groups over a common lower stress range (6/6 normal, k = 9.37 ± 1.23; 7/7 aortic stenosis, k = 9.34 ± 1.08). Over a higher σ* range, transition into a much steeper linear region occurred, and k values were much larger (4/7 aortic stenosis, k = 28.76 ± 2.02). When diastolic stress levels are elevated, passive stiffness-stress relations can be better described as bilinear, with a much greater wall stiffness constant in the higher than in the lower stress range. Dynamic effects of decaying systolic contractile wall stress components are important in the rapid filling phase in normal hearts as well as in those with aortic stenosis.


ANIMAL and clinical investigations have demonstrated that diastolic pressure-volume relations can be altered either by acute interventions, such as hypoxia and ischemia, or by chronic disease states such as pressure overload.1–3 Mathematical analyses4–6 have shown that the effects of changes in chamber geometry and wall mass have to be distinguished from those of changes in the elastic properties of the cardiac muscle itself. In such analytical models it is assumed that the ventricular wall acts as a passive medium and the models can be applied to the beating ventricle only in the latter part of diastole, a time when contractile stresses have decayed to negligible levels. In early diastole, after mitral valve opening, left ventricular pressure continues to fall, although the chamber is expanding.7,8 The early diastolic deviation from what is expected of a purely passively distended elastic chamber has continued to preclude a better understanding of the mechanical behavior of ventricular muscle throughout the entire diastole. In this study we have developed a model for assessing the influence of early incomplete ventricular relaxation on wall dynamics and the passive stiffness of cardiac muscle with data from the entire filling period.

Methods

General considerations. The elastic stiffness of intact passive ventricular muscle can be expressed by an incremental modulus concept. Although the overall myocardial stress-strain response curve is nonlinear, it is possible to consider it to be incrementally linear over small successive subranges of stress and strain. Rather than remaining constant, the incremental modulus of passive muscle increases with increasing stress levels, indicating a progressive stiffening of the wall. From the study of Misky and Rankin,5 the incremental modulus levels for the wall of a passive elastic chamber are proportional to the ratio of the increment of a stress to the associated increment of a strain. If the measured pressure is used to assess stiffness, this incremental modulus, as well as all other heretofore available stiffness criteria, attains implausible negative values with data from early diastole because passive dynamics are confounded by the decaying contractile wall tension.

Definition of passive stress over the entire filling period.
ventricular pressure following maximum negative $\frac{dP}{dt}$, which can be adequately described as an exponential decay. The lower cutoff pressure data point used in the regression exceeded the subsequently attained end-diastolic pressure level by at least 3 mm Hg to allow for the possibility that the isovolumic relaxation period might be shorter than is generally accepted.

From time $t = 0$, corresponding to $P_0$, the first point on the exponential portion of the pressure curve, up to the time of mitral valve opening, the left ventricular pressure decay conforms to the general equation:

$$P_R (t) = P_0 \cdot e^{-\alpha t} + P_B$$

where the subscript $R$ identifies the decaying variable as “relaxation pressure” and $P_B$ is an asymptote. In the method developed by Frederiksen et al. $P_B$ is zero, while in the approach introduced by Craig and Murgo it may assume nonzero values and can represent an additive baseline shift. Beginning with mitral opening, the rate of decline of the pressure that is actually measured, $P_M$, toward its diastolic minimum, falls short of the rate given by the above equation. This follows because $P_M$ values in the filling ventricle reflect not only the ongoing relaxation process, but also the simultaneous passive pressure buildup associated with filling. As time of mitral opening we thus take the nominal instant at which the measured pressure $P_M$ begins to diverge from the decaying relaxation pressure $P_R$. We assume that the deviation from the relaxation pressure $P_R$ in the presence of filling is caused by the development of the passive filling pressure component. This is in agreement with findings obtained by the mitral inflow occlusion technique in the intact beating ventricle of the dog when pressure traces from filling and nonfilling beats are superimposed, with the onset of filling the observed early diastolic pressure decay slows down markedly compared with its rate in the absence of filling. Thus the pressure measured with diastolic filling deviates from the decaying isovolumic relaxation pressure.

Assessment of passive stiffness levels during the entire diastolic filling period. Once passive stress $\sigma^*$ levels are ascertainment using the net filling pressure $P^*$ in the stress formulas, they can be combined with simultaneous geometric data over the entire filling period to assess operating levels of an elastic incremental modulus in the beating ventricle. The formula for the modulus then reduces to

$$E^{\text{inc}} = K \cdot \Delta \sigma^*/\Delta \ln B$$

where $\ln B$ denotes the natural logarithm of the midwall minor semiaxis and $k$ is a geometric factor that remains approximately constant through diastole.

In principle, if statistical analysis of passive stress vs $\ln B$ data indicates significant residual variation of stress not associated with the variation of $\ln B$, investigation of other components besides the elastic one would be in order. Potentially, other passive components might include rate-dependent mural viscous effects. Since our data showed only small residual variation, we did not take up viscoelastic analytical models in this study.

**Hemodynamic measurements.** Hemodynamic measurements were obtained after conventional diagnostic right and left heart catheterization in adult patients who had given informed consent. The patient population studied comprised six control patients with normal left ventricular function, catheterized because of atypical chest pain, and seven patients with moderate-to-severe pure aortic valvular stenosis without associated regurgitation. Hemodynamic data and indexes of systolic function for both groups are provided in table 1. Selective coronary arteriograms were normal in all cases, and there were no angiographic regional wall motion abnormalities or asynergy. The patients were premedicated with 10 mg chlordiazepoxide hydrochloride
TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>LVEDP (mm Hg)</th>
<th>LVEDV (ml)</th>
<th>LVSP (mm Hg)</th>
<th>LVESV (ml)</th>
<th>EF (%)</th>
<th>(+ dP/dt)max (mm Hg/sec)</th>
<th>P (sec⁻¹)</th>
<th>(−dP/dt)max (mm Hg/sec)</th>
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</table>

(+) = aortic stenosis

EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVSP = left ventricular systolic pressure; LVESV = left ventricular end-systolic volume; P = pressure; (+ dP/dt)max = maximal rate of rise of left ventricular pressure; (−dP/dt)max = maximal rate of fall of left ventricular pressure.

(Librium) administered orally 1 hr before catheterization. Details of the measurement methods and procedures used in obtaining the hemodynamic data and in the diagnostic catheterization studies have been presented in a previous publication. Briefly, digital left ventricular pressure-volume data for a complete cardiac cycle were obtained from simultaneous recordings of high-fidelity pressure and echocardiographic diameter. The resonant frequency of the Millar No. 7F micromanometer, introduced into the left ventricle through a No. 11.5F Brockenbrough transeptal catheter, is 25 to 35 kHz. The micromanometer was balanced and zeroed at 37°C before insertion and was calibrated against a conventional pressure tracing with a fluid-filled catheter. The frequency response of the recording system, including the tip transducer and the DC amplifier, was flat to beyond 100 Hz. Single-beam M mode echocardiograms (Ekoline 20A, Smith-Kline Instruments) were obtained with the patient in the anteroposterior or slightly right anterior decubitus position. A ¾ inch 2.25 MHz transducer, allowing a nominal axial resolution of 0.68 mm was used, transmitting 1 μsec ultrasound pulses at a rate of 1000/sec. The echocardiographic endocardial dimension was assessed from the septum to the posterior wall just below the mitral valve leaflets. The cardiac cycle for which the simultaneous LV pressure-volume data were digitized every 5 to 7 msec for analysis was selected from beats recorded over one full respiratory cycle. The criterion for selection was an end-diastolic pressure corresponding to the arithmetic mean of the highest and lowest end-diastolic pressures of a respiratory cycle. The cardiac cycles analyzed occurred approximately midway between the extremes of inspiration and expiration. Left ventricular cineangiography was performed with the patient in the right anterior oblique (RAO) position, and end-diastolic major and minor internal axes were measured angiographically according to Dodge's area-length method. End-diastolic wall thickness was determined from the left ventricular silhouette in the RAO position or from a second cineangiogram obtained in the anteroposterior projection.

Calculations: left ventricular dynamic geometry. The left ventricle is assumed to be an ellipsoid with uniform wall thickness. From the end-diastolic angiographic measurements, we obtained values for the wall volume Vw, and for the ratio (R) of the outer major L0 to minor Dw axis (R = L0/Dw) at end-diastole for each individual left ventricle studied. We assumed that Vw and R remain approximately constant throughout filling. The constancy of the outer ratio R is compatible with substantial change in the inner axes ratio because of considerable thinning of the thick wall with filling. Precise anatomic measurements on arrested canine hearts show that the outer ratio (R) changes by less than 5% between end-systole and end-diastole; yet, the corresponding change of the inner ratio amounts to over 25%. In agreement with these findings, under the assumption of a constant R, the change undergone by the inner ratio between end-systole and end-diastole was substantial (combined average, 19 ± 9.5% [SD]) and did not differ significantly between our two groups, ranging from 8% to 35% in both the normal and the aortic stenosis settings. These values are completely compatible with the changes undergone by the inner ratio, which were measured by automated quantitative video angiocardiography in normal subjects and in patients with aortic stenosis by Heintzen and Stephan. Using the angiographic R and Vw values and the digitized M mode echocardiographic measurements of the nominal inner minor axis D(t), we solved for D(t) throughout diastole according to the following cubic equation:

\[ D_o^3 - [(R - 1) \frac{2}{\pi}] D_o - \left( \frac{6 \cdot V_w + D^3}{R} \right) = 0 \]

Using these computed D(t) and the corresponding echocardiographic D(t) values, we evaluated instantaneous values for wall thickness h(t) and inner long axis L(t):

\[ h = \frac{(D_o - D)}{2} \]
\[ L = L_0 - 2h, \text{ where } L_0 = R \cdot D_o \]

The instantaneous midwall minor semiaxis B(t) and midwall major semiaxis A(t) were then computed as:

\[ B = \frac{(D + h)}{2} \]
\[ A = \frac{(L + h)}{2} \]

The B(t) values were used to compute the natural logarithm, ln B, throughout the filling period.

Strain rate calculation. The strain rate dε/dt that was used is equivalent to an instantaneous normalized midwall circumferential fiber lengthening velocity evaluated in terms of the midwall minor semiaxis B, namely:

\[ \text{de/dt} = \frac{(I/B) \cdot \text{dB/dt}}{d(\ln B)/dt} \]

Derivatives were obtained digitally by a Lagrangian numerical differentiation algorithm.

General expressions for stresses. The previously published general expression for the difference between circumferential \( \sigma_\theta \) and radial \( \sigma_r \) midwall stresses at the representative equatorial region is:

\[ \sigma = \sigma_\theta - \sigma_r = P \cdot (B/h) (1 - B^2/2A^2 - 3h^2/8B^2) \]

With the measured pressure \( P_M \) as the pressure factor, this
equation was used to assess the total stress $\sigma_T$ throughout diastole. This equation was also adapted to the assessment in the beating ventricle of the passive stress $\sigma^*$ throughout the entire filling period. This was done, as indicated in the section developing the model, by substituting the passive pressure $P^*$ as the pressure factor $P$ in the above general expression at all data points throughout the filling period. This point-by-point substitution also allows evaluation of the individual passive mural stresses (i.e., $\sigma_m^*$, $\sigma_s^*$, $\sigma^*$) throughout filling.

**Statistics.** Differences between group means for normal subjects and patients with aortic stenosis were analyzed statistically by an unpaired, two-tailed Student's t-test. When nonparametric alternatives to the t test were indicated, because no a priori assumption as to the normality of a specific population distribution seemed warranted, the sign test and the Wilcoxon signed-rank test were used. Differences were considered to be statistically significant at $p < .05$. Values are expressed as mean ± SEM unless stated otherwise. A standard deviation of the stress data points from the three-parameter modified exponential least-squares curve was calculated according to the approach of Noble et al. The square of these SD estimates is practically equal to the sum of squares per data point used by Rankin et al. A correlation coefficient was also estimated by the method of Noble et al.

**Results**

**Net passive filling pressure.** The net passive filling pressure $P^*$, the difference between total measured left ventricular pressure $P_M$ and relaxation pressure $P_R$, is demonstrated in figure 2. After the nominal instant of mitral valve opening, the point-by-point difference between $P_M$ and $P_R$ is seen to increase continuously throughout the filling period, in contrast to the measured left ventricular pressure itself, which first exhibits a minimum during early filling (see also figure 1). In the case shown, mitral opening takes place at a measured left ventricular pressure of about 12 mm Hg, corresponding to the instant at which the measured pressure starts to deviate from the decaying relaxation pressure. Values of the relaxation time constant $T$, which enters in the definition of the relaxation pressure $P_R$, did not differ significantly in the two groups studied (normal, 31 ± 4 msec; aortic stenosis, 37 ± 3 msec, p > .1). The correlation coefficient for the best exponential fit to the measured pressure data during the isovolumic phase of relaxation was high ($r > .99$, $F > 400$), indicating a strong, albeit not necessarily perfect, monoexponential relationship.

When applied to these beats, midway between the extremes of inspiration and expiration, the approach of Craig and Murgo, allowing for a finite asymptote in the isovolumic pressure decay, yielded small nonzero $P_b$ values (normal, $-0.63 ± 0.32$ mm Hg; aortic stenosis, $-0.44 ± 0.37$ mm Hg). These values were found not to differ significantly from zero, both by the robust sign test and the powerful Wilcoxon signed-rank test for location of the estimated medians of $P_b$ (normal, $-0.61$ mm Hg; aortic stenosis, $-0.49$ mm Hg; both groups combined, $-0.49$ mm Hg). Accordingly, the relaxation pressure estimated by the method of Frederiksen et al. could be used in the subsequent steps of the analysis. The question of how a nonzero $P_b$ level could modify the dynamic relationships that we develop is addressed in the Discussion (see figures 6 and 7).

**Total and passive filling stress vs ln B relations.** Simultaneous plots of total, $\sigma_T$, and passive filling stress, $\sigma^*$, vs ln B relations throughout the filling period are displayed in figure 3. In the representative normal ventricle (left panel), the total stress $\sigma_T$ remains practically constant while a considerable fraction of the operating stroke volume is being replenished, as indicated by the increasing ln B values. In the pattern that is more common in patients with aortic stenosis (right panel), $\sigma_T$ is found to continue to decline well into the filling phase. In striking contrast to $\sigma_T$, the passive filling stress $\sigma^*$ is seen to rise continuously beginning with mitral opening. The $\sigma^*$ vs ln B curves exhibit the exponential form characteristic of the elastic response.
The "local slope" of such nonlinear diagrams is the slope at any specified ln B value within the range of ln B values encompassed. The continuous increase in the local slope of such σ* vs ln B curves should be compared with the peculiar behavior during the early filling stages of the local slopes of the σ_T-ln B curves. In particular, note how the slope of the σ_T curve in figure 3, right, first changes from large negative values to zero in early diastole. The much higher levels of σ_T compared with those of σ* at corresponding ln B values are also notable; they expose the adverse effect that remaining contractile wall stresses exert on attainable atrioventricular driving pressure differences for early filling by enhancing the total left ventricular pressure.

**Estimated elastic response diagrams.** The least-squares curves fitted to the σ* vs ln B data of representative normal subjects and patients with aortic stenosis are displayed in figure 4. As exemplified in the right panel, in some cases it was preferable to fit the data in two distinct albeit somewhat overlapping regions. The regions were identified by numerically differentiating the raw data field in every case to obtain values of the local slope Δσ*/Δln B and preliminary plots of E*_{INC} vs σ*, which disclosed the discontinuity. The discontinuity was obvious by inspection of these preliminary plots despite the noise attendant to such treatment of raw data. The transition region always corresponded to a σ* level of 35 to 40 g/cm². Thus only when high diastolic stress levels were attained (four of seven patients with aortic stenosis) was it sensible to obtain curve fits to σ*-ln B data in two σ* ranges.

As demonstrated by the examples shown, there was very little deviation of data points from the elastic three-parameter modified exponential form, σ* = α + βe^{γσ*}. This was also shown statistically by high correlation coefficients (r > .99) and low standard deviations (SD < 0.80 g/cm²). The goodness of the fits to exponential forms characteristic of an elastic, rather than a rate-dependent viscoelastic passive response, is noteworthy. Maximum strain rates attained during the rapid filling phase were 2.2 ± 0.2/sec in the normal subjects and 1.7 ± 0.2/sec in the patients with aortic stenosis.

**Passive elastic stiffness-stress relationships.** Passive left ventricular muscle stiffness E*_{INC} vs stress relationships are illustrated in figure 5. Passive incremental modulus values were obtained according to the analytical expression E*_{INC} = Ky(σ* - α). However, raw σ* data values were employed, along with the least-squares estimators for α and γ that had been assessed by nonlinear fitting of σ*-ln B data. In any given
ventricle, the value of K at end-diastole differed by less than 2% from the value found at the onset of filling.

Note the bilinearity of passive stiffness-stress relationships when diastolic stresses attain high levels. The transition region is clearly demarcated at a $\sigma^*$ level of 35 to 40 g/cm² (figure 5, right). Linear regression correlation coefficients ranged from .99 to 1.00 in every instance. When compared at similar stress levels, i.e., over the common lower stress range, values of the stiffness constant k, the slope of $E^\text{inc}$ vs stress diagrams, were not different in the two groups. They
were 9.37 ± 1.23 in the normal subjects and 9.34 ± 1.08 in the patients with aortic stenosis, for the $E_{\text{INC}}^*$ vs $\sigma^*$ relation. However, in the higher stress range, such $k$ values were greatly augmented at 28.76 ± 2.02 for the four patients with aortic stenosis included. When a single linear passive stiffness-stress relation corresponding to a unique exponential relationship between passive stress and $\ln B$ for both the lower and the higher stress range was assumed for all seven patients with aortic stenosis, the single $k$ value of 12.30 ± 1.22 did not exceed the level found in the normal group ($p > .05$).

End-diastolic $E_{\text{INC}}^*$ levels were similar in the normal and in the three ventricles associated with aortic stenosis that did not attain high filling stress levels. They amounted to 317 ± 124 and 330 ± 85 g/cm², respectively. In the four patients with aortic stenosis who had elevated stress levels, end-diastolic $E_{\text{INC}}^*$ values of 945 ± 245 g/cm² were substantially higher.

**Discussion**

Previously available models for quantitating wall stiffness levels assume, in accordance with passive elastic dynamic requirements, that progressive distension of the chamber must be accompanied by an increasing ventricular pressure. However, following the nominal instant of mitral valve opening, left ventricular pressure continues to fall in the rapid filling phase in the face of substantial increases in chamber dimensions. Thus such models could not be applied to diastolic mechanics in the beating ventricle. We have developed a new method to assess in man passive properties of left ventricular muscle and the influence of relaxing contractile stresses on wall dynamics throughout diastole.

The proposed model is based on the idea that if the ventricle continued to relax isovolumetrically, its pressure decay would evolve as a first-order relaxation process, characterized by the time constant $T$, as was shown by Weisfeldt and collaborators and by Gaasch et al. With normal filling, the deviation of the measured left ventricular pressure from such an exponentially decaying time course reflects the simultaneous development of passive filling stresses. To quantify the net passive filling pressure, a globally valid relaxation time constant must exist to yield the relaxation pressure. Therefore, in its present form the model cannot be applied when global (monoeponential) estimates of the isovolumic relaxation time constant cannot be obtained or are probably not appropriate (e.g., cardiomyopathies, segmental coronary disease of the left ventricle).

The elastic incremental modulus is a globally derived index of ventricular wall stiffness. The assumption that the equations of linear elasticity apply over infinitesimally small intervals of stress and strain is implicit in its formulation. However, although constant over each stress interval, the effective modulus varies from one interval to the next. In this stepwise manner, an overall exponential and thus nonlinear elastic response diagram is built out of a series of infinitesimally small linear segments. The linearity of the corresponding elastic stiffness vs stress relation over relatively large stress and deformation ranges is simply a mathematical corollary of the exponential form of the elastic response of the wall.

Through most of the filling the total stress $\sigma_T$ exceeds substantially the corresponding passive stress $\sigma^*$. In both the normal subjects and the patients with aortic stenosis, the total and the passive filling stress eventually became indistinguishable from each other only in the last part of the filling process described in a stress–$\ln B$ diagram. By then, 3.5 to 4 time constants after the approximate time of maximum negative dP/dt, the active muscle stresses had decayed completely, for practical purposes. In the normal ventricle the total stress $\sigma_T$ tends to remain unchanged early on despite considerable increases in chamber volume. Here, chamber dimensions increase fast enough in the rapid filling phase so as to just offset the effect of the declining measured left ventricular pressure on the total stress levels. In ventricles with aortic stenosis, strain rates in the rapid filling phase were relatively low so that the developing increase in the geometric factor fell short in offsetting the effect of the simultaneous decline of measured pressure on the total stress levels. Thus $\sigma_T$ could actually decrease at first in the face of rising chamber dimensions. Other investigators have construed declining ventricular pressure and wall stresses in the face of rising chamber dimensions in the rapid filling phase as indicating that the ventricle consistently contracts down to end-systolic volumes beyond that corresponding to its "elastic equilibrium configuration." Subsequently, it actively sucks up blood in the early filling period as it recoils back toward elastic equilibrium. Hori et al. have provided evidence, using the mitral occlusion technique, that isovolumic relaxation can proceed to a negative pressure in the anesthetized dog, especially with high experimental inotropic drive and small operating ventricular volumes. It is unlikely that such a mode of ventricular function applies ordinarily in recumbent man. Indeed, this canine finding suggests that in recumbent man, the blood shift from the capacious hu-
man leg vein reservoirs to the intrathoracic compartment should yield relaxation pressure asymptotes in the absence of filling that should not exhibit any sensible departure from zero. This is suggested also by our \( P_b \) estimates by the method of Craig and Murgo,\(^{11}\) which were not statistically different than zero.

The physiologic significance of a nonzero \( P_b \) and the nature and relative importance of the various factors that could affect it have not been established. We therefore elected to use the relaxation pressure ascertained by the method of Frederiksen et al.,\(^9\) since in any event our \( P_b \) estimates did not deviate significantly from zero. The question of how a nonzero \( P_b \) could modify the dynamic relationships that we develop was addressed, and our findings are illustrated in figures 6 and 7. In the pressure–ln B plots, the decay of the relaxation pressure toward a negative \( P_b \) is associated with an upward shift of the corresponding passive filling pressure, relative to both the passive filling pressure with zero asymptote and to the measured pressure. In the passive stress–ln B plots, there is a corresponding upward parallel shift of the passive stress curve computed with a negative \( P_b \), relative to its levels with zero \( P_b \). The converse (a downward parallel shift) applies in the case of a positive \( P_b \) value. Such small parallel shifts associated with small nonzero \( P_b \) values do not influence perceptibly the passive stiffness–stress relations and stiffness constants obtained by the model developed in this study.

By the proposed model, beginning with the nominal

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**FIGURE 6.** Computer-generated pressure vs ln B plots: \( P_M \) is measured pressure; PRLN and PRPB are relaxation pressures with zero and nonzero asymptotes, respectively. The negative asymptote (\( P_b \approx -2 \text{ mm Hg} \)) yields an upward shift of the passive filling pressure, relative to the passive pressure with zero asymptote and the measured pressure.

**FIGURE 7.** Computer-generated passive filling stress, \( \sigma^* \), vs ln B plots corresponding to the pressure–ln B plots in figure 6. There is a parallel shift of the passive stress curve computed with \( P_b \approx -2 \text{ mm Hg} \), relative to its levels with a zero asymptote.
instant of mitral valve opening, total stress or pressure values reflect the continuously changing state of disequilibrium, which involves the opposing dynamic effects of two processes evolving simultaneously: (1) the active relaxation process of ongoing contractile wall stress decay and (2) the passive process of deformational wall stress buildup associated with the filling of the chamber. The premise that total pressure and stress are global additive manifestations of passive and active wall forces is in agreement with classic (Voigt model) muscle mechanics concepts. Moreover, the additivity of active and passive effects is in agreement with a parallel combination of active and passive branch elements.

The question of load dependence of relaxation must be addressed in the context of the formulation of the relaxation pressure, \( P_0 \). In the intact heart, load-dependent control could in principle involve hemodynamic loading before aortic valve closure, during isovolumic relaxation, and after mitral valve opening. Only loading before aortic closure has been actually demonstrated to exert an influence on relaxation in the intact beating left ventricle. However, as was shown by Raff and Glantz, the effect of load dependence before aortic closure, as well as any possible effect during isovolumic relaxation, are embodied in the formulation of the relaxation pressure \( P_0 \) and in the measurements needed for its determination: the pressure \( (P_0) \) at the first point on the exponential portion of the isovolumic pressure decay, and the time constant \( T \) for isovolumic relaxation. Extrapolation from interventions on isolated muscle specimens to the working ventricle is fraught with pitfalls, and there is no evidence in the beating ventricle for any load-dependent speedup of relaxation after mitral opening. Yellin et al. showed by elegant mitral occlusion experiments in dogs that with ordinary mitral unimpeded inflow the observed early diastolic pressure decay is indeed slowed markedly, compared with the decay in absence of filling. A load-independent relaxation at or after mitral opening could be associated with the then applying low rates of activation decay (calcium sequestration), which are reflected in the corresponding low rates of decline of the relaxation pressure. It should be remembered that the rate of decay of an exponential function is proportional to the instantaneously applying values of the exponential; the values of the relaxation pressure at or after mitral opening are low and this leads to correspondingly low rates of activation decay. That load dependence of relaxation may be absent or negligible when activation decay rate is low (e.g., after caffeine addition) has been established.

As is suggested by the work of Poggesi et al., load dependence of relaxation may be manifest when elongation of a muscle occurs at or soon after the peak of the contraction, when the applying rates of active tension decay are high, and absent late in the course of the twitch, when the applying active tension levels and their rates of decay are low.

As indicated by the high correlation and determination coefficients and the negligibly small values of the standard deviations of the data points from the exponential elastic curve, the elastic model was a satisfactory representation of passive stress—ln B relationships throughout the entire filling period. This applied not only for the patients with aortic stenosis who did not attain high strain rates, but also for the controls attaining strain rates in excess of 3/sec during the rapid filling phase. Thus strain rate—dependent simple viscous effects did not cause any serious departure from a simple elastic response under basal heart catheterization conditions. This finding is in harmony with Noble’s conclusion in his recent monograph that, in the intact beating ventricle, rate-dependent viscous resistance to stretch is probably minimal or absent under quiet resting conditions. Fioretti et al. are also in agreement that left ventricular viscoelastic properties, such as would be expected to result in increased pressure in early diastole for an elevated inflow rate, are overshadowed by relaxation processes. The strain-rate indifferent behavior of myocardial stress-strain relationships is a feature shared by many living tissues.

On the other hand, Rankin et al. found evidence for sensible strain rate—dependent viscous effects in conscious, chronically instrumented dogs.

The transition region is clearly demarcated in plots of the passive incremental modulus \( E_{\text{inc}} \) vs passive \( \sigma^* \) and vs passive circumferential muscle stress \( \sigma^*_{\text{g}} \). Midwall circumferential stress at the equatorial region of the left ventricle can be interpreted as midwall muscle fiber stress, since the fiber direction coincides with the circumferential direction through the midwall region. Over the common stress range, stiffness constant values for the normal and the aortic stenosis group in this study did not differ. In conventional analyses of mid- and late-diastolic data, Peterson et al. also demonstrated normal stiffness constants in patients with aortic stenosis.

We have recently suggested that in clinical aortic stenosis, muscle stiffness may be normal in contrast to that observed in short-term experimental animal pressure overload studies showing increased stiffness, probably caused by increased fibrosis. It is therefore interesting that the fact that normal stiffness constant
The bilinearity of the passive stiffness-stress plots when high late diastolic stress levels are attained brings forth the need to always note the stress range over which a particular elastic stiffness constant applies, even in a given ventricle. This bilinearity is probably an expression of the ensuing strong recruitment of very stiff fibrocollagenous composite wall elements at high diastolic stress levels. This effect was not discernible when a single stiffness constant, k, corresponding to a unique passive stiffness-stress relation was assumed to cover both the lower and the higher filling stress ranges in all seven patients with aortic stenosis. Thus, in analyzing elastic stiffness-stress relations, different conclusions may be derived if evaluation and comparison of stiffness constants are made with due attention to large differences in the applying filling stress ranges than if such differences are overlooked. Bilinear stiffness-stress relationships in biomechanics have been reported by others; for example, from his elegant studies of passive mechanics and connective tissue composition of canine arteries, Cox published ample data exhibiting bilinear stiffness-stress relationships over a wide range of distending stress.

As is true for all investigations of cardiac mechanics in conscious, closed-chest man, it was impossible to measure pericardial pressure and its contribution, along with right ventricular pressure, to transmural left ventricular pressure. However, these influences are small under the conditions of the present study, since the small positive right ventricular diastolic pressure in these recumbent subjects should offset the small negative pericardial pressure.

Although in principle the model is applicable irrespective of the form of the function to which the relaxation pressure is found to conform, in practice the relaxation pressure function must be modified appropriately before the model is applied to situations in which the isovolumic pressure decay does not conform to a monoexponential. The pressure fall during isovolumic relaxation does not conform adequately to a monoexponential decay in a number of clinically important disease states, such as regional ischemia associated with segmental coronary disease and hypertrophic cardiomyopathy. Evidence that lack of a monoexponential pressure decay may be directly connected to asynchronous relaxation has been provided both in a canine preparation, and in patients undergoing percutaneous transluminal angioplasty during transient coronary occlusion, when there are striking patterns of asynchronous segmental wall motion during isovolumic relaxation. The mathematical model developed by Brower and co-workers shows that a biexponential pressure decay is produced by a strongly asynchronous left ventricular relaxation. These investigators have shown that the early (slower) time constant of the biexponential pressure decay characterizing asynergy results from the combined action of that fraction of the myocardium in the process of relaxing and the smaller second fraction in which relaxation has not yet been initiated. After the entire myocardium has entered the relaxation phase, the measured pressure conforms to a monoexponential decay with the second (faster) time constant of the observed biexponential isovolumic relaxation process. Thus, if the two-time constant model recently described is correct, in the presence of a biexponential isovolumic pressure decay resulting from asynchronous left ventricular relaxation, it is the second (faster) exponential decay process that should be used to obtain the relaxation pressure.

In conclusion, we have developed a model to assess in man the influence of incomplete muscle relaxation on wall dynamics and the passive stiffness of left ventricular muscle. In the rapid filling phase, dynamic global effects of continuing contractile wall stress decay are shown to be important not only in patients with aortic stenosis but also in normal hearts. After subtracting the decaying active stress component, passive stiffness vs stress relationships and corresponding elastic stiffness constants may be ascertained. The new method can be adapted to the study of mechanisms underlying shifts in left ventricular pressure-volume relationships such as those observed with various pharmacologic interventions.

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