Nature of Enhanced Performance of the Dilated Left Ventricle in the Dog during Chronic Volume Overloading

By John Ross, Jr., and William H. McCullagh

ABSTRACT

The size and the performance of the left ventricle were examined in six conscious dogs early (within 1 week) and late (average 7 weeks) after the production of a large infrarenal arteriovenous fistula. Radiopaque beads were implanted near the endocardium of the left ventricle, and in each study the end-diastolic pressure was adjusted to 22 mm Hg by transfusion or bleeding. The shortening of the minor equator of the left ventricle and its mean velocity of shortening were compared in each dog before and after chronic left ventricular dilatation (ventricular end-diastolic volumes of 71 ml early and 101 ml late, P < 0.05). In five dogs the stroke volume increased by an average of 42% (P < 0.05) between early and late studies, but the percent change in circumference and the mean velocity of shortening remained unchanged (24.2 ± 2% (SE) and 23.6 ± 2%, 1.43 ± 0.12 circumferences/sec and 1.44 ± 0.09 circumferences/sec, respectively) at comparable heart rates. In one animal with congestive heart failure, the percent change in circumference and the mean velocity of shortening fell progressively to 19% and 0.74 circumferences/sec. It is concluded that in the absence of myocardial failure the enhanced performances of the chronically dilated left ventricle is mediated by normal performance of each unit of circumference of the enlarged chamber. The nature of this adaptation supports the application of several measures of contractility used for the assessment of chronic variations of inotropic state. Previously, diastolic sarcomere lengths were shown to be maximal and essentially the same after acute over-transfusion as they were during chronic volume overloading, and the present studies provide physiological support for the view that the chronic adaptation to volume overload need not involve the Frank-Starling mechanism at the sarcomere level. The observed adaptation provides a reserve mechanism, in addition to the usual factors regulating cardiac performance, by which chronic alterations in ventricular geometry allow the delivery of more external work.

KEY WORDS Frank-Starling mechanism volume overload velocity of fiber shortening chronic ventricular dilatation ventricular function left ventricular volume

- Under acute circumstances four primary factors determine the stroke volume of the left ventricle: preload (the Frank-Starling mechanism), the level of inotropic state or contractility, afterload, and heart rate (1, 2). However, whether such factors are involved in the late cardiac adjustments to chronic forms of stress has received little study. Diastolic sarcomere lengths are essentially the same after chronic left ventricular dilatation accompanied by mild hypertrophy as they are during acute volume overloading (3, 4). Therefore, we postulated that the adaptation of the heart to chronic volume overloading may not involve the Frank-Starling mechanism at the ultrastructural level (3). In the present study, we compared the size and hemodynamic performance of the left ventricle in conscious dogs

Circulation Research, Vol. XXX, May 1972

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early and late after chronic ventricular dilatation produced by a large systemic arteriovenous fistula. In the absence of myocardial failure, the enhanced stroke volume of the chronically dilated chamber was accomplished by normal performance of each unit of an enlarged circumference. This augmentation of ventricular performance, therefore, did not appear to be mediated through the usual factors that acutely affect ventricular function.

Methods

Six mongrel dogs weighing 16-32 kg were prepared for study. A thoracotomy was performed under sodium thiamylal and halothane anesthesia, the pericardium was opened, and beads (1/16-inch stainless steel ball bearings) were implanted subendocardially in the left ventricle with a 14-gauge needle and trocar, as described by Mitchell et al. (5). The left ventricular cavity was approximately outlined by placement of beads in the following positions: at the apex overlying the base and at the septal, anterior, posterior, and lateral aspects of the ventricular circumference at the minor equator. A small plastic catheter (0.44 mm o.d.) was inserted into the left ventricle for pressure measurements and brought out through an incision in the neck. The pericardium was left open and the chest was closed.

In one of the six animals control studies were carried out as outlined below, and the operation to construct the systemic shunt was performed later; in the remaining five animals this second operation was performed at the same time as the thoracotomy, an approach which gave better survival than the two-stage procedure. For the second operation, described elsewhere (6, 7), a midline abdominal incision was made, and after administration of heparin the aorta and inferior vena cava were exposed and cross-clamped. A side-to-side infrarenal aortocaval anastomosis 10-12 mm in length was then constructed. In each animal, a large shunt was evidenced by venous dilatation, a murmur, and a thrill. The abdomen was closed and the animal was allowed to recover; fluid and antibiotics were given as needed.

The animals had been trained to lie quietly on an x-ray table without medication, and early postoperative studies were started within the first week after surgery. Since we wanted to compare ventricular performance before and after chronic cardiac dilatation, early studies were performed within a few days (mean 3.6 days, range 2 to 6 days) after creation of the arteriovenous fistula. These data were then compared with similar data obtained about 7 weeks after surgery.

In each study, left ventricular dimensions and pressures were measured over a range of left ventricular end-diastolic pressures produced by infusion of saline or dextran over a period of 10-20 minutes or by controlled hemorrhage if the initial filling pressure was elevated. The data reported were obtained when an end-diastolic pressure of 22 mm Hg was achieved, a level selected because at this pressure diastolic sarcomere lengths at the middle of the left ventricular free wall are maximal during both acute and chronic volume loading (3, 4). Cineradiographic films were obtained in a single plane in the left anterior oblique projection at 200 frames/sec with a Philips unit and 16-mm camera. Left ventricular pressure was measured with a Statham P23Db transducer and recorded on a Clevite-Brush Mark 200 system at full-scale sensitivities of 0-200 mm Hg and 0-40 mm Hg. The zero reference level was taken as one-half the vertical distance from the anterior to the posterior chest wall. Pressure and cineradiographic data were correlated by the simultaneous inscription of an amplified pulse generated with each opening of the cinecamera’s shutter. At each study, the beads were aligned under fluoroscopic control by rotating the dog (7) until a crossed configuration was obtained in which the apex-to-base and medial-to-lateral axes were aligned; either the anterior or the posterior bead served as the center of the cross. Exact reproduction of the initial bead configuration fluoroscopically in a second study made it possible to readily detect changes in lateral rotation of less than 5°, and care was taken to align the beads in the same manner in each dog for the early and late studies.

After each study a grid made of crossed rows of beads a known distance apart was filmed at the level of the heart and at the same tube-to-image intensifier distance. The processed film was projected with a mirror to a ground-glass screen oriented horizontally under an electronic x-y plotter, and the change in the voltage from a potentiometer was supplied to an EAI 580 analog computer. The analog signal was then converted to digital form through an EAI 640 computer. Corrections for x-ray magnification and spherical distortion were made by digitizing the projected grid filmed at each study. The cinefilm was then positioned at the appropriate frame by counting the markers inscribed on the pressure recording, the pointer was moved between the appropriate beads, and time and distance were obtained in digital form by computer calculation and printout.

The transverse left ventricular diameter, the apex-to-base length at end-diastole, and the corresponding dimensions at end-systole (point of maximum shortening) were measured for each study. Ventricular volume was estimated.
from the formula for an ellipse: \[ \text{vol} = \frac{4}{3} \pi \left( \frac{L_1}{2} \right)^2 \times \left( \frac{L_2}{2} \right) \], where \( L_1 \) is the diameter at the minor equator and \( L_2 \) is the apex-to-base length. The calculated dimensions and volumes may not precisely equal the true major and minor equator dimensions and ventricular volumes because of small differences in the distances of the beads from the endocardium (5) and slight variations in the measured dimension from perpendicularity with the x-ray beam. However, in all autopsied specimens the beads were within 2 mm of the endocardium. The assumption that the minor equator is close to a circle has experimental support (3), and since each animal served as its own control the effects of many of these potential sources of error should have been minimized. The stroke volume was calculated by subtracting the end-diastolic volume from the end-systolic volume; the ejection fraction was represented by stroke volume divided by end-diastolic volume.

The mean velocity of circumferential fiber shortening (8) was calculated by subtracting the diameter at the minor equator at end-systole from that at end-diastole and dividing by the time from end-diastole to maximum shortening of the minor equator. This quotient was then normalized by dividing by the diameter at the minor equator at end-diastole and expressed as circumferences per second for comparison with a previous analysis (8).

A paired t-test was used for statistical analyses.

**Results**

The early and late studies for all six dogs are summarized in Table 1. The early studies in five dogs were carried out the week after the shunt was constructed, and in the control dog they were obtained prior to creation of the arteriovenous fistula. Late studies were performed at a mean of 48.8 days (range 27 to 60 days) after surgery. Heart rates and systolic left ventricular pressures did not differ significantly between the early and late studies. Each left ventricular contraction that was analyzed originated from a left ventricular end-diastolic pressure of 22 mm Hg.

One dog showed persistent clinical and hemodynamic evidence of a very large arteriovenous fistula and severe cardiac failure. These findings were supported by progressive deterioration of myocardial function with a reduction in ejection fraction, a low percent of shortening at the minor equator, and a mean velocity of shortening of the minor equator which fell from 1.07 to 0.74 circumferences/sec between early and late studies (Table 1). This dog subsequently died in congestive heart failure and was excluded from the mean analyses.

In the remaining five dogs, comparison of early and late studies showed an increase in mean end-diastolic volume from \( 70.8 \pm 9.1 \) (se) ml to \( 100.9 \pm 17.4 \) ml \( (P<0.05) \) and an increase in stroke volume from \( 32.4 \pm 5.4 \) ml to \( 47.0 \pm 9.2 \) ml \( (P<0.05) \) (Fig. 1). The calculated ejection fractions remained unchanged (Table 1).

The length of the minor axis of the left ventricle increased significantly \( (P < 0.01) \) from the early to the late studies in the five dogs without cardiac failure, but the increase in the length of the long axis was small and of borderline significance (Table 1). The extent of shortening of the minor axis increased somewhat \( (P < 0.02) \), but the extent and the percent of shortening of the long axis remained small and changed little (the latter being 5% and 8% at early and late studies, respectively) (Table 1).

The final two columns in Table 1 show the percent of shortening and the mean velocity of shortening, normalized for circumference, of the minor equator in each of the five dogs without heart failure. The average percent of shortening of the minor axis (percent of change in circumference) remained unchanged, being \( 24.2 \pm 2.1\% \) and \( 23.6 \pm 1.7\% \) \( (\times S) \), respectively, in early and late studies (Fig. 2). Likewise, the mean velocity of shortening was unchanged, \( 1.43 \pm 0.12 \) circumferences/sec in the early study and \( 1.44 \pm 0.09 \) circumferences/sec \( (\times S) \) in the late study (Fig. 2).

Figure 3A shows the average values for circumferences of the left ventricular minor equator and the calculated ventricular volumes at end-diastole and end-systole in the early and late phases of the present study. These changes are compared with a curve constructed from the actual volumes of cast of the left ventricular chambers of dogs in which the hearts were rapidly arrested and...
TABLE 1

Analysis of Left Ventricular Performance during Ejection during Chronic Volume Overloading

<table>
<thead>
<tr>
<th>Dog</th>
<th>HR (E)</th>
<th>HR (L)</th>
<th>Days postshunt</th>
<th>LVSP (mm Hg)</th>
<th>LVEDV (ml)</th>
<th>Stroke vol (ml)</th>
<th>Ejection fraction</th>
<th>End-diastole Li (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>165</td>
<td>125</td>
<td>6</td>
<td>115</td>
<td>120</td>
<td>57.7</td>
<td>22.7</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>165</td>
<td>120</td>
<td>4</td>
<td>125</td>
<td>125</td>
<td>44.5</td>
<td>22.1</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>180</td>
<td>160</td>
<td>2</td>
<td>110</td>
<td>115</td>
<td>88.2</td>
<td>46.6</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>180</td>
<td>160</td>
<td>4</td>
<td>145</td>
<td>175</td>
<td>92.7</td>
<td>43.6</td>
<td>0.47</td>
</tr>
<tr>
<td>5</td>
<td>180</td>
<td>160</td>
<td>13</td>
<td>135</td>
<td>100</td>
<td>72.8</td>
<td>30.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Mean</td>
<td>164</td>
<td>157</td>
<td>3.6</td>
<td>126</td>
<td>137</td>
<td>70.8</td>
<td>32.4</td>
<td>0.63</td>
</tr>
<tr>
<td>SE</td>
<td>4.3</td>
<td>8.8</td>
<td></td>
<td>6.4</td>
<td>11.3</td>
<td>9.1</td>
<td>5.3</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Dog 6, in which cardiac failure occurred, is not included in the mean values or statistical analyses. All values in the table were analyzed in beats originating from a left ventricular end-diastolic pressure of 22 mm Hg. E = early studies; L = late studies; HR = heart rate; LVSP = left ventricular systolic pressure; LVEDV = calculated volume of the left ventricle; Li = minor left ventricular axis; L2 = left ventricular long axis; ALi = Li at end-diastole minus Li at end-systole; AL2 = L2 at end-diastole minus L2 at end-systole; %ALi = percent change in Li from end-diastole to end-systole; Vcr = mean circumferential fiber shortening rate in the minor equator of the left ventricle normalized for end-diastolic circumference.

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**FIGURE 1**

End-diastolic volume and stroke volume (means ± se) for five dogs studied early (EPS) and late (LPS) after chronic volume overloading produced by an arteriovenous shunt.

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**FIGURE 2**

Extent of shortening of the minor equator of the left ventricle and circumferential fiber shortening rate (means ± se) for five dogs studied early (EPS) and late (LPS) after chronic volume overloading produced by an arteriovenous shunt.

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study and between the volumes calculated from an ellipsoidal reference figure.

**Discussion**

This study demonstrates that the enhancement of hemodynamic performance which occurs during chronic volume overloading does not appear to be accomplished by the usual mechanisms which operate under acute conditions. Instead, the augmentation of stroke volume in the chronically volume-overloaded ventricle is mediated by normal performance of each unit of an enlarged ventricular circumference. This adaptation, operating from an increased diastolic volume but without further increase in end-diastolic pressure, provides an additional reserve mechanism by which chronic alterations in ventricular geometry allow the muscular units to deliver more external cardiac work.

The changes in diastolic volume and stroke volume induced by the arteriovenous fistula were closely similar to those observed previously by more direct methods in the same preparation (Fig. 3A) (3); the similarity lends support to application of the single-plane radiographic method employed. Although the pressure tracings obtained through small implanted cardiac catheters were suitable for determining left ventricular end-diastolic and systolic pressures, they did not have sufficient fidelity to allow determination of the rate of rise of left ventricular pressure. Therefore, we analyzed the mean velocity of left ventricular wall shortening during ejection, a measure previously found to correlate well with velocity of fiber shortening at maximum wall tension, and used it as an indicator of the level of myocardial contractility (8). We wanted to compare ventricular performance before and after significant chronic dilatation had occurred, although the possible difficulties of studies made only several days after surgery are recognized. The fact that the animals were ambulatory and conscious, without depressant medications, and were transfused to a given level of end-diastolic pressure (avoiding problems with postoperative hypovolemia) mitigate against significant postoperative abnormality of myocardial function. Values of mean velocity of wall shortening in the same normal range described for human subjects tend to support further the absence of significant depression of the left ventricle (8). The adequacy of mean velocity of wall shortening for detecting changes in inotropic state, previously shown in man (8), also appeared to be verified by the marked decrease in this variable observed in the dog that developed congestive heart failure.

Our interest in the physiological correlates of chronic volume overloading was prompted by recent clinical studies (10) in which left ventricular size and function were analyzed before and after surgical correction of severe aortic regurgitation by placement of a Starr-Edward valve prosthesis. It was found that...
he diastolic pressure-volume relation of the left ventricle before surgery was shifted to the right, as in experimental chronic volume overloading (3, 7). In addition, some patients exhibited normal fiber shortening velocities, whereas in others fiber shortening velocity was distinctly reduced. After correction of valvular regurgitation in a patient having a normal velocity of fiber shortening before surgery, there was a substantial reduction in left ventricular size in several months, but no significant change in the velocity of fiber shortening occurred. On the other hand, patients who exhibited depressed velocities of fiber shortening before surgery had little reduction in heart size after surgery, and also they showed no substantial change in the velocity of fiber shortening despite hemodynamic correction of the aortic regurgitation (10). These observations raised the possibility that the velocities of wall shortening under these conditions reflected primarily the level of myocardial inotropic state and were relatively independent of chronic changes in left ventricular size.

The fact that the mean fiber shortening rate of the left ventricle was normal in five dogs and independent of chronic changes in heart size carries implications relative to the use of various indexes of myocardial contractility. In earlier studies, we were unable to show significant differences in the calculated force-velocity relations of completely isovolumic contractions of the left ventricle in sedated dogs subjected to chronic volume overloading compared to force-velocity relations in acutely over-transfused normal dogs (6, 11). These findings suggested that velocities derived from the isovolumic phase of contraction were independent of chronic left ventricular dilatation. Other recent investigations in dogs with surgically induced chronic heart block also suggested that several indexes of left ventricular contractility derived from isovolumic pressure tracings were unchanged when compared to normal dogs (12). Together with the present observations, these findings indicate that most of the indexes of velocity derived from ejecting or isovolumic contractions (13) may prove to be independent of chronic diastolic volume changes. If end-diastolic
sarcomere length is maximal and inotropic state normal under basal conditions, afterload should then prove to be the major determinant of the extent and the velocity of shortening (14) in the volume-overloaded heart of the normal dog. Since changes in cardiac shape and increased wall thickness tend to favor maintenance of normal wall stresses under conditions of chronic overload (3, 15), even afterload may have only a minor effect if left ventricular systolic pressure is normal (10). Therefore, determination of the level of inotropic state may constitute the single major factor which substantially affects contraction velocities under basal conditions. The present findings lend support to the commonly used practice of normalizing velocity and shortening data for ventricular circumference in comparing hearts of widely varying heart size (13), since in the chronically dilated heart of the normal dog sarcomere length and myocardial function per unit circumference appear to be normal.

It is of importance relative to interpretation of the present study that earlier studies in which fistulas of similar size were imposed for the same average time period (3) showed that sarcomere lengths at the left ventricular midwall averaged 2.19μ, a value at the apex of the sarcomere length-tension relation. Moreover, this sarcomere length was almost the same as that in normal ventricles fixed after left ventricular end-diastolic pressure had been acutely elevated, although ventricular volume in the acute studies was substantially lower (3, 9). In the present studies, as left ventricular dilatation occurred between the early and late studies there was a significant increase in stroke volume. This improvement in left ventricular performance was accompanied by an apparent shift to the right of the diastolic pressure-volume relation, since at the same left ventricular end-diastolic pressure (22 mm Hg) the left ventricular end-diastolic volume was significantly larger. As the heart dilated there was some increase in the extent of shortening of the minor axis, but the percent of shortening did not change. The advantages of this adaptation at the functional and ultrastructural levels are diagrammed in Figure 3. It is apparent from Figure 3A that, because of the shape of the ventricular volume curve, the larger stroke volume after chronic dilatation is delivered with only a moderate increase in the extent of shortening of the minor equator. The fact that the percent of shortening did not change at all (Table 1) indicates that the shortening per unit of circumference (the sarcomere, at the ultrastructural level) did not change. Thus, as shown in Figure 3B, since end-diastolic sarcomere length is near maximal (approximately 2.2 μ) after acute elevation of ventricular end-diastolic pressure (4) and remains maximal after chronic ventricular dilatation (3), the chronically dilated chamber is capable of delivering a larger stroke volume than normal within the constraint of a normal extent of sarcomere shortening.

We interpret the fact that diastolic sarcomere lengths are essentially the same before and after chronic ventricular dilatation to indicate that the Frank-Starling mechanism may play little or no adaptive role at the ultrastructural level under these conditions. There is ample evidence, on the other hand, that at sarcomere lengths below 2.2μ there is a direct relation both in isolated cardiac muscle and in the heart between sarcomere length and muscle performance (16-18), and it is undoubtedly at these lower sarcomere lengths (on the ascending limb of cardiac function) that the normal heart operates (6,19, 20). The increase in ventricular size in chronic volume overloading is related to an increased number of sarcomeres in series, a process for which evidence exists (21) and which, in turn, may be related to reported increases in myocardial cell size (22) and cell length (23) in hypertrophied cardiac muscle. A possible additional mechanism is slippage of myofibrils within the myocardial cell (3). Although the quantitative significance of the latter phenomenon remains unclear, it also would tend to allow an increase in cardiac chamber volume without further elongation of individual sarcomeres.
References


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Circ Res. 1972;30:549-556
doi: 10.1161/01.RES.30.5.549

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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