Assessment of Passive Elastic Stiffness for Isolated Heart Muscle and the Intact Heart

By Israel Mirsky and William W. Parmley

ABSTRACT

A sensitive method was developed for detecting stiffness changes in the left ventricle. Stress-strain relationships \( \sigma - \varepsilon \) were obtained in the form \( d\sigma /d\varepsilon = k\sigma + c \) from published studies on eight normal canine hearts, five infarcted canine hearts, and seven isolated cat papillary muscles. Utilizing pressure-volume relationships, the elastic stiffness \( d\sigma /d\varepsilon \) and the stiffness constant \( k \) were also evaluated in patients with normal ventricles, inappropriate hypertrophy, and congestive cardiomyopathy. The \( k \) values were 35.0 ± 1.7 (isolated muscle, 30°C), 37.3 ± 1.9 (normal canine, 23°C), and 23.9 (infarcted). For the patient groups, \( k \) and the passive elastic stiffness were 15.8 ± 0.3 and 249 ± 22.4 g/cm² for 13 normal patients, 26.4 ± 1.7 and 286 ± 32.0 g/cm² for 7 patients with inappropriate hypertrophy, and 20.1 ± 1.2 and 1360 ± 209 g/cm² for 6 patients with congestive cardiomyopathy. The results indicate that (1) \( k \) is sensitive to stiffness changes due to infarction, (2) hypertrophy causes an increase in the value of \( k \) although elastic stiffness remains within normal limits, and (3) \( k \) for the intact human heart is lower than it is for isolated muscle.

KEY WORDS: compliance, wall stiffness, intact heart, stress, strain, elastic modulus, pressure-volume relationships

There appears to be an increased interest in the assessment of ventricular compliance \( (dV/dP) \) from the pressure-volume relationship during diastole (1-13). The importance of quantifying compliance in the clinical situation is emphasized by the fact that left ventricular compliance has been reported to decrease in the presence of coronary artery disease, angina pectoris, and acute myocardial infarction (6, 11-13). Therefore, an increase in left ventricular end-diastolic pressure may be due to a decrease in ventricular compliance and may not necessarily signify failure and dilatation of the ventricle (5).

In the past, attempts to quantify ventricular compliance have centered on simple ratios such as that of end-diastolic volume to end-diastolic pressure or of changes in volume to changes in pressure \( (\Delta V/\Delta P) \). However, compliance is a continuously varying quantity and is a function of diastolic pressure. Thus compliance becomes a meaningless term unless the pressure at which \( \Delta V/\Delta P \) is evaluated is stated. Furthermore, the nonlinear relationship between pressure and volume makes it difficult to compare compliance values between ventricles.

Recent studies by Diamond et al. (9) have provided a more quantitative description of the pressure-volume relationship of the left ventricle. They expressed the reciprocal of compliance \( (dP/dV) \) as a linear function of the filling pressure in the form \( dP/dV = \alpha P + \beta \), and their results suggested that the slope \( \alpha \) of this relationship provides a sensitive means for detecting changes in left ventricular wall stiffness. Although this index has been shown to be essentially independent of initial ventricular volume and filling pressure and only slightly modified by ventricular geometry, there does appear to be considerable variability in \( \alpha \) from one ventricle to another. Use of this index may therefore be limited to detecting stiffness changes in an individual heart and may not be valid for comparative purposes.

An alternative approach to the problem of quantifying left ventricular wall stiffness is the introduction of terms such as stress (force per unit area), strain (change in length per unit length), and tangent modulus (elastic stiffness) which are employed in the theory of elasticity. With such terms, comparisons between elastic structures of different sizes and shapes become more meaningful.

The purpose of the present study was therefore to provide methods for evaluating the elastic stiffness...
in isolated heart muscle, the intact dog heart, and the intact human heart. We hoped that application of these methods would allow the development of more sensitive indexes for the detection of changes in left ventricular wall stiffness.

**Definitions**

Since much of the confusion and misunderstanding in cardiac mechanics stems from the inconsistent terminology employed, it is appropriate to define the terms to be employed in this study.

**Elasticity** is the property of recovery of a material from a stressed state to its initial configuration when the stresses are removed. If the material assumes its initial form entirely on the removal of the forces, it is said to be perfectly elastic; otherwise it is termed inelastic.

**Stress** may be defined as force per unit cross-sectional area of the material and is essentially a measure of the intensity of forces. The units commonly employed are dynes/cm², g/cm², etc.

**Strain** is a dimensionless quantity and is produced by the application of a stress. It represents the fractional or the percent change from the original or unstressed dimensions. In papillary muscle and intact heart studies, several definitions of strain have been used interchangeably, and therefore further clarification is necessary. **Lagrangian strain** is defined as \((l-l_0)/l_0\) where \(l_0\) is the length corresponding to a state of zero stress and \(l\) is the instantaneous length. Since zero-state lengths are technically difficult to measure, \(l_0\) is often replaced by the initial muscle length or the end-diastolic length. **Natural strain** is defined as \(\log_10(l/l_0)\) and is a more appropriate definition of strain for biological materials. In contrast to the Lagrangian strain, this definition does not assume that cross-sectional dimensions remain unaltered and that strains are uniform along the length of a fiber.

**Distensibility** is the change in volume \(V\) relative to a change in pressure \(P\) and is denoted by \(dV/dP\). It is often used interchangeably with the term **compliance**. This definition of compliance will be adopted in this study.

**Specific compliance** may be defined as the change in volume per unit volume relative to a change in pressure, i.e., \(dV/VdP\). The reciprocal of this quantity is referred to as **volume elasticity** and has the dimensions of stress.

**Young's modulus** describes the mechanical behavior of an elastic material which is stretched or compressed. For a material which obeys Hooke's law, the stress-strain relationship is linear and Young's modulus \(E\) is defined by \(\sigma = E\varepsilon\), where \(\sigma\) and \(\varepsilon\) are the stress and the strain, respectively (Fig. 1A). Most biological materials do not possess this linear relationship but generally follow a curvilinear one which is usually exponential in form. In this instance, Young's modulus is replaced by the term tangent modulus.

**Tangent modulus or elastic stiffness** defines the slope at any point of a stress-strain curve; if the relationship is exponential, the elastic stiffness-stress relationship is linear (Fig. 1B). It is this relationship which will form the basis for the present study. The dimensions of both Young's modulus and the tangent modulus are the same as those for stress, namely force per unit area.

**Methods**

**ISOLATED HEART MUSCLE**

Isolated papillary muscles taken from seven cats were placed in a myograph in oxygenated Krebs solution (30°C). Muscles were stimulated for 2 hours until they had stabilized; then the stimulator was turned off. All subsequent studies were done with the nonbeating muscles. One end of the muscle was fixed to a force transducer and the other end was constantly lengthened by a withdrawal pump. The rate of lengthening (approximately 0.02 mm/sec) produced an average rise in force of 10g from zero resting force in approximately 30 seconds. Duplicate determinations were reproducible within ±5%. Force data were

![FIGURE 1](image-url)

**Stress-strain and elastic stiffness (tangent modulus) vs. stress relationships. A:** Materials which obey Hooke's law are characterized by a linear relationship, and the slope \(E\) of this relationship is designated as Young's modulus. For biological materials, the stress-strain relationship is curvilinear and usually of an exponential form. The slope at any point on this curvilinear relationship denotes the tangent modulus or the elastic stiffness for each stress level. \(\varepsilon = \sigma\) = stress and \(\varepsilon = \sigma\) = strain. **B:** If the stress-strain relationship is exponential, the elastic stiffness vs. stress relationship is linear. The slope \(k\) of this line is termed the elastic stiffness constant and \(c\) is the intercept on the y-axis. Note that if the material obeys Hooke's law, the elastic stiffness is constant and is independent of the stress level.
recorded on a pressure-ink recorder (Hewlett-Packard 7858) and also on magnetic tape. The taped information was fed into a Sigma 3 computer, and the length-tension (strain-stress) data were fitted to an exponential curve by a nonlinear least-squares program. A typical stress-strain curve displayed in Figure 2 was expressed in the form

$$\sigma_1 = a_1 e^{b_1(l - l_0) + c_1},$$

where $a_1$, $b_1$, and $c_1$ are constants determined from the regression analysis and $l_1$ is the muscle length at a stress of 1 g/mm². Justification for the use of an exponential relationship is given in Figure 3 where a linear relationship is obtained between $\log \sigma_1$ and the strain $(l - l_0)/l_0$ over the stress range of 0.19 to 4.7 g/mm². Theoretically, the stress $\sigma_1 = 1$ g/mm² when $l = l_0$ (i.e., the straight line should pass through the origin). It should be emphasized that the strain definition $e_1 = (l - l_1)/l$ is a modification of the Lagrangian and natural strains defined earlier. To comply with these latter definitions the data must be reevaluated.

If we desire the Lagrangian form, the stress-strain relationship must be expressed as $\sigma = c/k (e^{b_1} - 1)$, where $\sigma = F/A_0$ and $e = (l - l_0)/l_0$; $A_0$ and $l_0$ are the cross-sectional area and the resting length of the muscle, respectively, and $F$ is the force on the muscle. In this form we observe that the stress $\sigma = 0$ when the strain $e = 0$. Differentiation of this stress-strain relationship yields the tangent modulus-stress relationship in the form $d\sigma/dl = k\sigma + c$ as obtained by Yeatman et al. (14). Thus $k$ represents the slope of this linear relationship and $c$ is the intercept on the $y$-axis (Fig. 1B).

Employing the natural strain definition, the instantaneous change in strain $\Delta e = d\Delta l/l$ and the instantaneous stress $\sigma_1 = F/A_0$, where $A_1$ is the instantaneous cross-sectional area. Usually, $A_1$ is replaced by $A_0$, since changes in the muscle length are small. However, small changes in length may not be the case in overstretched muscle, and for the present analysis we assumed that $A_1 = A_0$. The stress-strain curve shown in Figure 2 plotted on a logarithmic scale. The exponentiality of the stress-strain relationship is confirmed for the linear portion AB of the curve corresponding to the stress range of 0.19 to 4.7 g/mm². Ideally $e_1 = 1$ g/mm² when $e_1 = 0$, i.e., when $l = l_1$.

### Passive Elastic Stiffness in Cardiac Muscle

Data from the studies of Diamond et al. (9) and Forrester et al. (10) were employed for the evaluation of elastic stiffness in the intact dog heart. Acute myocardial infarction was induced by the injection of 0.5 ml of elemental mercury into the left circumflex coronary artery via a small pericardial incision. Infarctions so produced resulted in gross absence of the left ventricular surface. Exactly 1 hour after infarction, these hearts were removed. Pressure-volume curves were obtained in infarcted and noninfarcted hearts by a constant-infusion technique. For $P > 5$ mm Hg, the pressure-volume relationships followed an exponential curve in the form $dP/dV = \alpha P + \beta$, where $\alpha$ and $\beta$ are constants (Figs. 4, 5). With these published data in normal and infarcted hearts (9, 10), the present study considered
Typical continuous pressure-volume curve obtained from an isolated anoxic arrested canine heart. Since the infusion rate was constant, the rate of change of pressure per unit time \((\frac{dP}{dt})\) was directly proportional to the instantaneous stiffness \((\frac{dP}{dV})\). (Reproduced with permission of Diamond et al. [9] and the American Heart Association Inc.)

Evaluation of Elastic Stiffness for the Intact Heart.—In this section an expression will be developed for the passive elastic stiffness and the stiffness constant \(k\) for the intact heart in terms of the pressure-volume data. We seek therefore an expression in the form

\[
dP \over dV = k \sigma_m + c
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based on the following simplifying assumptions. (1) Since the data to be employed were evaluated on the basis of a spherical geometry, the pressure \(P\) and \(dP/dV\) at intervals of 5 mm Hg over the range from 5 to 30 mm Hg.

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obtained. From Eq. 3 we obtain, with the aid of the relationship $dP/dV = \alpha P + \beta$,

$$E_m = k\alpha_m + c = \left[3(1 + \alpha V)[1 + (V_m/V)\alpha^2/(\alpha^2 + b^2)] - 3b[(\alpha^2 - a^2)/(\alpha^2 + b^2)(2\alpha^2 + b^2)]\right] \alpha_m +$$

$$[3\beta V(\sigma_m/P)[1 + (V_m/V)\alpha^2/(\alpha^2 + b^2)]] \sigma. \quad (4)$$

where the subscript ed refers to the end-diastolic state. Thus equating both sides of Eq. 4 yields the expressions for $k$ and $c$ enclosed by the braces. An assessment of the assumptions made here will be discussed later.

Further simplifications can be made if we adopt the pressure-volume relationship employed by Gaasch et al. (7). These investigators used the empirically derived expression $P = 0.43e^{aV}$, which was based on left ventricular pressure-volume data obtained in dog hearts. The constant factor 0.43 compares favorably with the average for 27 dog studies performed by Spotnitz et al. (21) and with human data obtained by Gorlin et al. (22). Note that $a$ is the slope of the log $P$ vs. $V$ relationship and $e$ is the base of the natural logarithm. Since the pressure-volume relationship is not truly exponential at very low pressures, the preceding formula should not be employed for $P < 5$ mm Hg (Fig. 5).

With this simplified form, it is now possible to obtain the constant $a$ directly in terms of the end-diastolic pressure and volume in the form

$$aV_{ed} = \log eP_{ed} - \log 0.43 = \log e2.33P_{ed}. \quad (5)$$

As will be observed later in Results, the term $3b[(\alpha^2 - a^2)/(\alpha^2 + b^2)(2\alpha^2 + b^2)]$ in Eq. 4 contributes less than 4% and may be neglected. Thus the constant $k$ may be approximated by

$$k_A = 3(1 + \log 2.33P_{ed}) \left[1 + 1/(v + v^2/4(1 + v^2/2))\right], \quad (6)$$

where $v = V_{ed}/V_{ao}$. Therefore, the stiffness constant can be evaluated simply from a knowledge of end-diastolic pressure, end-diastolic volume, and wall mass.

### Table 1

Exponential Stress-Strain Relationships for Papillary Muscle

<table>
<thead>
<tr>
<th>Exp.</th>
<th>$k$</th>
<th>$e$ (g/mm²)</th>
<th>$k_1$</th>
<th>$e_1$ (g/mm²)</th>
<th>$a_1$ (g/mm²)</th>
<th>$b_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.5</td>
<td>0.69</td>
<td>34.0</td>
<td>-2.03</td>
<td>0.922</td>
<td>0.036</td>
</tr>
<tr>
<td>2</td>
<td>36.5</td>
<td>2.76</td>
<td>40.7</td>
<td>-0.42</td>
<td>0.996</td>
<td>-0.039</td>
</tr>
<tr>
<td>3</td>
<td>28.0</td>
<td>0.18</td>
<td>39.5</td>
<td>-2.03</td>
<td>0.959</td>
<td>0.021</td>
</tr>
<tr>
<td>4</td>
<td>25.6</td>
<td>0.39</td>
<td>22.2</td>
<td>-0.77</td>
<td>1.067</td>
<td>-0.008</td>
</tr>
<tr>
<td>5</td>
<td>24.4</td>
<td>0.24</td>
<td>38.7</td>
<td>-2.65</td>
<td>1.020</td>
<td>0.042</td>
</tr>
<tr>
<td>6</td>
<td>19.8</td>
<td>0.42</td>
<td>30.1</td>
<td>-3.42</td>
<td>0.982</td>
<td>0.032</td>
</tr>
<tr>
<td>7</td>
<td>25.7</td>
<td>3.26</td>
<td>32.2</td>
<td>8.86</td>
<td>1.71</td>
<td>-0.417</td>
</tr>
<tr>
<td>MEAN</td>
<td>25.8</td>
<td>35.0</td>
<td>32.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>±SE</td>
<td>2.0</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td>1.6</td>
</tr>
</tbody>
</table>

Temperature = 30°C. $e = (e/k)(e^4 - 1), \omega_1/d\omega_1 = k_1 \omega_1 + c_1$ and $\omega_1 = (\omega_1^{nat}) + c_1$, where $\sigma$ and $e$ are the Lagrangian stress and strain, respectively, $\sigma_1$ and $\omega_1$ are the instantaneous stress and strain (natural), respectively, and $\sigma_1$ and $\omega_1$ are the modified stress and strain, respectively, referred to the cross-sectional area $A_1$ and length $l_1$ at 1 g/mm². Ideally $\omega_1 = 1$ g/mm² when $e_1 = 0$, i.e., $(\omega_1 + c_1)$ should be unity. These three stress-strain relationships are generally valid over a stress range of 0.1 to 5 g/mm².

### Results

#### ISOLATED HEART MUSCLE

Stress-strain relationships were obtained from seven cat papillary muscles on the basis of both the Lagrangian strain and the natural strain definition. These results were compared with those obtained on the basis of a modified strain definition $e_1 = (l - l_1/l_2)$, where $l_1$ is the muscle length at 1 g/mm², a value close to $l_{max}$ the length at which maximum stress is actively developed. The values of the constants $k$, $c$, $k_1$, $c_1$, $a_1$, $b_1$, and $c_1$ are shown in Table 1; $k = 25.8 \pm 2.0$ (Lagrangian), $k_1 = 35.0 \pm 1.7$ (natural), and $b_1 = 32.2 \pm 1.6$ (modified). On the average, these exponential stress-strain relationships are valid over a stress range of 0.1 to 5 g/mm², which corresponds to a range of approximate length changes of 7 to 20% of the resting length $l_0$.

#### INTACT DOG HEART

In Table 2, pressure-volume data and stress-strain relationships are listed for eight control dogs; the mean values for a group of five dogs before and 1 hour after infarction (9, 10) are also presented.

Figures 4 and 5 are typical pressure-volume and $dP/dV$ vs. $P$ curves reproduced from the studies of Diamond et al. (9). The reason for computing stress-strain relationships for values of pressure $\geq 5$ mm Hg is apparent from the bimodal linear relationship between $dP/dV$ and $P$. Therefore, the natural strain definition was employed, since the geometrical data at and near $P = 0$ were unreliable. Figure 6 displays a typical linear relationship between the stiffness $E_m$ and the stress $\sigma_m$. This result implies that the stress-strain $(\sigma_m - \sigma_m)$ relation-
### Stress-Strain Relationships and Pressure-Volume Relationships* for Normal and Infarcted Dog Hearts

<table>
<thead>
<tr>
<th>Exp.</th>
<th>(\sigma_0) (ml/m²)</th>
<th>(\gamma) (ml)</th>
<th>(V_e) (ml)</th>
<th>(k) (g/mm²)</th>
<th>(\varepsilon) (g/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.112</td>
<td>-0.072</td>
<td>49.8</td>
<td>147</td>
<td>40.9</td>
</tr>
<tr>
<td>2</td>
<td>0.072</td>
<td>-0.028</td>
<td>71.5</td>
<td>105</td>
<td>30.8</td>
</tr>
<tr>
<td>3</td>
<td>0.117</td>
<td>-0.093</td>
<td>49.2</td>
<td>119</td>
<td>39.8</td>
</tr>
<tr>
<td>4</td>
<td>0.090</td>
<td>-0.175</td>
<td>84.4</td>
<td>138</td>
<td>43.7</td>
</tr>
<tr>
<td>5</td>
<td>0.074</td>
<td>-0.060</td>
<td>83.0</td>
<td>144</td>
<td>36.9</td>
</tr>
<tr>
<td>6</td>
<td>0.097</td>
<td>-0.615</td>
<td>61.5</td>
<td>83</td>
<td>34.3</td>
</tr>
<tr>
<td>7</td>
<td>0.119</td>
<td>-0.433</td>
<td>70.4</td>
<td>66</td>
<td>42.3</td>
</tr>
<tr>
<td>8</td>
<td>0.098</td>
<td>-0.110</td>
<td>52.1</td>
<td>60</td>
<td>29.9</td>
</tr>
<tr>
<td><strong>MEAN after infarction</strong></td>
<td>0.0480</td>
<td>0.086</td>
<td>83.3</td>
<td>110.0</td>
<td>23.9</td>
</tr>
<tr>
<td><strong>Infarcted Group (5 dogs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td><strong>MEAN before infarction</strong></td>
<td>0.0965</td>
<td>0.078</td>
<td>64.0</td>
<td>80</td>
<td>34.8</td>
</tr>
</tbody>
</table>

*The pressure-volume data have been taken from the studies of Diamond et al. (9) (control) and Forrester et al. (10) (infarction).

Temperature = 23°C. \(dP/dV = \sigma P + \gamma, V = (1/\alpha) \log_e (\sigma P + \beta) + \gamma, \) and \(d\sigma_m/d\varepsilon_m = k\sigma_m + c.\)

### Figures and Notes

- **Figure 6**: Stiffness-stress relationship for an individual dog is linear over the range 8 < \(\sigma_m\) < 60 g/cm², which corresponds to a pressure range of 7 to 30 mm Hg.

- **Figure 7**: Stiffness-stress relationships for patients typical of each group studied. It was assumed that the pressure-volume relationships were valid over pressure ranges typical for each group. The stiffness-stress relationships at end-diastole are shown for each patient in Figure 8. The mean values of \(k\) and \(E_m\) are, respectively, 15.8 ± 0.3 and 249 ± 22.4 g/cm² for the normal.

**INTACT HUMAN HEART**

Thirty-three patients were studied at cardiac catheterization by Gaasch et al. (7) who evaluated end-diastolic volume \(V_{ed}\), end-diastolic stress \(\sigma_{ed}\), ejection fraction, and the compliance factor \(\alpha\) for each patient. These patients were normal (13) or had inappropriate hypertrophy (9), aortic stenosis (5), or congestive cardiomyopathy (6). Table 3 includes in addition to the data of Gaasch et al. (7) values of the stiffness constants \(k\) and \(k_{A, e^{-}}\), \(V_{ed} - V_w\) ratios, and elastic stiffness \(E_m\) for each patient studied. It should be mentioned that the stresses \(\sigma_m\) were recomputed on the basis of a spherical geometry and therefore that the values are lower than those presented by Gaasch et al. (7) who employed the ellipsoidal geometry. The elastic stiffness \(E_m\) was approximated by the expression \(E_m = k\sigma_m\) since the constant \(\beta\) and hence \(c\) was assumed to be zero in the data given by Gaasch et al. (7). Because of the wide scatter in the data for patients with aortic stenosis, they were omitted from the present study.

Figure 7 displays the stiffness-stress relationships for patients typical of each group studied. It was assumed that the pressure-volume relationships were valid over pressure ranges typical for each group. The stiffness-stress relationships at end-diastole are shown for each patient in Figure 8. The mean values of \(k\) and \(E_m\) are, respectively, 15.8 ± 0.3 and 249 ± 22.4 g/cm² for the normal.
group, 26.4 ± 1.7 and 286 ± 32.0 g/cm² for the group with inappropriate hypertrophy, and 20.1 ± 1.2 and 1360 ± 209 g/cm² for the group with congestive cardiomyopathy.

**Discussion**

The results for the stiffness constants in these studies are predicated on the assumption that the stress-strain relationships for biological tissues are nonlinear and generally follow an exponential law. For isolated heart muscle, the log_{10} σ vs. strain relationship is linear over the range of 20 to 500 g/cm² (Fig. 3), and the elastic stiffness-stress relationship in the intact dog heart is linear over the pressure range of 7 to 30 mm Hg (Fig. 6). Both of these results appear to validate the assumption of exponentiality of the stress-strain relationships over the physiological ranges of stress and pressure. Although the assumption of the constancy of σ_m/P near end-diastole may not be valid at low end-diastolic pressures, the assumption is reasonably true over the pressure range of 10 to 40 mm Hg (Fig. 9).

With reference to the elastic stiffness constant k, the results indicate that (a) it is sensitive to stiffness changes due to myocardial infarction, (b) stiffness
Stiffness-stress relationships for patients typical of each group studied are approximately linear over pressure ranges typical for each group. For the normal patient (N), the patient with inappropriate hypertrophy (IH) and the patient with congestive cardiomyopathy (CC), the stiffness constants \( k \) are respectively 18.9, 28.1, and 23.0 corresponding to pressure ranges of 5 to 15 mm Hg, 10 to 25 mm Hg, and 15 to 40 mm Hg, respectively. The numbers in parentheses refer to the \( k \) values obtained from Eq. 4. The normal value of \( k = 18.9 \) agrees closely with the value 18.8 obtained from the dog data of Spotnitz et al. (21).

The stiffness constants are higher in isolated muscle than they are in the intact human heart, suggesting that caution must be exercised when attempts are made to extend results from papillary muscle studies to the clinical situation, and (c) in the intact heart \( k \) depends primarily on the end-diastolic pressure and the ventricular volume—mass ratio \( V_{ed}/V_w \). As observed from Eq. 6 for \( k_A \), high values of \( k \) are associated with elevated end-diastolic pressures and small values of \( V_{ed}/V_w \), whereas low values of \( k \) tend to be associated with patients having lower values of \( P_{ed} \) and higher values of \( V_{ed}/V_w \). (d) The high \( k \) value obtained from the control data of Diamond et al. (9) may be due to both a temperature effect and the dynamic loading procedure employed, since an analysis of the data of Spotnitz et al. (21) yields a value of 18.8 which is closer to the present results obtained for normal patients.

Of equal or more importance is the elastic stiffness, which in the present analysis has been approximated by the product of \( k \) and midwall end-diastolic stress \( \bar{E}_m = k \sigma_{ed} \). Since elastic stiffness \( \bar{E}_m \) is a function of the volume elasticity \( (VdP/dV) \), wall stress, and \( V_{ed}/V_w \), it represents a more reliable gauge of resistance to ventricular filling than do most other parameters currently employed. In Figure 8 it is observed that the highest stiffness values were obtained for those patients with congestive cardiomyopathy—a not unexpected result in view of their elevated end-diastolic pressures and volumes. However, the group with normal ventricles and the group with inappropriate hypertrophy had similar mean stiffness values but...
markedly different values for \( k \). Thus hypertrophy, as an adaptive mechanism, tends to maintain a normal elastic stiffness level. The ratio of end-diastolic pressure to end-diastolic volume and \((dP/dV)_e\) however yield conflicting results for these three groups of patients and should not be considered reliable indexes of stiffness.

**LIMITATIONS OF THE PRESENT ANALYSIS**

There are several limitations to the present analysis which require further study. It would appear from Eqs. 4 and 6 for \( k \) and \( k_s \), that the stiffness constants are preload dependent at the low preloads but only slightly preload dependent at the high preloads. Furthermore, the results displayed in Figure 7 appear to indicate that stiffness constants may be underestimated by 20% for the normal group and 10% for both the inappropriate hypertrophy and the congestive cardiomyopathy groups. These discrepancies may be partly due to the simplified pressure-volume relationship employed and the assumption that pressure-volume relationships are unaffected by preload variations.

Since \( k \) is a determinant of the stress-strain relationship, there is no reason to believe that it is affected by the geometry. In fact our own unpublished studies have shown that the \( k \) values are similar for an ellipsoid of revolution. However, the elastic stiffness may be underestimated by the reduction in the wall stress as a consequence of the assumption of spherical geometry.

The limitations on the measurements of wall mass are well known (23, 24), and serious errors could arise in those patients with marked hypertrophy since the outline of the ventricular borders may not be well defined. Furthermore, pressure-volume relationships are technically difficult to obtain in diastole in the clinical situation with any degree of accuracy. In addition, the assumption that pressure-volume data can be expressed by the simple relationship \( P = 0.43e^{x^2} \) requires further justification in view of the fact that the numerical factor was obtained on the basis of dog data. This relationship could be modified by employing the expression \( P = \alpha e^{x^2} + b \) and evaluating the constants \( \alpha \), \( \alpha \), and \( b \) from a regression analysis on the basis of additional pressure-volume data. In their present form, however, the relationships \( dP/dV = \alpha P \) and \( VdP/dV = (\alpha V)P \) are a function of pressure only, implying that the volume elasticity or specific compliance \( VdP/VdV \) is independent of ventricular volume, geometry, and wall mass—a result that one would not expect.

**GENERAL CONSIDERATIONS AND FINAL CONCLUSIONS**

Since the constant \( k \) in this analysis is representative of the stiffness constant of the parallel elastic element in the three-element model of cardiac muscle (25), it would appear that the parallel elastic stiffness constant increases in hypertrophy. This result is in agreement with the findings of Bing et al. (26) in their studies of experimental hypertension in rat cardiac muscle. However, elastic stiffness remains at normal levels, since the stress level is usually below the normal value. In this respect the results are in agreement with those of Spann et al. (27) who showed that passive length-tension curves of hypotrophied muscle differed little from those of normal isolated papillary muscle. Furthermore, the values of \( k \) also depend on the strain definition (Table 1). This dependence may explain the reasons for the discrepancies in the results by Bing et al. (26) and Spann et al. (27).

Clinical studies support the view that hypertrophy is associated with a reduction in left ventricular diastolic compliance as assessed from the diastolic pressure-volume relationships (28–30). However, if we define elastic stiffness by the relationship \( d\sigma/d\epsilon \) rather than by \( dP/dV \), then hypertrophy tends to maintain a normal level of stiffness at least in those patients with idiopathic hypertrophic subaortic stenosis. These studies suggest that invalid interpretations of ventricular function and misdiagnosis of heart failure can result from a failure to distinguish between changes in left ventricular wall stiffness and changes in the contractile state. Furthermore, characterization of wall stiffness requires the measurement of left ventricular end-diastolic pressure and volume and in particular left ventricular wall mass. Although such measurements are difficult to obtain at present, it may be possible in the future to estimate these parameters at the bedside using echocardiography and pulmonary capillary wedge pressures and thus to consider the clinical applications of these concepts.

**Appendix 1**

**EVALUATION OF THE STIFFNESS CONSTANT \( k \)**

**FOR THE SPHERE**

In the following analysis, the stiffness constant \( k \) will be determined on the basis of the exact theory for a thick spherical shell.

It was shown in the text that the midwall stress \( \sigma_m \) may be written in the form \( \sigma_m = P(V/V_w) \left(1 + b^2/2R^2 \right) \), where the quantities have been previously defined. The instantaneous change in the stress is therefore \( \sigma_m = dP(V/V_w) \left(1 + b^2/2R^2 \right) + (P/V_w) \left(1 + b^2/2R^2 \right) dV + P(V/V_w) \left[(3b^2/2R^2)db - (3b^2/2R^2)dR \right] = (\sigma_m/P)dP + (\sigma_m/V)dV + \sigma_m(3b^2/2R^2)(db -

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\[ \frac{b^2 dR}{R} / (1 + b^3 / 2R^3) \text{, and the instantaneous change in strain at the midwall is } \varepsilon_m = \frac{b^2 dR}{R}, \text{ where } R = (a + b^2 / R^2). \]

Thus, the elastic stiffness is given by

\[ E_m = \frac{8\pi a^2 b^2 R (V_m / V)}{(a^2 + b^2)(a^2 + b^3 / 2R^3)}, \]

simplifies to

\[ 4\pi a^2 b^2 R (V_m / V) \]

Hence

\[ \frac{dV}{dR} = \frac{d^2 r}{dR} = 4\pi a^2 b^2 / (a^2 + b^3 / 2R^3). \]

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References


Assessment of Passive Elastic Stiffness for Isolated Heart Muscle and the Intact Heart
ISRAEL MIRSKY and WILLIAM W. PARMLEY

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