Left Ventricular Stress and Compliance in Man

With Special Reference to Normalized Ventricular Function Curves

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SUMMARY

Left ventricular circumferential end-diastolic stress (Sed), peak systolic stress (Sps), and compliance at end-diastole ([dV/VdP]ed) were estimated in 13 subjects with normal left ventricles (N group), nine subjects with inappropriate hypertrophy (IH group), five with aortic valvular stenosis (AS group), and six with congestive cardiomyopathy (CC group). The product of Sed and (dV/dP)ed was employed as an index of "muscle fiber stretch" and related to systolic indices of ventricular performance. Compliance was significantly less than normal in IH (P < 0.001), in AS (P < 0.01), and in CC (P < 0.001), while end-diastolic volumes were smaller than normal (P < 0.05), normal (P = NS), and larger than normal (P < 0.001) in the three groups, respectively. Sed was normal in IH and AS but elevated in CC (P < 0.001), while Sps was decreased in IH and normal in AS and CC. "Muscle fiber stretch," however, was substantially less than normal in IH (P < 0.001), indicating that the low Sps is due at least in part to short sarcomeres. In CC, despite a markedly elevated preload, "muscle fiber stretch" was normal (P = NS), while work indices of the ventricle were diminished indicating depressed ventricular function. Thus, the product of Sed and (dV/VdP)ed provides a normalized index of "muscle fiber stretch," which permits one to compare length-tension or length-work relationships in diseased ventricles of varying dimensions and compliance.

Additional Indexing Words:
Length-tension relationships  Pressure-volume relations  Inappropriate hypertrophy  Congestive cardiomyopathy

STUDIES OF ISOLATED heart muscle have demonstrated that sarcomere length is directly proportional to muscle length along the ascending limb of the length-active tension curve, and as such provides the ultrastructural basis for Starling's law of the heart. Ventricular function curves, which relate performance of the intact heart to some measure of sarcomere length, are generally constructed using end-diastolic volume or end-diastolic pressure as the yardstick of sarcomere stretch. In the normal heart this is both appropriate and useful, particularly when serial heterometric interventions are employed to characterize the mechanical performance of a given ventricle. In the diseased ventricle, however, measurements of either end-diastolic

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pressure or normalized end-diastolic volume fail to provide a measure of sarcomere stretch since compliance of the muscle is frequently abnormal. This approach is particularly unsatisfactory when performance of the heart is examined at a single end-diastolic pressure or volume.

In the present study, stress and compliance were calculated at end-diastole in an effort to assess relative sarcomere lengths in diseased human left ventricles. In this manner, the product of end-diastolic stress and compliance was used as an index of "muscle fiber stretch" and related to systolic indices of ventricular performance in subjects with normal left ventricles and in those with appropriate hypertrophy, in those with inappropriate hypertrophy, and in subjects with advanced left ventricular failure.

Methods

Animal Studies

Five mongrel dogs weighing between 18 and 20 kg were anesthetized with sodium pentobarbital (30 mg/kg). In each animal a left thoracotomy was performed, the heart was exposed, and the animal was sacrificed. The heart was rapidly removed from the thorax and, after the ventricular cavity was flushed clear of blood, two large metal clamps were used to close the mitral and aortic orifices. A large-bore catheter was inserted into the left ventricular apex and was secured with heavy silk sutures. The heart was then suspended in saline, and intraventricular pressure was measured with a Statham P23 Db pressure transducer and recorded on an Electronics for Medicine photographic recorder. Filling pressures of the ventricle were recorded while saline, colored with indocyanine green, was infused in 2-cc increments. The pressure transducer was placed at the level of the midventricle for zero reference. Adequate sealing of the ventricle was insured by complete recovery of the infused fluid. The entire experiment was carried out in each case within 30 min from the time of animal sacrifice. Ventricular volume was normalized for body surface area (BSA) using the formula:

\[ \text{BSA} = 0.112 \times \left( \frac{\text{body weight, in kg}}{2}\right)^{2/3} \]

Human Studies

For the purposes of this study, 33 patients studied at cardiac catheterization were divided into four groups. The first group consisted of 13 patients with hemodynamically and angiographically normal left ventricles (N group). The second group of nine patients had inappropriate left ventricular hypertrophy (IH group), seven with outflow obstruction (IHSS) either at rest or during isoproterenol stimulation and two patients without outflow obstruction. Four of the seven patients with IHSS had no subvalvular gradient at rest and, in the remaining three, the gradient ranged from 32 to 70 mm Hg. The third group of five patients had valvular aortic stenosis (AS group); left ventricular hypertrophy was evident by X-ray and electrocardiogram in all cases. The fourth group of six patients had congestive cardiomyopathy (CC group) either idiopathic (four patients) or on the basis of diffuse coronary artery disease (two patients). Patients with more than minimal valvular regurgitation were excluded from the study. All patients were in normal sinus rhythm.

The patients underwent cardiac catheterization in the fasting state following 7.5-10 mg of diazepam premedication. Pressures were measured with Hewlett-Packard model 267 BC pressure transducers from a zero reference point halfway between the table top and the angle of Louis and recorded on an eight-channel photographic recorder (Hewlett-Packard model 4560). The left ventricular end-diastolic pressure was taken as the junction of the downslope of the a wave with the upstroke of the ventricular pressure wave. The left ventricular systolic ejection fraction (SEF) was derived from single-plane cineangiography in the right anterior oblique projection, using an ellipsoid model similar to the method described by Green et al.\(^5\) The long axis (L) of the ventricular cavity was measured from the apex to the junction of the mitral and aortic cusps. The area (A) of the cavity was determined by planimetry and the short axis or width (W) was calculated as an average width from the equation of an ellipse: \( W = 4A/\pi L \). Cardiac output was determined utilizing the Fick method, and the left ventricular end-diastolic volume was derived by dividing the average stroke volume by the SEF. All volumes were indexed for body surface area.

Calculations

For the purposes of this study, it was assumed that the left ventricular diastolic pressure-volume relationship is exponential and can be represented by the equation:

\[ P = be^{kV} \]  

where \( P \) equals left ventricular end-diastolic pressure in mm Hg, \( V \) equals left ventricular end-diastolic volume in cc/m\(^2\), \( b \) equals the extrapolated left ventricular end-diastolic pressure at zero \( V \), \( k \) is the slope of the log P-V relationship, and \( e \)
Postmortem left ventricular pressure-volume relations. (A) Log pressure-volume relations of five dog hearts are shown. The data for each experiment were fitted to a straight line (least squares) and the slope ($K_1$) was obtained. The average pressure intercept (b) was 0.43 mm Hg. The data points indicated by the open circles represent the average pressure-volume (P-V) coordinates of 27 dog ventricles studied by Spotnitz et al.3 (B) For each of the five experiments shown in A, slopes ($K_2$) were calculated using the average intercept (b) and single log P-V coordinates measured at 6 mm Hg. See text for details.

is the base of the natural logarithm. Since the P-V relationship is not exponential at low values of P, data obtained at pressures less than 3 mm Hg were excluded (fig. 1). Equation 1, thus, can be rewritten as $\ln P = kV + \ln b$, or:

$$k = \frac{(\ln P - \ln b)}{V} \tag{2}$$

The constant b cannot easily be derived experimentally in the human heart. It was assumed, therefore, that the average value for b derived from animal studies approximates that of the human heart, and this constant was used to calculate k in the human studies.

The index of distensibility, defined as change in volume per unit change in pressure, was calculated at a given diastolic volume as follows:

$$dV/dP (\text{cc/m}^2/\text{mm Hg}) = e^{-kV}/kb \text{ or } 1/kP \tag{3}$$

Compliance was defined as the normalized index of distensibility and was calculated as:

$$dV/VdP (\text{mm Hg}^{-1}) = dV/dP \times 1/V \tag{4}$$

Left ventricular wall stress was calculated by the formula of Sandler and Dodge,6 which uses a prolate spheroid as a model. The stresses calculated represent mean wall stresses at the equator. In the present study circumferential stress was calculated as:

$$S = \frac{Pb}{h} \left(1 - \frac{b^2}{a^2 [2b + h]}\right) \tag{5}$$

where P equals ventricular pressure ($10^3$ dynes/cm$^2$), h equals wall thickness, a equals one half the longitudinal chamber axis, and b equals the minor semiaxis.6 The major axis is the measured distance from the apex to the junction of the aortic and mitral cusps and the minor axis is a calculated average using the area method.
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as in the right anterior studies described above. Wall thickness (h) was determined as the average thickness of the middle one third of the left ventricular free wall as visualized in the right anterior oblique projection. Calculations of wall stress were made at end-diastole and during ejection. The left ventricular end-diastolic dimensions and wall thickness are combined as factor Xed. Thus:

\[ Xed = \frac{b}{h} \left( 1 - \frac{b^8}{a^2 [2b + h]} \right) \]

(6)

where a, b, and h are measured at end-diastole. End-diastolic circumferential stress is represented as:

\[ Sed = LVEDP \left( 10^3 \text{ dynes/cm}^2 \right) Xed \]

(7)

Substituting end-systolic for end-diastolic dimensions in equation 6, Xed was calculated. Peak systolic stress (Sps) was estimated at a point one third through ejection as:

\[ Sps = P Xps \]

(8)

where P equals left ventricular peak systolic pressure \( \left( 10^8 \text{ dynes/cm}^2 \right) \) and \( Xps = \frac{2 Xed + Xes}{3} \).

Peak developed systolic stress was calculated as Sps minus Sed. A work index of the ventricle was provided by the product of peak developed systolic stress and stroke index and is expressed in units of \( 10^6 \) dyne-cm.

Determinants of end-diastolic fiber length include not only the force acting to lengthen the fiber (Sed), but also the passive resistance to the lengthening force (parallel elasticity). It was considered, therefore, that true stretch of the muscle fiber might best be estimated as the product of end-diastolic stress and the compliance of the ventricle at end-diastole. Thus, an index of muscle fiber stretch (MFS) is provided by the following equation:

\[ MFS = Sed \ (dV/VdP)_{ed} \times 100 \]

(9)

and is expressed in arbitrary units.

Results are expressed as averages, ± the standard error of the mean. Comparison of averages between groups was accomplished using an unpaired t test.

**Results**

**Animal Studies**

Pressure-volume data from five in vitro dog hearts were plotted as log pressure vs volume in figure 1A. Data at pressures less than 3 mm Hg were excluded. Using least-squares principles, the data from each ventricle were fitted to a straight line and the slope \( (k_1) \) was obtained. As shown in figure 1A, the slopes obtained from different ventricles were similar. The average intercept \( (b) \) at zero volume was 0.43 ± 0.13 mm Hg. In vitro pressure-volume data from 27 dog ventricles studied by Spotnitz et al.\(^8\) were also represented in figure 1A. Each data point represents the average of 27 ventricles, normalized for body surface area using the average weight of the dogs. The value for \( k_1 \) obtained from these 27 ventricles (0.44) is similar to the average obtained from the five dogs reported in this study.

Using the average intercept (0.43 mm Hg) and a single pressure-volume coordinate from each ventricle, slopes \( (k_2) \) of the log pressure-volume relationship were calculated. It was elected to use the volume at 6 mm Hg pressure as this single coordinate, since 6 mm Hg can be considered a normal left ventricular end-diastolic pressure, and this point is approximately the midpoint of the experimental data. The values for \( k_2 \) as well as the graphic representation of these data are presented in figure 1B. It can be seen that the slope \( (k_2) \) of each line calculated from the two coordinates does not fall outside the range of the slopes obtained by least-squares analysis \( (k_1) \).

It would appear, therefore, that: (1) the end-diastolic pressure-volume relations above 3 mm Hg are exponential; and (2) the slopes of the log pressure-volume lines are relatively constant in the normal dog and are little changed by construction from a zero-volume intercept of 0.43 mm Hg and a single log pressure-volume coordinate at 6 mm Hg.

**Human Studies**

*Left Ventricular End-Diastolic Pressure-Volume Relations and Ventricular Compliance.* Data from 33 patients studied at cardiac catheterization are presented in table 1. In figure 2, a semilogarithmic plot of left ventricular end-diastolic pressure-volume coordinates for each patient is shown, as well as the average values ± SEM for each group. The average slope \( (k) \) of each group of patients is represented by a line connecting the average.
Table 1

Data from 33 Patients Studied at Cardiac Catheterization

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<th>Heart rate (beats/ min)</th>
<th>Cardiac index (liters/ min/m²)</th>
<th>Aorta Pressure (mm Hg)</th>
<th>LV syst</th>
<th>LVED</th>
<th>SEF</th>
<th>EDV (cc/m²)</th>
<th>(dV/dP)ed (mm Hg)</th>
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Inappropriate hypertrophy (IH)

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With obstruction (IHSS):
**Aortic stenosis (AS)**

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**Abbreviations:** BSA = body surface area; SEF = systolic ejection fraction; k = slope of the log P-V relationship; (dV/dP)ed = index of distensibility at end-diastole; SED = end-diastolic stress; and SpS = peak systolic stress.

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The average end-diastolic volume in patients with aortic stenosis (8 ± 6 cm³) did not differ significantly from normal (5 ± 3 cm³). The average end-diastolic pressure in patients with aortic stenosis was significantly lower in the normal group (7 ± 4 mm Hg) than in the group with AS (15 ± 6 mm Hg, P < 0.001). The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.

The average end-diastolic volume in patients with CC (8 ± 4 cm³) was significantly greater than normal (5 ± 3 cm³). The average end-diastolic pressure in patients with CC (15 ± 6 mm Hg) was significantly lower in the normal group (7 ± 4 mm Hg) than in the group with CC (15 ± 8 mm Hg, P < 0.001). The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.

The average left ventricular end-diastolic pressure for each of the three groups of patients with abnormal ventricular end-diastolic pressure for each of the normal groups (7 ± 4 mm Hg) was significantly less than normal in the left ventricle (7 ± 4 mm Hg, P < 0.001). The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.

The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.

The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.

The average end-diastolic pressure in patients with CC (15 ± 8 mm Hg) was significantly higher than normal.
**Left Ventricular Wall Stress.** The left ventricular end-diastolic circumferential wall stress (Sed) in the 13 normal subjects averaged $26 \pm 2 \times 10^3$ dynes/cm$^2$, while peak systolic circumferential wall stress (Sps) in this group averaged $377 \pm 12 \times 10^3$ dynes/cm$^2$. The calculated values for Sed and Sps in all 33 patients are given in table 1 and are shown graphically in figure 4.

The average Sed of the group of patients with IH (24 $\pm$ 3 $\times$ 10$^3$ dynes/cm$^2$) did not differ significantly from normal (table 3). The average Sed of the subgroup with IHSS (20 $\pm$ 2 $\times$ 10$^3$ dynes/cm$^2$) was lower than
normal, but the difference was not significant at the 0.05 level. The range of Sed in patients with AS varied widely (29–120 \times 10^3 dyne/cm²), and while the average Sed was elevated above normal the difference was not significant. All patients with CC had elevated

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>(dV/dP)_{ed} cc/m^2</th>
<th>mm Hg</th>
<th>P value</th>
<th>(dV/dP)V60 cc/m^2</th>
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<th>P value</th>
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<td>IH</td>
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<td>1.1 ± 0.3</td>
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<tr>
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<td></td>
<td>&lt;0.02</td>
<td>12.4 ± 2.7</td>
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</table>

Abbreviations: IH = inappropriate hypertrophy; AS = aortic stenosis; CC = congestive cardiomyopathy; (dV/dP)_{ed} = index of distensibility at end-diastole; and (dV/dP)V60 = index of distensibility at a ventricular volume of 60 cc/m².
values of Sed, the average \((102 \pm 13 \times 10^3\) dyne/cm\(^2\)) being significantly higher \((P < 0.001)\) than the normal group.

The average Sps in the group of patients with IH \((213 \pm 31 \times 10^3\) dyne/cm\(^2\)) was significantly less \((P < 0.001)\) than normal \((377 \pm 12 \times 10^3\) dyne/cm\(^2\)). Among the patients with IHSS, the lowest peak systolic stresses were seen in those with no resting outflow obstruction, and the highest systolic stresses were observed in those with the greatest outflow pressure gradient. Three patients with fixed aortic valvular obstruction had Sps in the normal range, and two patients had markedly elevated Sps. The average Sps of the AS group \((460 \pm 51 \times 10^3\) dyne/cm\(^2\)) was greater than normal, but the difference was not significant. The average Sps of the group of patients with CC was \((423 \pm 27 \times 10^3\) dyne/cm\(^2\)) greater than normal, but again the difference was not significant.

Active Length-Tension Relationships. In figure 5A, peak systolic stress \((Sps)\) is plotted against end-diastolic stress \((Sed)\) for all 33

---

Table 3

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Sed 10^3 dynes/cm^2</th>
<th>P value</th>
<th>&quot;Muscle fiber stretch&quot; 10^3 cm/cm^2</th>
<th>P value</th>
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<tr>
<td>Normal</td>
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<td>25 ± 2</td>
<td>—</td>
<td>116 ± 6.3</td>
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<tr>
<td>IH</td>
<td>9</td>
<td>24 ± 3</td>
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<td>49 ± 7.7</td>
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<td>AS</td>
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<td>58 ± 18</td>
<td>NS</td>
<td>61 ± 9.6</td>
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<tr>
<td>CC</td>
<td>6</td>
<td>102 ± 13</td>
<td>&lt;0.001</td>
<td>97 ± 10.8</td>
<td>NS</td>
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*Calculated using equation 9. See text.
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subjects. While Sed in the subjects with IH was not significantly different from the normal group, Sps was substantially lower than normal. Despite a marked increase in Sed, the subjects with CC generated only slightly greater Sps than normal (P = NS). In AS, both Sed and Sps were slightly greater than normal, although the differences were not significant.

In order to better assess the active length-tension relationships in these hearts, the product of Sed and end-diastolic dV/VdP (equation 9) was employed as an index of muscle stretch and was plotted against Sps (fig. 5B). When examined in this fashion, it will now be seen that “muscle fiber stretch” in the IH group is significantly less than normal (P < 0.001). It would appear, therefore, that at least part of the reduced Sps in patients with IH is due to a less than normal fiber stretch. Likewise, “muscle fiber stretch” in the group of patients with AS is significantly less (P < 0.001) than normal, whereas the Sed in this group was slightly but insignificantly greater than normal (table 3). “Muscle fiber stretch” in the CC group, however, was not significantly different from normal, despite a markedly elevated preload.

In figure 6A peak developed systolic stress is plotted against “muscle fiber stretch.” Using this approach, the active length-tension relationships of the normal, AS, and IH groups were not altered significantly. In the CC group, peak developed systolic stress was somewhat less than normal, while total peak systolic stress was greater than normal. In order to credit the ventricle with both force-generating and fiber-shortening capabilities, a ventricular function curve was constructed from all 33 patients by plotting a work index (peak developed systolic stress times stroke index) against “muscle fiber stretch” (fig. 6B). The lowest values for “muscle fiber stretch” and work were seen in the IH group. Both indices were lower than normal in the AS group and these subjects occupied an intermediate position between the IH and normal groups. The average coordinates for these three groups

Figure 5

Active length-tension relationships. (A) Peak systolic stress is plotted against end-diastolic stress for each of the 33 subjects. Mean values ± sem are shown for each group. (B) Peak systolic stress is plotted against “muscle fiber stretch” (Sed [dV/VdP]ed). It will be seen that the length-tension relations plotted in B demonstrate a reduced fiber stretch in the subjects with IH which is not apparent when end-diastolic stress is examined (see A). The relative positions of the normal, AS, and CC groups also differ substantially in these two assessments of length-tension relations (see text).
suggest that all three groups may be functioning on a single work-length curve. The very low work indices and the normal values for “muscle fiber stretch” seen in the CC group indicate markedly depressed ventricular function.

**Discussion**

It has long been known that the stress-strain relationship of resting muscle, like most biologic tissue, does not obey Hooke’s law. While a number of equations have been used to characterize this relationship, an exponential equation has been found to be quite accurate in isolated skeletal muscle,7,8 in the in vitro heart,9 and in the heart of conscious dogs.9 This is so except at the extremes of the stress-strain relationship. In the present study it was found that the log P-V relationship was linear at physiologic pressures above 3 mm Hg, and thus values below this level were not utilized in these analyses.

It should also be pointed out that pressure-volume relationships were determined under static conditions in the in vitro dog studies and only at end-diastole in the human studies. Under these conditions, therefore, it is primarily the elastic properties of resting heart muscle which are being examined rather than viscous properties. Indeed, Noble et al.9 have demonstrated that the “series viscous element is not an important determinant of the diastolic pressure-volume relationship” in conscious dogs. In addition, it was found that plastic properties of heart muscle appeared to be too small to be detected by these methods.

The estimations of diastolic compliance of the left ventricle presented in the present study are predicated upon two very important assumptions. First, it has been assumed that the log P-V relationships at various end-diastolic volumes in a given ventricle are linear in both the normal and diseased left ventricle. Since serial measurements of pressure and volume were not made in each subject, this has not been established for the patients reported in this study. However, there is ample evidence that the pressure-volume curve of the normal ventricle is exponential at physiologic pressures (vide supra), and the studies of Hood et al.,10 shown in figure 7, also indicate that the same is true of dogs with experimental myocardial infarction. In these animals with less compliant ventricles, the log P-V relationship remained linear while the slope of the log P-V curve increased 45%.

The second important assumption is that the pressure intercept (b) of the log P-V relationship varies little and that the slope of this relationship can be estimated from a single coordinate of log P and V and a constant intercept (b). In the normal dog heart, there is good reason to believe that this is so. When the data from 27 dog ventricles...
studied by Spotnitz et al. were examined, the average intercept (0.63 mm Hg) was close to that found in the present study (0.43 ± 0.13 mm Hg). Relatively little such information is available in the diseased left ventricle. As shown in figure 7A, however, the pressure intercept (b) obtained from both sham-operated dogs and those with less compliant myocardial infarctions studied by Hood et al. were virtually the same (0.42 and 0.45, respectively), and similar to the average normal values reported here. Some additional information is provided by the report of Gorlin et al. of subjects with normal left ventricles and with severe aortic stenosis. In this study, two coordinates of pressure and volume were provided by the administration of isoproterenol or norepinephrine. Thus, when the two log P-V coordinates were linearly extrapolated to zero volume, the pressure intercept (b) obtained from both normal and diseased left ventricles only varied between 0.31 and 0.46 mm Hg (fig. 7B). These observations suggest that the pressure intercept (b) varied little when compliance is reduced by experimental myocardial infarction and is similar in the normal and hypertrophied human left ventricle. On the

\[ \text{Figure 7} \]

(A) Average postmortem left ventricular pressure-volume relations of six sham-operated dogs and 10 dogs with experimental infarction (3-5 days) reported by Hood et al. are plotted as log pressure vs volume. The log P-V relationships are linear in both the sham-operated and the infarcted ventricles. The pressure intercept (b) in the sham-operated animals (0.42 mm Hg) and in the infarcted animals (0.45 mm Hg) is the same as that reported in the present study (0.43 ± 0.12 mm Hg). (B) Average left ventricular end-diastolic pressure-volume relations are plotted as log pressure vs volume for nine patients with normal left ventricles and seven patients with aortic stenosis reported by Gorlin et al. Two pressure-volume coordinates were provided in each patient by the administration of isoproterenol (I) in the aortic stenosis and normal groups and also by an infusion of norepinephrine (NE) in the normal group. Extrapolation of the log P-V relations in each group yielded pressure intercept (b) varying between 0.30 and 0.46 mm Hg. See text for further details.
basis of these observations, it was thought reasonable to assume that compliance of the ventricle could be estimated from a single coordinate of log P and V and a constant pressure intercept (b). It is clear, however, that this issue will only be resolved by a careful analysis of series pressure-volume relationships in a given patient and that in this way the degree with which variations in k and b determine altered compliance of the diseased ventricle can be clarified.

It would, perhaps, be proper to consider what effect a variable b intercept would have on the observations made in these human studies. The patients with CC, for example, were found to have a less compliant ventricle at end-diastole than normal. Assuming a normal b intercept, the calculated dV/dP at a common volume of 60 cc/m² was found to be much greater than normal (see table 2). If, in the process of dilatation and hypertrophy (be it by fiber slippage and/or in series replication) the pressure-volume relations were such that no change in k occurred and only the b intercept changed, the calculated dV/dP at end-diastole would be reduced further from 1.4 to 0.8 cc/m²/mm Hg. On the other hand, dV/dP calculated at V60 would increase from 12.4 to 21.3 cc/m²/mm Hg. Thus, by assuming a constant pressure intercept (b), the estimates of ventricular distensibility in CC given in table 2 may underestimate the variations from the normal; the index of distensibility at end-diastole, therefore, may be even less, and that at V60 even greater, than the values calculated. Assuming a normal value for k and a variable b intercept in the group with IH, dV/dP at end-diastole will increase only from 1.0 to 1.4 cc/m²/mm Hg and dV/dt at V60 will increase slightly from 0.7 to 0.9 cc/m²/mm Hg.

Notwithstanding some evidence to the contrary, it is possible that the extrapolated b intercept of log P-V plots of diseased ventricles may be different from normal ventricles. The extent to which a variable b intercept will affect compliance calculated at end-diastole and at V60 in the groups with CC and IH has been discussed above. These calculations define the range of error introduced by assuming a constant intercept (b), but do not alter qualitatively the conclusions reached in the analysis of the data presented. Since there is some experimental evidence to suggest that altered compliance of diseased ventricles is associated with changes in the slope of the log P-V relationship without a significant change in the b intercept, the human data were analyzed in this fashion.

Bristow et al. estimated dV/dP at end-diastole in 18 patients by measuring the changes in left ventricular volume during the last 0.2 sec of diastole (cineangiography at 60 frames/sec) and dividing this value by the increment in left ventricular diastolic pressure produced by left atrial contraction. In their studies (dV/dP)ed varied considerably in patients with normal left ventricles (0.1–5.5 cc/m²/mm Hg) and particularly in patients with chronic coronary heart disease (0.1–15.0 cc/m²/mm Hg). In the present study the range for all patients studied was 0.3 to 4.0 cc/m²/mm Hg, and in the normal group from 2.0 to 4.0 cc/m²/mm Hg. The wide variations found by Bristow et al. are likely due to technical difficulties in accurately measuring pressure-volume changes during the last 0.2 sec of diastole. It is of interest, however, that the average (dV/dP)ed calculated by Bristow in normal subjects (2.8 cc/m²/mm Hg) was quite similar to the mean of the normal group reported in the present study (3.0 cc/m²/mm Hg). This observation suggests that calculation of dV/dP using the log P-V relationship and an intercept (b) of 0.43 provides values which are not dissimilar to those derived from direct dynamic end-diastolic measurements.

From the data presented, it would appear that compliance at end-diastole is decreased in IH, in AS, and in CC. In IH this decrease in compliance is observed in ventricles which are significantly smaller than normal (P <0.05), in AS in ventricles which have a normal end-diastolic volume (P = ns), and in CC in ventricles which are larger than normal (P <0.001).
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End-Diastolic and Peak Systolic Stress

The normal values for left ventricular end-diastolic stress (Sed) found in the present study (26 ± 2 × 10^3 dynes/cm^2) are similar to those reported by Hood, Rackley, and Rolett (30 ± 4 × 10^3 dynes/cm^2), but slightly less than those found in normal children (37 ± 12 × 10^3 dynes/cm^2) by Graham et al.14 In patients with left ventricular hypertrophy in the absence of congestive heart failure, Sed has generally been found to be normal.13, 14 Although the range was great, Sed in the group of patients with aortic stenosis reported in the present study was also not significantly greater than normal. All six patients with CC, however, exhibited marked elevations in calculated Sed. Less constant elevations of Sed have been reported in patients with left ventricular failure.6, 13, 15 Only a few measurements of Sed have been made in patients with inappropriate hypertrophy, and as in the present study these have all been either normal or low.13, 15

The calculations of equatorial peak systolic stress (Sps) in the present study are not precise but represent an estimate derived only from measurements of end-diastolic dimensions, end-systolic dimensions, and peak systolic pressure. A number of studies have shown that normally peak systolic stress is achieved early during the ejection period.6, 13, 16, 17 On the basis of these observations, it was reasoned that Sps could be approximated by estimating ventricular dimensions one third through the ejection period (see equation 8). Using this approach, the average Sps found in patients with normal left ventricles (377 ± 12 × 10^3 dynes/cm^2) was similar to that reported by Hood et al.13 (327 ± 24 × 10^3 dynes/cm^2) who measured wall stress throughout the cardiac cycle. Although the force-time curve in large failing hearts tends to be more isotonic and may peak later in systole than in the normal heart,18, 19 the error introduced in calculating Sps using equation 8 should be small by virtue of smaller changes in systolic dimensions and wall thickness in these hearts. The calculation of Sps in the small thick-walled hearts of patients with IH, however, is more tenuous. End-systolic dimensions are difficult to measure in these hearts, particularly in the presence of asymmetric hypertrophy. Furthermore, while Sps is still achieved early during ejection in these hearts, peak systolic pressure occurs late.13 Thus, the values for Sps in IH shown in table 1 and figures 5 and 6 are probably higher than they should be, since peak stress is achieved at a ventricular pressure which is lower than peak systolic pressure.

Length-Tension Relations

The relationship between Sps and Sed shown in figure 5A represents an effort to assess ventricular function in hearts with different chamber dimensions. Since the basic tenet of the Frank-Starling mechanism is that heart muscle contracts more forcefully from a longer initial fiber length, it is clear that this may be shown for different end-diastolic pressures or volumes only when either is indeed indicative of relative changes in fiber length. The ultrastructural basis for the Frank-Starling mechanism lies, then, not on the absolute length of a muscle fiber but the degree to which the fiber is stretched.

Assuming that the compliance of all hearts studied was the same at end-diastole, the Sps and Sed relationships shown in figure 5A should be representative of the relative length-tension relations of these hearts. Since the patients with IH generated far less Sps at the same Sed, one would conclude that either the contractile state of these hearts is depressed or their afterload is greatly decreased. The group with CC, on the other hand, demonstrated an Sps only slightly greater than normal at an average Sed which was four times normal. The data from the five subjects with AS varied widely but did not differ significantly from normal.

Since the true stretch of the muscle fiber and its sarcomeres is determined by both the preload (Sed) and the extensibility of the fibers, a more accurate assessment of the length-tension relations of these hearts is provided by relating Sps to the product of Sed and (dV/VdP)ed. When this index of "muscle

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fiber stretch" is plotted against Sps (fig. 5B), the length-tension relations described above are altered. For example, it is now clear that the low values for Sps found in the IH group are associated with significantly less \((P < 0.001)\) "muscle fiber stretch" than the normal group. Thus, irrespective of changes in contractile state at least part of the performance of hearts with IH can be explained by short sarcomeres. When examined in this fashion, the subjects with CC were found to have values for "muscle fiber stretch" which were not significantly different from normal, although their preload (or Sed) was four times normal. When Sed and "muscle fiber stretch" are examined in the group with AS, important differences are again observed. While Sed in AS was slightly higher than normal, "muscle fiber stretch" is lower than normal \((P < 0.001)\) and intermediate between the group with IH and the normal subjects. In figure 6A where "muscle fiber stretch" is plotted against peak \(d\) developed systolic stress, relatively little change in the length-tension relationships is observed except for a disproportionate reduction in the stress generated by the CC group.

Finally, the performance of these ventricles can be compared more effectively by relating "muscle fiber stretch" to a work index of the ventricle. Such an index is provided by the product of peak developed systolic stress and stroke index (fig. 6B). This type of ventricular function curve is particularly informative, not only because it provides an estimate of relative sarcomere length, but because it also considers the consequences of variable afterloading, i.e., fiber shortening. When this is done, it appears that the normal, AS, and IH groups define a work-length curve in which each group differs only in the degree of heterometric recruitments to determine performance. Thus, patients with IH, particularly those with IHSS who have little or no resting gradient in the recumbent position, have short sarcomeres and perform "low down" on the ventricular function curve. Subjects with AS appear to function slightly lower on the curve than normal subjects, while those with CC clearly are on a depressed curve at sarcomere lengths that are in the normal range.

**General Considerations**

As the index of "muscle fiber stretch" reported in this study was derived from volume data, a comparison of the cube root of these values should be meaningful in light of the sarcomere length-tension relationship. When this is done, it will be seen that the linear muscle fiber stretch in the group with IH is 27% less than the normal group. Since the physiologic range of sarcomere lengths is not likely to exceed 20%, these reported deviations in "muscle fiber stretch" from the normal appear excessive. While inaccuracies in the calculation of Sed in the diseased ventricle may in part be responsible, a more likely source of error lies in estimation of ventricular compliance at end-diastole. For example, while there is good reason to believe that \(k\) is high in patients with IH, if one assumes a variable intercept \((b)\) and a normal value for \(k\) in IH (vide supra), the calculated "muscle fiber stretch" will increase from a value of 49 to 67, a value closer to that of the normal group. Thus, if the intercept \((b)\) does not remain constant in hypertrophy, compliance in the IH group may be somewhat higher than estimated and the calculated "muscle fiber stretch" more in keeping with the constraints of the sarcomere length-tension relationship. Despite these limitations, certain conclusions appear warranted from the data presented.

In subjects with chronic congestive cardiomyopathy, despite a markedly elevated preload, "muscle fiber stretch" is normal. This finding suggests that the sarcomeres of these patients are not overstretched and may even be in the normal range at end-diastole. Interestingly, Ross et al.\(^{20}\) found that the average end-diastolic sarcomere length of the chronically dilated dog left ventricle \((2.19 \, \mu)\) was only 5.8% greater than the normal ventricle \((2.07 \, \mu)\). If, indeed, end-diastolic sarcomere length is normal in chronic CC, these large hearts may still be functioning on the ascending limb of the sarcomere length-tension curve. Depending upon the slope of the depressed
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ventricular function curve, then, further dilation may improve performance, although at the price of increased pulmonary venous congestion.

The patients with hypertrophy, particularly those with inappropriate hypertrophy, were found to have low values for "muscle fiber stretch" despite the fact that their preload was normal. The implication of this finding is that patients with IHSS have short sarcomeres. Whether this observation represents a primary defect or is the consequence of dynamic outflow obstruction is not clear. In either case, however, there is good reason to believe that this phenomenon may play an important role in the progression of this disease. Once IHSS is present, reductions in preload or afterload facilitate dynamic obstruction and provide a further stimulus to hypertrophy. As hypertrophy progresses, diastolic compliance falls further, and inflow obstruction to the ventricle increases.21 As a consequence of this diminished compliance, "muscle fiber stretch" is reduced and, in turn, accentuates outflow obstruction unless this can be offset by a commensurate increase in preload. Since ventricular dimensions are of signal importance in this disease, the trend can be viewed as a struggle between preload and compliance.

Acknowledgments

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Left Ventricular Stress and Compliance in Man: With Special Reference to Normalized Ventricular Function Curves
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