Diastolic Geometry and Sarcomere Lengths in the Chronically Dilated Canine Left Ventricle

By John Ross, Jr., Edmund H. Sonnenblick, Roger R. Taylor, Henry M. Spotnitz, and James W. Covell

ABSTRACT

In 10 dogs left ventricular geometry and ultrastructure were examined 3 to 12 weeks after chronic ventricular dilatation was induced by means of a large arteriovenous shunt. Following cardiac catheterization, the hearts were arrested and fixed in diastole at the left ventricular end-diastolic pressures (LVEDP) which existed in the beating heart. Transmural LVEDP were increased in all animals (avg. 27 mm Hg). The diastolic pressure-volume relationship was shifted to the right, the average end-diastolic volume of the chronically dilated ventricles (avg. 103 ml) being larger than that of previously studied acutely dilated ventricles (avg. 72 ml, P < .01), but calculated diastolic wall stress values were not different. Sarcomere lengths in the chronically dilated hearts averaged 2.19 ± .02 μ (SE) (range 2.11 to 2.27), a value near the apex of the sarcomere length-tension curve, but not significantly different from sarcomere lengths in acutely dilated ventricles. Slippage between myofibrils, reflected by a loss of normal alignment of the Z lines, appeared to be one mechanism underlying this adaptation. The findings indicate that sarcomeres in the canine left ventricular wall are remarkably resistant to chronic as well as to acute overstretch. They further imply that little or no Frank-Starling reserve mechanism was available in these ventricles and raise the possibility that a descending limb of the heart's performance as a pump need not reflect a descending limb at the sarcomere level.

KEY WORDS

ultrastructure diastolic pressure-volume curve ventricular hypertrophy myofibril slippage

The development of a method for the rapid arrest and fixation of the left ventricle has allowed examination of the structure of the normal canine heart in systole and diastole (1-3). In those experiments, it was shown that overdistension of the normal left ventricle, produced by acute volume overloading in the open-chest animal, caused increases in mid-wall sarcomere lengths in hearts fixed in diastole to an average of 2.25μ (2), a value near the apex of the sarcomere length-tension curve of cardiac muscle (4, 5). Thus, even at very high end-diastolic pressures and volumes the sarcomeres could not, on the average, be forced onto a descending limb of the sarcomere length-tension relation.

In the presence of chronic disease of the left ventricle, the ventricular end-diastolic volume may be greatly increased. However, it is not known whether chronic cardiac dilatation and failure are associated with further elongation of the sarcomeres and operation of the ventricle on a descending limb of the sarcomere length-tension relation. It seemed possible, for example, that mechanisms such as interfiber slippage and hypertrophy could prevent overstretching of sarcomeres under...
Hemodynamic Data, Geometry, and Sarcomere Lengths in Chronically Dilated Canine Left Ventricles

### TABLE 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Wt. (kg)</th>
<th>Days postop.</th>
<th>Autopsy</th>
<th>LV wt (g)</th>
<th>LV vol (ml)</th>
<th>LV vol/(100 g LV)</th>
<th>Circ.</th>
<th>Calc. avg ( r_s )</th>
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<td>19.1</td>
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<td>100/27</td>
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<td>2+ ascites</td>
<td>172/30</td>
<td>30</td>
<td>91</td>
<td>102</td>
<td>112  17.4 2.75</td>
</tr>
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<td>147/29</td>
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<td>118</td>
<td>107</td>
<td>91      16.3 2.60</td>
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<td>56</td>
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<td>155/30</td>
<td>25</td>
<td>117</td>
<td>94</td>
<td>80      16.6 2.65</td>
</tr>
<tr>
<td>7</td>
<td>22.8</td>
<td>22</td>
<td>2+ ascites</td>
<td>145/34</td>
<td>32</td>
<td>138</td>
<td>109</td>
<td>79      18.6 2.65</td>
</tr>
<tr>
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<td>18.7</td>
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<td>2+ ascites</td>
<td>128/21</td>
<td>21</td>
<td>87</td>
<td>99</td>
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<tr>
<td>13</td>
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<td>53</td>
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<td>140/19</td>
<td>19</td>
<td>129</td>
<td>123</td>
<td>95      17.5 2.89</td>
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<tr>
<td>Avg.</td>
<td>20.4</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>21.8</td>
<td>40</td>
<td>2+ ascites</td>
<td>145/33</td>
<td>17</td>
<td>110</td>
<td>92</td>
<td>84      16.9 2.70</td>
</tr>
<tr>
<td>10</td>
<td>20.5</td>
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<td>2+ ascites</td>
<td>148/33</td>
<td>10</td>
<td>94.5</td>
<td>105</td>
<td>112     17.1 2.75</td>
</tr>
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<td>11</td>
<td>22.3</td>
<td>36</td>
<td>2+ ascites</td>
<td>115/31</td>
<td>11</td>
<td>126</td>
<td>105</td>
<td>83      17.7 2.90</td>
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<tr>
<td>Avg.</td>
<td>21.5</td>
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</tbody>
</table>

Dog weights are those before creation of the arteriovenous fistula. LV pr. = transmural left ventricular systolic/end-diastolic pressure in the sedated dog prior to thoracotomy. Ascites and edema were assessed on a 0 to 3+ scale, 3+ representing marked edema at the lower extremities and abdominal wall and a large quantity of ascitic fluid in the abdomen.

Fix. pr. = pressure in the left ventricle arrested in diastole at the time of cardiac fixation. Circ. = circumference of the cast at the minor equator of the left ventricular cavity. Calc. avg \( r_s \) = average internal radius at the minor equator calculated from cast circumference. AB = distance on cast from ventricular apex to base of aortic leaflets. Mean diam. = diameter determined with calipers on the cast, X and Y diameters being minor equator axes (perpendicular and parallel, such circumstances. Therefore, the present investigation was undertaken to extend our previous observations in the normal ventricle to an analysis of the geometry and ultrastructure of the dilated left ventricle of dogs subjected to chronic ventricular dilatation by means of a large arteriovenous fistula.

### Methods

Ten dogs were prepared 3 to 12 weeks prior to study by techniques described previously (6). In brief, under sterile conditions an infrarenal vena caval-aortic anastomosis was performed, thereby producing a large systemic arteriovenous fistula. In two animals (expt. 12 and 13), the pericardium was removed at the time the fistula was constructed. In the remaining animals, the chest was not opened and the pericardium was intact. Several weeks later, at the time of definitive study but prior to administration of general anesthesia and thoracotomy, the animals were lightly sedated (promazine, 1.5 mg/kg, promethazine, 1.5 mg/kg, and morphine, 3 mg/kg) and with local anesthesia a cardiac catheter was inserted retrogradely into the left ventricle via the carotid artery. By means of a Statham P23Db transducer, the left ventricular pressures were recorded on a direct-writing oscillograph. Intrathoracic pressure was recorded simultaneously through a self-retaining Foley catheter inserted through the right chest wall, and the transmural intraventricular pressures were then calculated by subtraction of intrapleural pressure from measured intraventricular pressure. At the time of left ventricular pressure measurement, the heart rates ranged from 117 to 240 beats/min. Venous pressure was kept low, i.e., at 2 to 5 cm Hg.
### Structure in Chronic Cardiac Dilatation

<table>
<thead>
<tr>
<th>Meas. diam.</th>
<th>Mitral annulus</th>
<th>LV circ. (cm)</th>
<th>Wall thickness (cm)</th>
<th>Diast. LV wall stress (g/cm²)</th>
<th>Sarcomere length (µm)</th>
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</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>X/Y</td>
<td>AM</td>
<td>AB</td>
<td>Mean ± SD</td>
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<td>4.6</td>
<td>0.94</td>
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<td>5.0</td>
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<td>4.6</td>
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<td>4.8</td>
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<td>0.95</td>
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<tr>
<td>Group 1</td>
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<td>4.7</td>
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<td>0.96</td>
<td>6.5</td>
<td>7.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

respectively) in a plane bisecting the heart at the minor equator (1). AM = distance on cast from ventricular apex to mitral annulus. The X and Y diameters of the mitral annulus are the horizontal and vertical diameters, respectively. LV circ. = measured circumference at the minor equator of the outer surface of the fixed ventricle. Wall thickness = calculated thickness of the ventricular wall at the minor equator taken as the difference between the radius calculated from the measured external circumference and r. Wall stress = \[ \frac{P \cdot r}{h} \left( 1 - \frac{2 \cdot r^2}{AM^2} \right) \], where P = pressure at fixation and h = wall thickness.

150 (average 132) beats/min. Except for slightly lower left ventricular end-diastolic pressure values, none of the data from the two animals in which the pericardium was removed were obviously different from those in the remaining animals. Cardiac output was measured in all animals by left ventricular injection and aortic root sampling of indocyanine green dye.

After the pressure and cardiac output had been measured, the animals were anesthetized with sodium pentobarbital (30 mg/kg), the catheters were removed, and a median sternotomy was performed. Anticoagulation was provided with heparin, 3 mg/kg. The pericardium was opened, and left ventricular pressure was monitored through a plastic cannula inserted through the left atrial appendage and into the ventricle. Diastolic arrest and fixation of the left ventricle was achieved by a technique described elsewhere (method 2) (1). As previously, the heart was arrested by rapid infusion of potassium citrate in blood. It should be emphasized that the potassium solution was infused in an amount adequate to produce a flaccid arrest of the heart and sufficient time was allowed before the injection of fixative (2 to 3 minutes) to ensure that all electrical and local mechanical activity had ceased. The aorta and brachiocephalic artery were then occluded, and the left ventricular pressure was adjusted by withdrawal or infusion of blood through a cannula positioned in the left atrium. In 7 of the 10 animals (group 1), the pressure was adjusted to a level close to the left ventricular end-diastolic pressure observed previously in the intact, sedated animal. In six of these experiments the pressures were exactly matched or within 1 to 2 mm Hg; in one it was 5 mm Hg lower (Table 1). In three animals (group...
level approximately one-half that observed prior to thoracotomy. The hearts were then fixed by rapid injection of glutaraldehyde through a cannula positioned in the ascending aorta. It is possible that a discrepancy could have existed between the pressure-volume curve of the potassium-arrested heart and that of the in vivo diastolic ventricle; however, recent studies have shown that the mitral valve area is not compromised, the diastolic compliance and pressure-volume curves of the potassium-arrested ventricle agree well with those observed in vivo using cineangiography (7). In six experiments, we also have made such comparisons between ventricular volumes measured by biaxial cineventriculography and in the passively arrested left ventricle, corrected for acute changes in right ventricular filling, in which the mitral valve was cross-clamped (8-10). The cineangiography was performed at 60 frames/sec in the same animal prior to cardiac arrest, and transmural ventricular pressure was recorded during the filming. Alterations in ventricular filling were induced by transfusion. Cineradiographic pictures exposed at end-diastole were corrected for x-ray distortion, and ventricular volume was calculated assuming the left ventricle to be an ellipsoid figure and using an ellipsoidal formula (11). Calculated volume was then corrected by employing a regression equation derived from studies on radiopaque ventricular casts of known volumes studied on the same radiographic system, where true volume = 0.889 calculated volume — 3.5 ml; R = 0.991; and SD = ± 1.5 ml.

The correlation coefficients between these two methods for determining ventricular volume averaged 0.94, and the regression equation between the ventricular volume obtained from the pressure-volume curve following potassium arrest and that obtained in the same hearts by cineangiography was: volume of arrested ventricle = 1.14 (± 0.12) cine volume — 5.33 (±0.68) ml (8). Since it was not necessary to occlude the mitral valve in the present study, the pressures and volumes in the arrested hearts should have closely approximated those existing in vivo. After the hearts had been well fixed by immersion in glutaraldehyde for 4 hours, they were stored in isotonic phosphate buffer solution. A cast of the chamber of each left ventricle was made using silicone rubber. Measurements of the casts and the ventricles, determination of ventricular volume, preparation of sections for electron microscopy, and determination of average midwall sarcomere lengths were carried out as described previously (1, 2). The value for sarcomere length represents the mean of at least 300 sarcomere measurements taken at random from pictures derived from two blocks of tissue and four separate grids.

The possibility exists that the free-wall biopsy employed was not representative of the remainder of the diastolic left ventricle. Variability at different sampling sites has been examined previously in seven cat hearts fixed in diastole at diastolic pressures ranging from 2 to 20 mm Hg. Two to three biopsies were obtained from the free wall and one from the interventricular septum. The maximum range of sarcomere lengths in each heart varied from ±0.03 to ±0.16 μ, while the average range was ±0.08 μ. In addition, it has been shown that the scatter in sarcomere lengths is less at higher filling pressures, ranging from 0.04 to 0.09 μ at pressures less than 12 mm Hg, and from 0.01 to 0.04 μ at pressures over that value (5). This decrease in scatter at higher diastolic pressures should have tended to reduce variations in sarcomere lengths in the hearts in the present study, in which the diastolic pressures were elevated.

We have previously employed the formula for wall stress given in Table 1 (12-13). Although more complex equations have been derived (14), it is generally agreed that mean wall stress probably can be represented adequately by simplified formulas (15, 16). Therefore, our formula for mean circumferential wall stress at the minor equator of an ellipse would appear adequate for comparisons between static mean diastolic forces in the present analysis. The range of ventricular volumes was small and is reported in Table 1 both as ml and as ml/100 g left ventricular weight. Ventricular weights in terms of mg/kg body weight are given in the text. For comparison with our earlier study, absolute ventricular volumes are shown in the figures, relative plots of the figures as ml/100 g revealed no important differences in the positions of the points. The average ventricular measurements presented when comparing the chronically dilated hearts with previously studied acutely dilated hearts are those from the seven animals in group 1, except where specifically indicated.

Results

The findings in all animals are summarized in Table 1. All 10 dogs exhibited some degree of ascites or edema, widened systemic arterial pulse pressures, and a patent arteriovenous shunt at postmortem examination. Stroke volumes in group 1 averaged 57.0 ml (range 44.8 to 94.1 ml) or 2.79 ml/kg body weight, and in group 2 they averaged 64.9 ml (range 48.2 to 90.7 ml).
STRUCTURE IN CHRONIC CARDIAC DILATATION

Silicone rubber casts of left ventricular chambers arrested in diastole show the relatively more spherical shape and larger volume of the chronically dilated chambers (below), compared with the acutely dilated chambers (above). Left: Lateral view. Right: View from apex.

ml) or 3.02 ml/kg body weight. All animals had elevated left ventricular end-diastolic pressures (EDP) when studied under sedation by cardiac catheterization, the transmural left ventricular EDP ranging from 19 to 34 mm Hg, (average 27.1 mm Hg). In the seven ventricles fixed at high filling pressures (group 1), the EDP at the time of cardiac fixation ranged from 19 to 34 mm Hg (averaged 26.3 mm Hg). In the animals in group 2, EDP prior to thoracotomy ranged from 31 to 33 mm Hg (average 32.3 mm Hg), while at the time of cardiac fixation the EDP in these animals ranged from 10 to 17 mm Hg.

VENTRICULAR GEOMETRY IN CHRONIC VENTRICULAR DILATATION

In the 10 animals, the left ventricular weights averaged 110 g (range 87 to 129 g) or 5.27 g/kg body weight. Measurement of the casts of the ventricular cavities (Table 1) showed the circumferences at the minor equator to average 16.6 cm (range 15.5 to 17.5 cm) and the calculated internal radii (ri) at the minor equator to average 2.65 cm (range 2.45 to 2.80 cm). The external circumferences of the fixed left ventricles at the minor equator averaged 21.9 cm (range 20.2 to 23 cm) and the calculated wall thicknesses at the minor equator averaged 0.84 cm (range 0.70 to 1.05 cm).

In the animals in group 2, the left ventricular EDPs were comparable to those in group 1 prior to thoracotomy, but all three ventricles in group 2 were fixed at substantially lower left ventricular pressures (average 12.7 mm Hg) (Table 1). Although the ventricular volumes undoubtedly were smaller.
at the time of fixation than when the pressures were measured prior to thoracotomy, the volumes in groups 1 and 2 overlapped.

**Comparison of Geometry of the Chronically and Acutely Dilated Ventricle**

Figure 1 compares a cast of the left ventricular cavity representative of those obtained in the present study in group 1 animals with a cast obtained in our previous study in which normal ventricles were arrested following acute dilatation by overtransfusion (1). The average weight of all 10 chronically dilated ventricles relative to body weight (5.27 g/kg) was significantly larger than the average of the 19 normal ventricles analyzed in our previous study (4.75 g/kg, \( P < 0.025 \)), indicating that some hypertrophy of the left ventricle had occurred during the period of chronic volume overloading (average duration 6 weeks). In addition, the average measured wall thickness was somewhat greater in group 1 animals (0.84 cm) when compared with five acutely dilated hearts in which this measurement was made (0.79 cm) (1).

The left ventricular EDPs at the time of cardiac fixation in the present study were similar to those of the acutely dilated ventricles in the previous study (average 26 mm Hg and 38 mm Hg, respectively; \( P > 0.05 \)) but the left ventricular volumes were much larger in the chronically dilated than in the acutely dilated ventricles (average 103 ml and 72 ml, respectively; \( P < 0.01 \); 94 and 67.5 ml/100 g left ventricle). Therefore, as shown in Figure 2, chronic volume overloading produced a marked shift to the right of the diastolic pressure-volume relation of the left ventricle, so that a larger volume occurred for any given end-diastolic pressure.

There was a considerable difference in the shape of the acutely and chronically dilated ventricles (Figure 1). Normally, the minor equator of the left ventricle in diastole is quite symmetrical, the ratio of the two minor equator axes (X, Y) being 0.91 (1). During acute cardiac dilatation, this symmetrical shape of the minor equator of the left ventricular cavity was not preserved, X/Y averaging 0.77 (range 0.73 to 0.84). However, in the chronically dilated ventricles, the minor axes again became circular, X/Y in the present study averaging 0.95 (range 0.91 to 1.02). The average distance from apex to mitral annulus (AM) was slightly greater in the chronically than in the acutely dilated ventricles (7.0 and 6.5 cm, respectively), as was the average apex-to-base distance (AB) (7.88 and 7.40 cm).
STRUCTURE IN CHRONIC CARDIAC DILATATION

Relation between left ventricular volume and sarcomere length in previously studied normal canine left ventricles arrested in systole (squares), normal diastole (solid circles), and after acute dilatation (open circles). The chronically dilated ventricles in the present study (solid triangles) fall to the right of the theoretically predicted curve (see text).

The average diastolic wall stress in the chronically dilated ventricles (80.4 ±5.16, [SE] g/cm²) was not significantly different from that in the acutely dilated ventricles (97.8*15.5 g/cm²). These values, together with the average stress in normally filled left ventricles are plotted against ventricular volume in Figure 3. The curves indicate that the passive volume-tension relation of the chronically dilated ventricles was shifted to the right, a larger volume being sustained for any level of wall stress in the chronically dilated ventricles. The diastolic wall stress values in group 2 animals were substantially lower than those in group 1.

SARCOMERE LENGTHS IN CHRONIC VENTRICULAR DILATATION

In group 1, the sarcomere lengths from the left ventricular midwall averaged 2.19 ± 0.2μ (μm) range 2.11 to 2.27 (Table 1). Those in the three animals in group 2 were 2.08, 2.06 and 2.14μ.

There was no difference between the two groups in the range of sarcomere lengths in any one heart. Although the data suggest that the sarcomere lengths were less in group 2 (average 2.00μ) than in group 1 (average 2.19μ) (Table 1), the numbers are too small for statistical comparison.

ULTRASTRUCTURAL CHANGES IN CHRONIC VENTRICULAR DILATATION

The ultrastructural components of the chronically dilated ventricles could not be distinguished from those of normal hearts. Surface membranes, mitochondria, intercalated discs and myofibrils revealed no obvious abnormalities. However, between myofibrils the usual alignment (or register) of the Z lines of adjacent sarcomeres seen in ventricular muscle from normal ventricles (Fig. 5, top) appeared to be distorted in the chronically dilated hearts (Fig. 5, bottom).

Calculations are based on alterations in the circumference of a thick-walled sphere, with an initial wall thickness of 5 mm.
Top: Electron micrographs of a normal diastolic canine left ventricle fixed acutely at an elevated end-diastolic pressure. Note relatively uniform alignment of Z lines throughout the muscle.
Similar loss of Z-line register was observed in all of the chronically dilated hearts and was accompanied by angulation of elements of the transverse tubular system (Fig. 5, bottom).

Discussion

Certain potential limitations in the methods employed for these studies, in addition to those mentioned in the methods section, deserve discussion. In this and our earlier study, the chest was opened at the time of cardiac fixation, the heart rates were higher than those in unanesthetized dogs, and it is known that the size and shape of the ventricle can be influenced by heart rate and thoracotomy (17, 18). It seems unlikely that in the present experiments, in which end-diastolic pressures were matched, that ventricular volume was substantially different after thoracotomy, as discussed earlier, although it is possible that the shapes of the hearts fixed in diastole were not strictly comparable to ventricular shapes observed in closed-chest, awake animals. The pericardium was open at the time of cardiac fixation in both the acute and chronic experiments. Since the pericardium was also open for pressure measurements in the beating heart in our previous acute experiments, the influence of intrapericardial pressure on end-diastolic pressure could be ignored. However, it is possible that in vivo ventricular pressures in the chronically dilated hearts, in which the pericardium was closed, could have differed because of this factor from those measured after cardiac arrest, when the pericardium was open. Therefore, in two animals the pericardium was removed at the time of initial operation, eliminating this factor as a source of error. Intrapericardial pressure has been shown to influence intraventricular pressure importantly in the closed-chest intact animal during acute overtransfusion (19). However, under normal conditions intrapericardial pressure is essentially zero (20), and the chronic pericardial dilatation that accompanies chronic cardiac dilatation make this factor unlikely to have been of major significance (19). If intrapericardial pressures were positive in vivo in some of the experiments in the chronically dilated hearts, the adjustment of intracardiac pressure at the time of cardiac arrest should have resulted in even higher diastolic pressures than those existing in vivo. This effect should have caused us to observe greater extension of the sarcomeres than existed in vivo; nevertheless, overextension of sarcomeres was not observed.

The chronic arteriovenous shunt used in the present experiments resulted in substantial dilatation of the left ventricle. This was evidenced by approximately a twofold increase of end-diastolic volume over that of the normal left ventricle and a 43% increase in volume over that of the normal left ventricle distended acutely to comparable levels of end-diastolic pressure (1). The latter finding implies that chronic volume overloading produced a shift to the right of the passive pressure-volume relation of the ventricle (Fig. 2). Although directionally similar shifts in this curve can be induced acutely by sudden large increases in left ventricular volume (21, 22), the volumes of the chronically dilated ventricles were substantially larger than those obtainable in such acute experiments. This phenomenon may be in part related to history-dependent stress-strain properties of isolated muscle (16) such as stress relaxation (in which if the resting muscle is stretched to a longer length force gradually falls) and creep (in which application of increased force results in gradual elongation of the resting muscle) (23). Whatever the mechanism involved, this chronic adaptation allowed further augmentation of diastolic ventricular volume, without concomitant elevation of mean left atrial and pulmonary capillary pressures. Similar rightward displacement of
diastolic pressure-volume relations also have been observed in patients with heart disease (11, 12a).

Despite the substantially higher diastolic volumes in the chronically dilated than in the acutely dilated ventricles, the calculated diastolic wall-stress values were similar in the two groups (Fig. 3). The average EDP was somewhat lower in the chronically dilated ventricles, but even if the EDP in the acutely dilated ventricles is used for calculating wall stress, the values for diastolic wall stress in the chronically dilated ventricles are not higher than those in the acutely dilated hearts. This results from a decrease in the major-minor axis ratio and hypertrophy causing greater wall thickness, which tend to produce a lower calculated stress in the chronically dilated hearts (see equation in footnote, Table 1). This altered geometry, together with the adaptation which allowed a lower pressure at a larger diastolic volume, appeared to prevent marked elevations of the diastolic wall stress.

It has been shown that at the apex of the length-active tension curve of the isolated papillary muscle, sarcomere length averages 2.2/A (24). We have previously demonstrated that in the acutely overdistended left ventricle, even at high end-diastolic pressures (up to 40 mm Hg) (2), midwall sarcomere lengths were not forced significantly beyond the apex of the sarcomere length-tension curve. This finding recently has been extended by Monroe and co-workers in the isolated dog heart arrested and fixed in a similar manner, in which at acutely induced diastolic pressures averaging 100 mm Hg, an average sarcomere length of 2.3/A was reported (25). In the present study, midwall sarcomere lengths were approximately the same in chronic ventricular dilatation as in the acutely dilated heart. This observation suggests that the chronic adaptation to severe volume overload need not have utilized the Frank-Starling mechanism in this preparation. It is clear, moreover, that no reserve remained and that any further increase in volume could not have increased optimal overlap in the sarcomeres.

Since the maximum average sarcomere length observed in any ventricle in the present study was 2.27/A, sustained overstretch of the sarcomeres onto a descending limb of the sarcomere length-tension curve did not appear to play an important causative role in the observed congestive failure. However, although circulatory congestion was present, the question whether true myocardial failure existed in all or some of the present group of animals cannot be answered with assurance. Thus, despite the presence of ascites and edema, studies of active tension-velocity relations of left ventricles in a similar preparation showed that in many animals myocardial function appeared to be sustained when compared with that in acutely overtransfused normal dogs (6).

Our studies indicate, then, that the sarcomeres in the left ventricular muscle are remarkably resistant to overstretch even in the chronically dilated heart. The well-known increased stiffness of a normal resting cardiac muscle relative to skeletal muscle (26) and the fact that calculated diastolic wall stress was not higher in the chronically dilated heart, as indicated above, undoubtedly are important factors in this phenomenon. Another significant mechanism may be "slippage" of the fibrils within the cell evidenced by the loss of Z-line register between fibrils observed in distended ventricles (Fig. 5). In addition, it is likely that with hypertrophy, additional sarcomeres were developed in series. Thus several mechanisms including hypertrophy, altered ventricular geometry, intrinse resistance to passive stretch, and internal slippage appear to defend the sarcomeres of the left ventricle against chronic overstretch. The functional significance, if any, of the observed distortion of the transverse tubules associated with the loss of Z-line register remains to be determined.

Although sarcomere length was not increased, other mechanisms related to augmented volume may have provided advantages for the chronically dilated ventricle. The average stroke volume of 57 ml in group 1 animals was nearly double the calculated ejection volume in normal hearts fixed in...
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Since end-diastolic volume of the dilated hearts averaged 103 ml, this observation implies that the average ventricular volume at end-systole was 46 ml. If sarcomere shortening in the dilated heart followed a curve parallel to the normal (Fig. 4), sarcomere length would have been approximately 1.8 at end-systole. To achieve this stroke volume, the acutely dilated normal heart would have had to reach an end-systolic volume of 17 ml and even shorter sarcomere lengths, observed only in potentiated hearts. Therefore, the shift of the ventricular volume-sarcomere relation allowed the chronically dilated heart an enhanced stroke volume within the constraints of relatively normal sarcomere shortening. Through this mechanism, stroke volume could be preserved in the chronically enlarged ventricle even when reduced shortening of the ventricular wall (27) and sarcomeres exist in myocardial failure. In addition, wall hypertrophy and the shape changes discussed previously could allow the chronically dilated ventricle to sustain relatively less wall stress passively and to require relatively less active tension development for a given systolic pressure than an acutely dilated chamber of comparable size, thereby providing further mechanical advantages to the chronically dilated chamber.

In the failing heart, diminished active shortening of the fibers and sarcomeres undoubtedly is primarily responsible for depression of the left ventricular function curve (27). However, our findings in the diabetic heart suggest some interpretations concerning the characteristics of function curves relating left ventricular end-diastolic volume or pressure to stroke volume and stroke work. In the dilated ventricles fixed at low filling pressures (group 2), the data suggest that average sarcomere length decreased as filling was reduced in the chronically dilated ventricle. Therefore, during reductions in venous return to the ventricle, it might be expected that two factors are operative: reduction in diastolic sarcomere length, which would tend to diminish stroke volume, and reduction in heart size, which by lowering afterload (wall stress) would tend to enhance stroke volume (28). In the failing human ventricle, the net effect of this interplay could result in the relatively flat relationship of the curve relating left ventricular end-diastolic volume or pressure to stroke volume when venous return is acutely reduced, stroke volume shows no change or a fall (29). That stroke volume cannot be enhanced substantially by augmenting venous return to the chronically dilated and failing heart seems a logical consequence of the fact that in chronic cardiac dilatation the sarcomeres already are maximally extended. In the normal ventricle, when aortic pressure, or afterload, is increased a compensatory augmentation of end-diastolic pressure and volume can occur so that the stroke volume remains unchanged or is augmented (30). If, under experimental conditions, aortic pressure and hence wall force or afterload is increased while ventricular end-diastolic volume is held constant, a reduction of fiber shortening and stroke volume ensues (28). In patients with severe myocardial disease and chronic cardiac dilatation in whom aortic pressure was elevated by administration of a pressor agent, a fall in stroke volume was observed in the face of an increasing left ventricular end-diastolic pressure (30). This phenomenon may be analogous to the effects of enhanced afterload-in the normal heart with resting fiber length held constant. Thus, in the diseased ventricle, unable to compensate by further increasing diastolic sarcomere length, increased aortic pressure might be expected to cause a reduction in stroke volume. Under these conditions, and perhaps during volume overloading of the failing heart as well, we would speculate that a descending limb of the function curve of the ventricle need not reflect diastolic overextension of the sarcomeres, but rather the effect of increased systolic pressure and volume which augment afterload via the Laplace relation and thereby cause a reduction of stroke volume. These findings raise the possibility that a descending limb of the heart’s performance as a pump need not reflect the existence of a descending limb at the sarcomere level.
References


heart characterized by force-velocity relations in variably afterloaded and isovolumic beats.


Diastolic Geometry and Sarcomere Lengths in the Chronically Dilated Canine Left Ventricle
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