SPECIAL ARTICLE

The Effects of Geometry, Elasticity, and External Pressures on the Diastolic Pressure-Volume and Stiffness-Stress Relations

How Important is the Pericardium?

ISRAEL MIRSKY AND J. SCOTT RANKIN

SUMMARY The concept of an incremental elastic modulus is applied in the quantification of passive elastic stiffness-stress relations of intact heart muscle, and a transmural pressure-volume relation for the left ventricle is subsequently derived in terms of geometry, muscle elasticity, and external pressures to assess their importance. Physiological and clinical applications of this method indicate that: (1) stiffness-stress relations obtained on the basis of pressure-volume data from dog hearts are not significantly different from those obtained from muscle strips excised from these same hearts; (2) shape and the presence of right, ventricular, pericardial, or pleural pressures are of secondary importance in an assessment of passive elastic stiffness; and (3) dramatic shifts in the left ventricular intracavity pressure-volume relations following drug interventions are primarily due to the presence of substantial pericardial pressures; however, the transmural pressure-volume relations are not markedly altered, implying no alteration in the intrinsic ventricular compliance.

Theoretical Considerations

Rationale for Use of the Incremental Elastic Modulus and Natural Strain

The concept of incremental elastic modulus stems from the basic studies of Biot (1965) and has...
been employed in studies of the elastic properties of arteries (Bergel, 1961a, b; Patel and Vaishnav, 1972). From elasticity theory, it can be shown that an arbitrary state of stress is expressible as the sum of a hydrostatic and a deviatoric stress (Bisplinghoff, 1965). As the name implies, the hydrostatic stress is similar to the state of stress in a body submerged in a fluid at rest; i.e., stresses are the same on all planes. The deviatoric stress is that portion of the stress that remains after subtracting the hydrostatic stress. In a similar manner the state of strain may be decomposed into a hydrostatic (volumetric) strain and a deviatoric strain, the former being a measure of the change in volume per unit volume and the latter a measure of the change in shape.

For an incompressible elastic material, all the strain is deviatoric (since volumes are preserved), and thus the deviatoric stress alone is determined by the strain. The hydrostatic stress is determined from the boundary values of the stress. Thus in an r, $\theta$, $\phi$ coordinate system, the total stress components $\sigma_i$ may be expressed in terms of the strain components $e_i$ as (Timoshenko, 1951)

$$
\begin{align*}
\sigma_r &= -P_0 + \frac{2}{3}Ee_r; \\
\sigma_\theta &= -P_0 + \frac{2}{3}Ee_\theta; \\
\sigma_\phi &= -P_0 + \frac{2}{3}Ee_\phi.
\end{align*}
$$

(1)

where $P_0$ is a uniform hydrostatic pressure, $E$ is Young's modulus, and $r$, $\theta$, $\phi$ are, respectively, the radial, circumferential, and meridional coordinates. Note that the second terms in Equations 1 represent the deviatoric stress components.

From Equations 1 it is observed that the differences of the stress components are independent of the hydrostatic pressure $P_0$ and in particular,

$$
\sigma_r - \sigma_\theta = (2/3)E(e_r - e_\theta).
$$

(2)

Thus Equation 2 provides us with a definition for incremental modulus $E_{inc}$ given approximately by

$$
E_{inc} = \frac{(3/2)\Delta(\sigma_r - \sigma_\theta)}{\Delta(e_r - e_\theta)}.
$$

(3)

Equation 3 assumes that $E$ is constant over small intervals of stress but varies from interval to interval.

We consider now the rationale for the choice of natural strain ($\log \epsilon / \epsilon_0$) in preference to Lagrangian strain ($\zeta / \zeta_0$). A practical advantage is that stiffness-stress relations may be quantified without knowledge of the reference length $\zeta_0$ (zero stress length), a quantity that is difficult to measure in the clinical and physiological settings. More specifically, the increment of natural strain is $d\epsilon / \epsilon_0$ as opposed to $d\zeta / \zeta_0$. Furthermore, for large deformations the differences between Lagrangian strain and natural strain are considerable, and the latter definition provides a simple incompressibility condition that can be shown as follows:

Consider for example the change in volume $V$ of a cube of material that is subjected to strains $e_x$, $e_y$, $e_z$ in the directions of its sides (Timoshenko, 1956). Following deformation, the volume of the cube is $(1 + e_x)(1 + e_y)(1 + e_z)V$, and since the volume remains constant for an incompressible material such as heart muscle,

$$
V = (1 + e_x)(1 + e_y)(1 + e_z)V
$$

or

$$
(1 + e_x)(1 + e_y)(1 + e_z) = 1.
$$

(4)

If the strains are not small, Equation 4 for incompressibility involves the products of the strains and is rather complex. However, on the basis of the natural strain definition, taking the logarithm of both sides of Equation 4 yields

$$
\log(1 + e_x) + \log(1 + e_y) + \log(1 + e_z) = 0
$$

or

$$
e_{xN} + e_{yN} + e_{zN} = 0,
$$

(5)

where $e_{xN}$, $e_{yN}$, $e_{zN}$ are the natural strains. In the $r$, $\theta$, $\phi$ coordinate system, a similar analysis yields the condition:

$$
(e_r + e_\theta + e_\phi)N = 0,
$$

(6)

and in particular, the increment of strain $de_{MN}$ based on the natural strain is defined as

$$
de_{MN} = dB/B,
$$

(7)

where $B$ is an instantaneous length. Equations 3, 6, and 7 form the basis of the derivations for elastic stiffness to be developed in the later sections.

Expressions for Wall Stress in a Left Ventricle Subjected to Transmural Pressures

In an earlier model developed for the quantification of wall stresses (Mirskey, 1969), it was assumed that only intracavity pressures were acting on the LV. However, the model is readily adaptable to the situation in which external pressures are present.

Since the analyses are lengthy and laborious, we present here the final approximate expressions for the midwall stresses at the equator of an ellipsoid which is the assumed shape for the LV:

$$
\begin{align*}
\sigma_r &= -\frac{P_r}{2}(1 - 3h/4B) - P_0, \\
\sigma_\theta &= P_T(B/h)(1 - B^2/2A^2 - h/2B + \eta h^2/A^3) - P_0, \\
\sigma_\phi &= P_T(B/2h)(1 - h/2B^2) - P_0.
\end{align*}
$$

(8)

In the above expressions, $\sigma_r$, $\sigma_\theta$, $\sigma_\phi$ are, respectively, the radial, circumferential, and meridional stresses; $A$, $B$ are the instantaneous midwall semimajor and semiminor axes; $h$ is the uniform wall thickness; $P_r$, $P_T$, $P_0$ are, respectively, the transmural pressure, LV pressure, and effective external pressure ($P_e = P - P_0$). The parameter $\eta$ in the expression for $\sigma_\phi$ takes on the values 0.125, -0.09, -0.05 for $A/B = 1, 1.5,
and 2.0, respectively, and generally the term \( \eta \, h^2 / A^2 \) may be neglected relative to the remaining terms. It should be emphasized here that midwall stresses in this theory are average stresses.

Partial validation of the above formulas may be given in two instances, namely: (1) when \( P_T = 0 \) or \( P = P_o \) (i.e., the ventricle is in a state of hydrostatic stress) and Equations 8 yield the desired result \( \sigma_r = \sigma_o = -P_o \) and (2) for the special case of the sphere (\( A = B \)):

\[
\sigma_r = \sigma_o = P_T(B/2h)(1 - h/2B)^2 - P_o,
\]

which is the exact expression for the average stresses.

Expression for Incremental Modulus \( E_{inc} \)

In assessing elastic stiffness on the basis of the incremental modulus concept, one recognizes the nonlinear behavior of the muscle material response, and from the studies of Patel and Vaishnav (1972), the stress difference \( \sigma \) may be written as

\[
\sigma = \sigma_o - \sigma_r = P_T(B/2h)(1 - h/2B)^2 - P_o,
\]

where we have assumed that \( (2 + B^2/A^2) \) is constant over the pressure range of interest, and that changes in Lagrangian strain are approximated by changes in natural strain. It is important to note that the factor \( K_i = (3/2)/(2 + B^2/A^2) \) takes on the value \( \frac{1}{2} \) for a sphere (\( A = B \)) and 3/4 for a cylinder (\( A \to \infty \)), which values agree with the exact values and are the limiting geometries for an ellipsoid of revolution (Mirsky, 1973).

Relation between LV Pressure, Ventricular Geometry, External Pressures, and Muscle Elasticity

In the present study, transmural pressure \( P_T \) is defined as \( P_T = P - P_0 \), where the effective external pressure \( P_0 \) is a weighted function of the right ventricular pressure \( P_{RV} \) and the pericardial or intrapleural pressure \( P_P \). Thus \( P_0 \) may be expressed as

\[
P_0 = f P_{RV} + (1 - f) P_P,
\]

where \( f \) is the fractional surface area of the LV epicardium acted on by the right ventricular pressure.

In Appendix 1, the LV pressure \( P \) is derived in the form

\[
P = P_0 + (P_0 - c/k + \beta B^{1/G}) G,
\]

where \( k, c \) are constants defined by the linear stiffness-stress relation \( E_{inc} = k \sigma_o + c \); \( A_1, \alpha, \beta, \gamma \) are curve-fit parameters given by

\[
\sigma = A_1 \sigma_o + B_1; \quad \sigma_r = \alpha + \beta B^\gamma
\]

and \( G, G_1 \) are geometric parameters. As can be seen from Equation 16, the LV pressure is a complex function of the elastic stiffness constant \( k \), ventricular geometry, and external pressure \( P_0 \). Equation 16 is employed later to explain the shifts in the pressure-volume relations following drug interventions.

Results

Effect of Ventricular Geometry on Stiffness-Stress Relations

In this section, the expressions for muscle stiffness and stress derived earlier are applied to data from the dog studies of Glantz and Kernoff (1975) to validate experimentally the model and assess the effects of ventricular geometry on the stiffness-stress relations.

In their studies, Glantz and Kernoff (1975) obtained pressure-volume curves from dog hearts by filling the LV with Ringer's solution at a constant rate (0.765 ml/min) until the pressure reached approximately 40 mm Hg, and emptying at the same rate until the pressure returned to zero. This procedure was repeated three times, and at the end of each experiment the ventricle was weighed and the wall thickness measured.
After wall thickness measurements were made, the right ventricle was opened and from two to five papillary muscles or other thin muscle strips were dissected free from its inside wall. Force-displacement curves were then obtained by stretching the muscle in 0.5-mm intervals until the total force exceeded 5 g.

Figure 1 is a representative plot of the stress-log radius \((\sigma - \log B)\) and associated stiffness-stress relations \((E_{\text{inc}} - \sigma)\) for one of the dogs studied, assuming major-minor axis ratios of 1.0, 1.5, 2.0. For each dog, an analysis was performed on three pressure-volume curves obtained in the loaded state. Table 1 includes the mean values of the elastic stiffnesses for each dog at various levels of muscle stress \(\sigma_t\). These stiffnesses are obtained by interpolation of the printout data for stiffness and stress. Also included in Table 1 are mean values of stiffness for isolated muscle strips excised from the same dog hearts. Single exponential curve fits were obtained for the stress-log radius and stress-strain relations over a physiological range of stress 0–150 g/cm².

Effects of External Pressures on the Stiffness-Stress Relations

In the studies described in the previous section, external pressures were absent. Since these pressures are always present in the clinical setting, it is necessary to examine their effects on the stiffness-stress relations. These effects may now be studied with the aid of data obtained by Spotnitz and Kaiser (1971) in isolated dog hearts and by Rankin et al. (1977) in intact dog hearts. Spotnitz and Kaiser (1971) measured the pressure-volume relations in dog hearts with and without the pericardium. Figure 4 (left panel) displays the pressure-volume relations as evaluated from Equation 16 under the following conditions, with the assumption that \(P_0 = 0\): (1) wall mass increased 30%, (2) LV geometry is spherical, and (3) muscle elasticity increased by 30%, (i.e., \(k, c\) increased 30%). These curves are compared with raw pressure-volume data following methoxamine infusion. External pressure-volume relations \((P_0 - V)\) required to yield the best curve fit to the data following methoxamine infusion are shown in Figure 4 (right panel) for the conditions (1) muscle elasticity, geometry, and wall mass unaltered, and (2) elasticity increased by 30%. A more detailed analysis of these curves is described in Appendix 2. In Appendix 3, a theoretical proof is given to demonstrate that transmural pressure-volume relations are unaltered by the drugs.

**Limitations of the Analyses**

There are several limitations to the present analyses, and these may be outlined as follows:

1. The model was developed to quantify these various factors; however, many simplifying assumptions were necessary because of a lack of adequate clinical data. The present model described earlier and in Appendix 1 is much simpler, does not require the solution to a differential equation, and involves fewer assumptions.

2. Many different hypotheses have been proposed recently to explain the possible causes for the dramatic shifts that take place in the pressure-volume relations after drug interventions (Alderman, 1976, Brodie, et al., 1977) and pacing-induced angina (Barry et al., 1974, Mann et al., 1977). However, none of these studies has made possible the quantification of the effects of the various factors that may be involved.

3. Figure 4 (left panel) displays the pressure-volume relations as evaluated from Equation 16 under the following conditions, with the assumption that \(P_0 = 0\): (1) wall mass increased 30%, (2) LV geometry is spherical, and (3) muscle elasticity increased by 30%, (i.e., \(k, c\) increased 30%). These curves are compared with raw pressure-volume data following methoxamine infusion. External pressure-volume relations \((P_0 - V)\) required to yield the best curve fit to the data following methoxamine infusion are shown in Figure 4 (right panel) for the conditions (1) muscle elasticity, geometry, and wall mass unaltered, and (2) elasticity increased by 30%. A more detailed analysis of these curves is described in Appendix 2. In Appendix 3, a theoretical proof is given to demonstrate that transmural pressure-volume relations are unaltered by the drugs.

**Factors Causing Shifts in the Pressure-Volume Relations after Drug Interventions**

Many different hypotheses have been proposed recently to explain the possible causes for the dramatic shifts that take place in the pressure-volume relations after drug interventions (Alderman, 1976, Brodie, et al., 1977) and pacing-induced angina (Barry et al., 1974, Mann et al., 1977). However, none of these studies has made possible the quantification of the effects of the various factors that may be involved.

In two earlier studies by Minsky (1977, 1978), a model was developed to quantify these various factors; however, many simplifying assumptions were necessary because of a lack of adequate clinical data. The present model described earlier and in Appendix 1 is much simpler, does not require the solution to a differential equation, and involves fewer assumptions.

Figure 4 (left panel) displays the pressure-volume relations as evaluated from Equation 16 under the following conditions, with the assumption that \(P_0 = 0\): (1) wall mass increased 30%, (2) LV geometry is spherical, and (3) muscle elasticity increased by 30%, (i.e., \(k, c\) increased 30%). These curves are compared with raw pressure-volume data following methoxamine infusion. External pressure-volume relations \((P_0 - V)\) required to yield the best curve fit to the data following methoxamine infusion are shown in Figure 4 (right panel) for the conditions (1) muscle elasticity, geometry, and wall mass unaltered, and (2) elasticity increased by 30%. A more detailed analysis of these curves is described in Appendix 2. In Appendix 3, a theoretical proof is given to demonstrate that transmural pressure-volume relations are unaltered by the drugs.

**Limitations of the Analyses**

There are several limitations to the present analyses, and these may be outlined as follows:
Table 1  Elastic Stiffness at Various Stress Levels for Isolated Heart and Excised Muscles

<table>
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<tr>
<th>Dog</th>
<th>Elastic stiffness g/cm³</th>
<th>n</th>
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<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
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<th>60</th>
<th>70</th>
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<th>90</th>
<th>100</th>
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<td>382</td>
<td>588</td>
<td>788</td>
<td>959</td>
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<td>1342</td>
<td>1517</td>
<td>1801</td>
<td>2018</td>
</tr>
<tr>
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<td>145</td>
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<td>666</td>
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</tr>
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<td>1998</td>
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<td>405</td>
<td>584</td>
<td>764</td>
<td>943</td>
<td>1122</td>
<td>1302</td>
<td>1482</td>
<td>1661</td>
<td>1840</td>
<td>2020</td>
</tr>
<tr>
<td></td>
<td>( a/b = 1.5 )</td>
<td>2</td>
<td>29</td>
<td>213</td>
<td>465</td>
<td>692</td>
<td>900</td>
<td>1165</td>
<td>1384</td>
<td>1608</td>
<td>1831</td>
<td>2044</td>
<td>2259</td>
</tr>
<tr>
<td></td>
<td>( a/b = 2.0 )</td>
<td>2</td>
<td>35</td>
<td>241</td>
<td>496</td>
<td>753</td>
<td>1029</td>
<td>1352</td>
<td>1771</td>
<td>2003</td>
<td>2280</td>
<td>2515</td>
<td>2766</td>
</tr>
</tbody>
</table>

Difference

- \( E_H \) cf. \( E_M \) \( a/b = 1.0 \) (P < 0.01) \( a/b = 0.025 \) \( a/b = 0.025 \) \( a/b = 0.025 \) \( a/b = 0.025 \) \( a/b = 0.025 \)

Data based on studies of Glanz and Kornoff (1976). NS = not significant. \( E_H \) = mean stiffness based on pressure-volume relations in the isolated heart; \( E_M \) = mean stiffness of excised muscle; \( a/b \) are, respectively, the semimajor and semiminor axes at the endocardium.

* Muscle strips in rigor and excluded from the statistical analyses.
† Data for isolated heart unavailable.
1. The assumption that average stress and mid-wall strain at the equator of an ellipsoid are representative of the global average may not be valid. However, qualitative results are similar to those obtained from large deformation analyses (Mirsky et al., 1976), and unpublished analyses indicate that stiffness-stress relations are not altered significantly if global average stress is employed.

2. Intact heart muscle behaves as a nonhomogeneous elastic material, and elastic stiffness may vary from the endocardium to the epicardium. On the other hand, Janz et al. (1976) have shown that stiffness-stress relations at the midwall based on a homogeneous or nonhomogeneous material are not markedly different.

3. External pressures do not act uniformly over the epicardium of the LV at any given diastolic pressure, and thus transmural pressures on the free wall and septum may differ.

4. The assumption of constancy of the major-minor axis ratio employed in the analysis of the data for dogs from the studies by Glantz and Kerhoff (1975) may not be valid at the low pressure levels. This may be one reason for the poor agree-
ment at low levels of stress (Table 1). However, the studies on dogs by Rankin et al. (1977) and the present clinical data indicate that this ratio varies by approximately 10% only, over wide pressure ranges.

5. Errors arise in curve fitting of data and the subsequent differentiation might induce added errors. In the present analysis, both polynomial and exponential curve fits were performed and the latter gave the best fits in the "least squares" sense. The process of differentiation could be eliminated entirely if necessary, by curve fitting directly the transmural pressure-radius relation (Eq. 16) in terms of three parameters. However, this approach presents problems in distinguishing between curve-fitting parameters and physiological parameters as evidenced in the studies by Glantz and Kernoff (1975).

6. Viscous effects have been neglected entirely in this analysis and may not be too critical in studies on the isolated animal heart. These effects, however, are important during the rapid-filling phase (Rankin et al., 1977) and to some extent during atrial systole. In the clinical study presented here, and in the analysis of the Rankin data, care was taken to analyze the pressure-volume data from the end of the rapid-filling period so that viscous effects were minimized. Regardless of these factors, future studies should account for the viscoelastic behavior of heart muscle.

7. Catecholamines have been shown to have no effect on the passive elasticity of well oxygenated papillary muscle (Sonnenblick, 1962), and therefore the assumption of unaltered elasticity is reasonable, at least for the subject studied here who had no evidence of coronary artery disease. If coronary artery disease is present, hypoxia may alter the elastic properties of muscle (Bing et al., 1971; Tyberg et al., 1970), and such changes could be significant if muscle is driven to contracture (Henderson et al., 1971; Pool, 1967).

8. The success of mathematical models depends not only on the assumptions made but on the adequacy and quality of the data available for their quantification. The use of the natural strain definition circumvents the technical difficulty of measuring zero transmural stress dimensions clinically, but the inability to measure pericardial or pleural pressures in the clinical setting routinely is the most serious limitation of the model.

Discussion of Results and Conclusions

In earlier studies (Glantz and Kernoff, 1975; Mirsky and Parmley, 1973; Mirsky et al., 1974), muscle stiffness was evaluated on the basis of models that did not account for the presence of external pressures acting on the LV. Although this is an adequate assessment for stiffness in studies on the isolated animal heart in which external pressures generally are absent, it may not suffice in a number of cases in the clinical setting, particularly in cases of volume overload and constrictive pericarditis. Furthermore, these models have not been validated experimentally. The model proposed by Glantz and Kernoff (1975) is deficient from the mathematical and phys-
iological points of view, since (1) elastic stiffness cannot be quantified, (2) stiffness constant $\beta^*$ cannot be determined unless the data are manipulated in a special manner, (3) approximately 20% of the muscle strips were in rigor and should have been omitted from the analysis, and (4) analysis of the pressure-volume data included averaging of both loading and unloading states in the presence of significant amounts of hysteresis.

The present model is more general in its application, since it accounts for changes in shape of the LV and for the presence of external pressures. Considering the assumptions involved, the agreement between theory and experiment is remarkable. In particular, Table 1 indicates that elastic stiffness, as evaluated from the model, is not statistically different from that evaluated from excised isolated muscle strips, over wide ranges of stress. These ranges varied from $30 < \sigma_0 < 80 \text{ g/cm}^2$ for the sphere to $20 < \sigma_0 < 100 \text{ g/cm}^2$ and $20 < \sigma_0 < 60 \text{ g/cm}^2$ for the ellipsoidal geometry. The closest agreement occurred with the ellipsoidal geometry ($a/b = 1.5$), a value more appropriate to canine ventricular geometry (Rankin et al., 1977). Figure 1, however, does indicate that ventricular shape plays a minor role in the assessment of stiffness over low stress ranges.

Figures 2 and 3 support the claim that, in the control state, stiffness-stress relations can be quantified with reasonable accuracy solely on the basis of LV pressure-volume and wall mass data, even though substantial external pressures may be present. This result is in agreement with the studies by Padiyar et al. (1978) and is of extreme importance in the clinical assessment of stiffness, since external pressures such as pleural or pericardial pressures are not routine catheterization measurements.

Although the pericardium and right ventricle play a secondary role in the assessment of muscle stiffness, their importance becomes more evident during drug interventions (Alderman and Glantz, 1976; Shirato et al., 1978). Early studies by Noble et al. (1969) indicated that volume loading and atrial pacing result in ventricles operating on the higher portion of the same pressure-volume curve; however, the pericardium was left open in their experiments. Recent studies demonstrate that drugs (Ludbrook et al., 1977) and atrial pacing (Mann et al., 1977) result in dramatic shifts in the diastolic pressure-volume relations. Explanations for such shifts have varied; however, the results displayed in Figure 4 clearly indicate that although changes in wall mass, elasticity, and ventricular geometry could substantially alter the pressure-volume relations, parallel shifts following certain drug interventions are primarily accounted for by the presence of substantial external pressures. These theoretical results are supported by the recent experimental studies of Shirato et al. (1978).

In summary, although ventricular systolic function may not be adequately assessed without consideration of the right ventricle (RV) and other external factors, these factors are less important, except in isolated situations, in the evaluation of the passive elastic properties of heart muscle. As for the directions of future research in this area, we suggest the following. (1) Experimental efforts should be concentrated on the measurements of transmural pressures (i.e., of LV, RV pleural-pericardial pressures) in the assessment of pressure-volume relations. On the basis of such studies, empirical relations can be developed in terms of physiological quantities that are measurable in the clinical setting. Only then will it be possible to assess more accurately diastolic function, and in particular systolic function, by a ventricular function-curve analysis. (2) The viscoelastic properties of intact heart muscle and the influence of incomplete ventricular relaxation in early diastole should be more carefully examined. (3) The possibility that muscle elasticity may alter during pacing-induced angina should be considered. (4) Finally, the stiffness-stress and stress-strain relations in both low and high stress ranges should be studied in more detail in an attempt to describe the mechanical behavior of elastin and collagen in the normal and pathological states.

**Appendix 1**

**Functional Relation between LV Pressure, External Pressures, Muscle Elasticity, and Ventricular Geometry**

The stress difference $\sigma = \sigma_0 - \sigma$, may be expressed as a linear function of muscle stress $\sigma_F$ in the form

$$\sigma = A_1\sigma_F + B_1. \quad (1.1)$$

Hence from Equation 14 of the text,

$$E_{\text{loc}} = K_1\sigma/d(\log B) = K_1A_1\sigma_F/d(\log B). \quad (1.2)$$

If $\sigma_F$ is curve fitted in the form

$$\sigma_F = \alpha + \beta e^{k\log B} = \alpha + \beta B^k, \quad (1.3)$$

Equation 1.2 yields

$$E_{\text{loc}} = K_1A_1\gamma(\sigma_F - \alpha) = k\sigma_F + c, \quad (1.4)$$

where the constants $k$, $c$ are defined as

$$k = K_1A_1; \quad c = -ak. \quad (1.5)$$

Thus from Equations 1.3 and 1.5 we obtain

$$\sigma_F = -c/k + \beta B^{k/k_1A_1}, \quad (1.6)$$

$$= P_r(B/h)(1 - B^2/2A^2 - h/2B) - P_0,$$

employing Equation 8 of the text.

With geometric parameters $G, G_1$ defined by

$$G = (h/B)/(1 - B^2/2A^2) - h/2B); \quad G_1 = K_1A_1, \quad (1.7)$$
the LV pressure \(P\) is expressed as

\[
P = P_0 + (P_0 - c/k + \beta B^{k/G}) G,
\]

which is the desired result.

**Appendix 2**

**Quantification of the Stiffness-Stress and \(P - V\) Relations under Various Conditions**

The raw pressure-volume and ventricular geometry data are given in Table 2 for a subject in the control state and following methoxamine infusion.

The wall volumes \(V_w\) in the control and intervention states, respectively, were determined to be 148 and 156 ml, and an average value of 152 ml was employed. The quantities \(a, b\) are the semimajor and semiminor axes of the LV cavity, and the midwall radii \(A = a + h/2\), \(B = b + h/2\) were obtained by solving a cubic equation for the thickness \(h\).

Since the ventricular volume \(V\) and wall volume \(V_w\) are defined by

\[
V = 4(\pi/3)ab^2;
\]

\[
V + V_w = 4(\pi/3)(a + h)(b + h),
\]

the cubic equation is determined to be

\[
h^3 + h^2(a + 2b) + h(b^2 + 2ab) - (3V_w/4\pi) = 0.
\]

Thus the stress \(\sigma\) may be evaluated from the relation

\[
\sigma = \frac{Pt}{h}(1 - B^2/2A^2 - h/2B) - P_0,
\]

using the tabulated data and the equations above.

It should be noted that the quantity \(2 + B^2/A^2\) is reasonably constant over the pressure ranges of interest for both the control and methoxamine states and therefore validates the assumption made earlier. An average value of \(K_i = (3/2)/(2 + B^2/A^2) = 0.667\) is employed in the calculations, and the stress-log radius \((\sigma - \log B)\) relation is obtained in the form

\[
\sigma = 16.14 + 0.0000281 e^{13.89 \log B}
\]

for the control state, assuming \(P_0 = 0\). This curve-fit enables the stiffness-stress relation \((E_{inc} - \sigma)\) to be expressed in the linear form

\[
E_{inc} = K_i A_i d\sigma/d(\log B) - K_i A_i (13.89)(\sigma - 16.14) - k_0 + c,
\]

where \(A_i = 1.15, K_i = 0.667, k = 10.65\), and \(c = -172\) g/cm².

There remains now to evaluate the pressure-radius \((P - B)\) and external pressure-radius \((P_0 - B)\) relations for various conditions by employing the expression

\[
P = P_0 + (P_0 - c/k + \beta B^{k/G}) G
\]

derived in Appendix 1.

**Control**

For the control state, we assume \(P_0 = 0\), and from Equations 2.4, and 2.5 the remaining parameters are: \(c/k = -16.14, \beta = 0.0000281\), and \(\gamma = k/G_1 = 13.89\). Hence

\[
P = (16.14 + 0.0000281 B^{13.89}) G
\]

**After Methoxamine Infusion (Mass ↑ 30%, \(P_0 = 0\))**

Muscle elasticity and ventricular geometry remain unaltered, hence \(\alpha = -c/k = 16.14, A_i = 1.15, K_i = 0.664\), and \(\gamma = k/G_1 = 13.85\). The parameter \(\beta\) is determined from the relation \(\sigma_0 = \alpha + \beta B^2\), employing the initial condition \(\sigma_0 = 49.0\) g/cm², \(B = 2.717\) cm. This corresponds to the pressure-volume point \(P = 26.8\) mm Hg, \(V = 84.7\) ml (see data for methoxamine, Table 3). Thus \(\beta = 0.0000289\) and

\[
P = (16.14 + 0.0000289 B^{13.89}) G
\]
After Methoxamine Infusion (Spherical Geometry, \(P_0 = 0\))

Mass and muscle elasticity are unaltered, hence \(A_1 = 1.15, c/k = -16.14\). The spherical geometry yields \(K_1 = 0.5\), thus \(\gamma = k/K_1 = 16.05/(0.5 \times 1.15) = 18.52\). The initial condition \(P = 26.8\) mm Hg, \(V = 84.7\) ml yields the value \(B = 3.28\) cm, \(a_\phi = 37.08\) g/cm\(^2\), hence \(\beta = 5.85 \times 10^{-4}\) and

\[
P = [16.14 + 0.585(10^{-6})B^{18.52}]G. \quad (2.9)
\]

After Methoxamine Infusion (Muscle Elasticity \(\uparrow 30\%), P_0 = 0\))

Mass and geometry are unaltered, hence \(A_1 = 1.15, K_1 = 0.0667\). The constants \(k, c\) are both increased by \(30\%\), thus \(c/k = \gamma = 18.05\). The initial condition \(P = 26.8\) mm Hg, \(V = 84.7\) ml yields \(a_\phi = 60.30\) g/cm\(^2\), \(B = 2.605\) cm, \(\beta = 1.38(10^{-4})\), and

\[
P = [16.14 + 1.38(10^{-6})B^{18.09}]G. \quad (2.10)
\]

After Methoxamine Infusion (\(P_0\) Present, Mass, Elasticity, and Geometry Unaltered)

Here we desire to evaluate the external pressure \(P_0\) required to simulate the actual raw pressure-volume data following methoxamine infusion. Rearranging the pressure-radius relation (Eq. 16), we obtain

\[
P_0 = [P - (\alpha + \beta B^2)]G/(1 + G). \quad (2.11)
\]

Since mass, elasticity, and geometry are unaltered, \(\alpha = c/k = 16.14, k = 10.65, K_1 = 0.667, A_1 = 1.15, \gamma = 13.89\). To evaluate the parameter \(\beta\), we assume that near end-diastole the transmural pressure \(P_T\) is unchanged. Thus at \(V = 110.2\) ml, the transmural pressure in the control state is \(P_{TC} = P_C = 18.9\) mm Hg, \(V = 84.7\) ml yields \(B = 3.28\) cm, \(\alpha = 29.61\) g/cm, and \(\beta = 1.38(10^{-4})\), where \(P_0\) is the LV pressure at \(110.2\) ml after the drug infusion, and \(P_{TD}\) is the corresponding transmural pressure. This corresponds to values for stress and radius given by \(a_\phi = 29.61\) g/cm\(^2\) and \(B = 2.780\), yielding \(\beta = 0.915 \times 10^{-5}\) and

\[
P_0 = [P - (16.14 + 0.0000915B^{18.09}]G/(1 + G). \quad (2.12)
\]

After Methoxamine Infusion (Mass and Geometry Unaltered, Elasticity \(\uparrow 30\%), P_0\) Present

A similar analysis to that presented above yields \(k = 13.84, \alpha = 16.14, \gamma = 18.05, \beta = 1.30(10^{-7})\), and

\[
P_0 = [P - (16.14 + 0.13 \times 10^{-3}B^{18.09}]G/(1 + G). \quad (2.12)
\]

Appendix 3

Transmural Pressure-Volume Relations are Unaltered by Drug Interventions: A Theoretical Proof

In the following analysis, it is shown that transmural pressure-volume relations (\(P_T - V\)) are preserved following drug interventions if one assumes that muscle elasticity and ventricular geometry are unchanged.

From Equations 10 and 17 of the text, we may write

\[
s = P_T(B/h)(1 - B^2/2A^2 - 3h^2/8B^2) = P_T F \quad (3.1)
\]

\[
s = \alpha + \beta B^2, \quad \sigma = A_1 a_\phi + B_1, \quad \sigma_{TD} = \sigma_{FC}, \quad \text{and thus } \sigma_{TD} = \sigma_{FC}, \quad (3.3)
\]

where \(A_1, B_1, \sigma_{TD}, \sigma_{FC}\) denote, respectively, the control and drug states. Hence Equation 3.1 yields

\[
P_{TC} = P_{TD} \quad (3.4)
\]

Since shape is preserved at each volume, \(V = F_C = F_D\), therefore

\[
P_{TC} = P_{TD} \quad (3.5)
\]

which is the desired result.

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