Adaptations of the Left Ventricle to Chronic Pressure Overload

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SUMMARY Left ventricular (LV) function during the adaptation to chronic pressure overload produced by an ascending aortic constriction was analyzed in conscious dogs, instrumented with intraventricular micromanometers and pairs of ultrasonic crystals for measurement of LV wall thickness (WTh) and internal LV chamber diameter. During inflation of the cuff to produce LV pressures averaging 220 mm Hg, calculated peak wall stress (WSt) increased by 55% above control while percent shortening decreased by 24%. During the phase of concentric hypertrophy (mean 2½ weeks), CSA increased further to 15% above control and WSt fell to 22% above control, while EDD and percent shortening returned to control and mean VCP was reduced to -12% of control, respectively.

The canine left ventricle is a useful model for the study of experimental circulatory lesions, but investigations of chronic pressure overloading produced by aortic constriction have been complicated by the frequent occurrence of aortic rupture. 2 We have overcome this problem in part by placing a Dacron graft beneath an inflatable aortic cuff; in experimental circulatory lesions, but investigations of cuff over several weeks, and following its release. Chronic pressure overloading produced by aortic constriction was analyzed in conscious dogs, instrumented with intraventricular micromanometers and pairs of ultrasonic crystals for measurement of LV wall thickness (WTh). The subendocardial and epicardial crystals was not damaged.

THE PERFORMANCE of the heart and of cardiac muscle in chronic hypertrophy has been investigated intensively, but whether the myocardium of the intact hypertrophied left ventricle exhibits depression of the inotropic state has remained unresolved. 3 In addition, little information is available concerning the time course of the functional adaptations that follow the application of a chronic pressure overload.

The canine left ventricle is a useful model for the study of experimental circulatory lesions, but investigations of chronic pressure overloading produced by aortic constriction have been complicated by the frequent occurrence of aortic rupture. 5 We have overcome this problem in part by placing a Dacron graft beneath an inflatable aortic cuff; in addition, the ultrasonic technique for measurement of left ventricular (LV) regional dimensions 3 has been adapted to allow serial measurements of LV wall thickness (WTh) and internal diameter. This model for chronic pressure overload in the conscious dog has been applied to assess LV function before and during sustained inflation of the ascending aortic cuff over several weeks, and following its release.

**Methods**

Twelve mongrel dogs weighing 19–36 kg (average, 26.7 kg) underwent right thoracotomy in the 4th intercostal space under sodium pentobarbital anesthesia (25 mg/kg, iv). The pericardium was widely opened and the ascending aorta was exposed and dissected free. A woven Dacron tube was wrapped around the intact ascending aorta as a supporting sleeve (Fig. 1). 2 This procedure proved necessary to prevent sudden death from rupture of the aorta due to compression necrosis of the aortic wall. An inflatable cuff (Jacobson cuff, Davol Rubber Co.) was then placed around the graft, tubing leading to the cuff was brought out between the ribs, and the injection bulb was implanted subcutaneously. A high fidelity micromanometer (Konigsberg P-22) was inserted into the LV chamber through a stab incision at the ventricular apex, and a Silastic catheter also was positioned in the left ventricle to obtain zero pressure reference and to calibrate the micromanometer. 3 Pacing electrodes were sutured to the right atrial appendage.

For the measurement of internal chamber diameter one pair of 5 mHz piezoelectric disks, each 5 mm in diameter, was positioned via small stab incisions at the anterior and posterior endocardial surfaces of the LV cavity, near the minor equator. 4 A second pair of crystals was placed across the LV free wall (Fig. 1) for the continuous measurement of left ventricular wall thickness (LVWTh). The subendocardial crystal of this pair (1.5 mm in diameter) was held at the tip of a small Teflon tube and advanced diagonally through the myocardium via a tunnel created by an 18-gauge hypodermic needle such that the myocardium between the endocardial and epicardial crystals was not damaged.

To measure ventricular internal diameter and WTh the minimum transit time of sound traveling between the ultrasonic transducers was measured and calibrated in terms of the distance separating the transducers. 3 An index of LV muscle hypertrophy was estimated by calculating the cross-sectional area (CSA) of the LV wall in a transverse plane from dimensions at end-diastole:

$$\text{CSA} = \pi \left( \frac{\text{EDD}}{2} + \text{EDWTh} \right)^2 - \pi \left( \frac{\text{EDD}}{2} \right)^2$$
where EDD is internal chamber diameter at end-diastole and EDWTh is end-diastolic wall thickness.

Stroke excursion from end-diastole to the end of shortening was corrected by dividing by EDD and expressed as percent shortening. The mean velocity of circumferential fiber shortening (mean VCF) was obtained by dividing the stroke excursion by the ejection period [defined as the time from peak velocity of LV pressure rise (peak dP/dt) to the nadir of the diameter tracing] corrected for EDD. This definition of ejection time was based on our observations in dogs subjected to retrograde aortic catheterization which established that the onset of pressure rise in the aorta immediately above the aortic valve coincided with peak dP/dt both before and during aortic constriction.

In the present experiments the shape of the first derivative of LV pressure (LV dP/dt) was markedly distorted by notching and by reduction of the peak value as the cuff was inflated (Fig. 2). In the supravalvular chamber just below the constricting cuff abnormally low aortic pressures at the end of diastole were measured by retrograde aortic and ventricular catheterization. Thus, premature opening of the aortic valve appeared to limit the development of maximum dP/dt during aortic constriction. Aortic regurgitation was excluded in three dogs by retrograde arteriography; therefore, an abrupt pressure drop secondary to low distensibility of the supravalvular chamber and rapid runoff of coronary blood flow probably contributed to the low aortic end-diastolic pressure. Because of these findings, peak LV dP/dt was analyzed only before and after release of the cuff, not during constriction of the aorta.

The LV wall stress (WSt) was computed during LV ejection at 10-msec intervals; a spherical model was used: \[ WSt = \frac{PD}{4} - WTh \], where \( P \) = LV pressure and \( D \) = internal LV diameter. Peak WSt values are reported.

In four of eight ventricles that were fixed in diastole at post mortem, the endocardial and epicardial crystals were placed appropriately across the LV free wall, and the average difference between directly measured WTh and EDWTh obtained from the final dimension recording in vivo was within 1 mm (average, 12.1 ± 0.1 and 11.8 ± 0.4 mm, SEM, respectively). However, in two dogs the endocardial crystal was located within the myocardium at about 30% of the distance to the epicardial surface; this resulted in recorded wall thicknesses that were thinner than the true values (8.6 vs. 12 mm and 9.1 vs. 13 mm). In the remaining two dogs the crystals faced somewhat diagonally; the last recorded values for EDWTh were 17.0 and 16.9 mm.
whereas the actual value was 13 mm in each ventricle. Thus, the dimensions obtained in some animals did not correspond to the true transverse \(W_{\text{Th}}\); however, we have assumed that the recorded values adequately reflected relative changes that occurred during serial studies in the same animal.

In all hearts the atria and right ventricles were separated, and combined LV and septal weights were related to body weights. The average LV and septum to body weight ratio was 6.4 g/kg (range, 5.6-6.8 g/kg). (For control animals the average is 4.7 g/kg.) These data indicate that the 2½-week period allowed sufficient time for the development of substantial hypertrophy.

After the dogs had recovered from the operation we performed control studies on different days with the dogs lying quietly awake on the floor during spontaneous sinus rhythm and during atrial pacing at heart rates expected during subsequent pressure elevation. Seven to 10 successive beats were averaged in each tracing. Following the control studies, the aortic cuff was inflated by the percutaneous injection of 75% sodium diatrizoate (Hypaque) into the bulb to produce a peak LV systolic pressure (LVSP) elevation to the maximum level that each dog could tolerate without development of extrasystoles or pulmonary edema, and care was taken not to allow LV end-diastolic pressure (LVEDP) to exceed 25 mm Hg. We also checked for mitral regurgitation at each study by auscultation and by search for any change in phasic pattern of wall shortening during isovolumic systole. The pressures then were measured and the cuff inflation was changed if necessary 24 hours later. LVSP was maintained subsequently at approximately 50% above the control value for the duration of the experiment.

Of the 12 dogs included in this study, two died of aortic rupture at 5 and 10 days after inflation of the cuff; one dog developed acute pulmonary edema 4 days after aortic constriction, and in one dog the experiment was terminated early because of loss of the ultrasonic signals. In the remaining eight dogs the cuff was released at an average of 19 days after constriction, when the CSA had become relatively stable and no further increase in wall shortening was evident. The study was terminated in five dogs at 24 hours after release of the cuff, while three dogs were followed for 6 to 7 days after release of the cuff.

The data were analyzed before constriction, at three stages during aortic constriction (immediate response, at the stage of maximum LV dilation, and at the stage of stable hypertrophy), and immediately and 24 hours after release of the cuff. Immediate responses were measured 5–30 minutes after inflation of the cuff; studies on the early dilation phase were performed at an average of 9 days after inflation of the cuff (range, 4–16 days), and studies on the period of compensated hypertrophy were performed at an average of 2½ weeks thereafter (range, 7–23 days).

A paired \(t\)-test was used for all statistical analyses.

Results

Tracings illustrating the variables measured are reproduced in Figure 2, and data are summarized in Figure 3 and Table 1.

**Acute Responses to Aortic Constriction**

Resting heart rate prior to pacing was 82 ± 5 (SEM) beats/min. A pacing rate of 100 beats/min was chosen to achieve comparable heart cycles for hemodynamic analysis, except during the immediate response to aortic constriction, when the heart rate increased spontaneously to 109 ± 4 beats/min. Average LVSP was elevated from 140 to 220 mm Hg (Fig. 3) and LVEDP from 11 to 17 mm Hg (Table 1). LVEDD was increased from 31.0 to 31.8 mm, and percent shortening fell to 22.4% from a control of 30.0%. EDWTh averaged 11.8 mm in the control period during pacing and decreased to 11.6 mm after acute aortic constriction, while the calculated CSA remained constant during

![Figure 3](http://circres.ahajournals.org/)

*Figure 3* Averages changes (\(\Delta\)) from control in left ventricular systolic pressure (LVSP), cross-sectional area (CSA), left ventricular end-diastolic diameter (LVEDD), percent shortening of the internal diameter, peak left ventricular wall stress (WSl), and normalized mean circumferential fiber shortening velocity (mean \(V_{CF}\)) in circumferences/sec immediately (acute), and at early (9 days) and late (2½ weeks) studies during chronic aortic constriction. Studies immediately (acute) and at 24 hours after release of the cuff also are shown. Numbers above the bars indicate \(P\) values compared to control, and values below the bars are compared to immediate preceding period; * = comparison of pre- vs. postrelease values; the brackets represent standard errors; NS = not significant.
Table 1  Effects of Aortic Constriction and Release on Left Ventricular Function

<table>
<thead>
<tr>
<th>Variables measured</th>
<th>Acute response to AC (n = 12)</th>
<th>Early study after AC (n = 12)</th>
<th>Late study after AC (n = 8)</th>
<th>Acute response to release (n = 8)</th>
<th>24 hr after release (n = 7)</th>
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<tr>
<td>LVEDP (mm Hg)</td>
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<td>C</td>
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<td>11.5 ± 1.4</td>
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<tr>
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<tr>
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<td>140 ± 6</td>
<td>142 ± 6</td>
<td>139 ± 7</td>
<td>137 ± 8</td>
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<td>Res</td>
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<td>Δ</td>
<td>82 ± 6</td>
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<td>CSA (%)</td>
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<tr>
<td>Res</td>
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<td>119 ± 1.1</td>
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<td>Δ</td>
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<td>ED (mm)</td>
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<tr>
<td>C</td>
<td>31.8 ± 2.2</td>
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<td>&lt;0.01</td>
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<td>EDD (mm)</td>
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<td>22.4 ± 2.0</td>
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<td>25.2 ± 3.0</td>
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<td>29.2 ± 3.0</td>
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<tr>
<td>Res</td>
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<td>Δ</td>
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<td>mean Vc (circ/sec)</td>
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<tr>
<td>C</td>
<td>1.80 ± 0.18</td>
<td>1.73 ± 0.18</td>
<td>1.51 ± 0.18</td>
<td>1.63 ± 0.18</td>
<td>1.68 ± 0.20</td>
</tr>
<tr>
<td>Res</td>
<td>1.08 ± 0.11</td>
<td>1.38 ± 0.17</td>
<td>1.41 ± 0.19</td>
<td>1.86 ± 0.20</td>
<td>1.85 ± 0.22</td>
</tr>
<tr>
<td>Δ</td>
<td>-0.74 ± 0.09</td>
<td>-0.35 ± 0.08</td>
<td>-0.11 ± 0.05</td>
<td>0.24 ± 0.06</td>
<td>0.17 ± 0.09</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
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<tr>
<td>EDWSt (×10⁴ dynes/cm²)</td>
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</tr>
<tr>
<td>C</td>
<td>10.5 ± 1.4</td>
<td>10.3 ± 1.3</td>
<td>12.4 ± 1.3</td>
<td>10.8 ± 0.9</td>
<td>10.2 ± 1.1</td>
</tr>
<tr>
<td>Res</td>
<td>15.7 ± 2.0</td>
<td>20.4 ± 3.4</td>
<td>17.9 ± 2.0</td>
<td>14.0 ± 1.8</td>
<td>13.3 ± 1.9</td>
</tr>
<tr>
<td>Δ</td>
<td>5.5 ± 1.4</td>
<td>10.5 ± 2.9</td>
<td>5.3 ± 1.6</td>
<td>3.4 ± 1.4</td>
<td>3.5 ± 1.8</td>
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<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
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<tr>
<td>Peak WSt (×10⁴ dynes/cm²)</td>
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<tr>
<td>C</td>
<td>112 ± 12</td>
<td>118 ± 13</td>
<td>137 ± 13</td>
<td>124 ± 13</td>
<td>123 ± 16</td>
</tr>
<tr>
<td>Res</td>
<td>162 ± 17</td>
<td>156 ± 17</td>
<td>159 ± 16</td>
<td>113 ± 11</td>
<td>107 ± 10</td>
</tr>
<tr>
<td>Δ</td>
<td>51 ± 9</td>
<td>39 ± 8</td>
<td>22 ± 7</td>
<td>-12 ± 6</td>
<td>-17 ± 8</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
</tr>
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</table>

All the measurements were made at matched heart rates in each dog. Early and late studies were made at the average 9 ± 1 days and 18 ± 2 days after aortic constriction.

AC = aortic constriction; n = number of dogs studied; C = control value for each group; Res = response to aortic constriction or release; Δ = changes compared to control value; P = probability, as compared to control value before aortic constriction; P = probability as compared to previous value; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; Δ p = peak velocity of left ventricular pressure rise; EDWSt = end-diastolic wall thickness; ESWTh = end-systolic wall thickness; CSA = cross-sectional area of the left ventricular wall in a transverse plane; EDD = left ventricular end-diastolic diameter; % shortening = ratio of extent of shortening to EDD; mean Vc = mean velocity (in circumferences/sec) of left ventricular circumferential fiber shortening corrected for end-diastolic circumference; EDWSt = end-diastolic wall stress; peak WSt = peak wall stress; NS = not significant (P > 0.05).
this intervention (Fig. 3). End-systolic wall thickness (ESWTh) was reduced by constriction from 14.3 to 13.4 mm. Peak systolic WSt was augmented by 55% over a control average value of $112 \times 10^3$ dynes/cm$^2$, and the mean $V_{CF}$ was reduced by 39% from a control value of 1.80 circumferences/sec (Fig. 3).

PHASE OF EARLY VENTRICULAR DILATION (AVERAGE 9 DAYS)

In the early LV dilation stage LVEDP continued to increase to 22 mm Hg (10 mm Hg above control). LVSP was maintained at 210 mm Hg. LVEDD continued to increase in the early stage of chronic aortic constriction and maximum chamber dilation was observed at an average of 9 days after constriction, being augmented to 32.4 mm from the control value of 31.3 mm (Fig. 3). Resting heart rate was 95 ± 4 beats/min and paced heart rate was 101 ± 1 beats/min.

WTh gradually increased both at end-diastole and end-systole in the face of chronic pressure overload, resulting in a continuous increase in CSA by 10% during the early stage. There was a concomitant reduction of peak WSt to 37% above control, the initially depressed percent shortening increased to 12% below control, and mean $V_{CF}$ increased to 20% below control (Fig. 3).

End-diastolic wall stress (EDWSt) was elevated to $20 \times 10^3$ dynes/cm$^2$ (average increase, $11 \times 10^3$ dynes/cm$^2$ over the control value) (Table 1).

PHASE OF COMPENSATION (AVERAGE 2½ WEEKS)

Average LVSP remained the same between the early and late phases (210 and 211 mm Hg, not significantly different). LVEDP remained elevated at 19 mm Hg. EDD decreased gradually to a level 1% smaller than control, and percent shortening returned to control (Fig. 3). Resting heart rate was 95 ± 5 beats/min and paced heart rate was 101 ± 3 beats/min.

Wall thicknesses increased further and CSA was increased by 15%. Peak WSt was lower, 22% above control, and mean $V_{CF}$ also recovered gradually, being decreased by only 7% (not significant, compared to control). EDWSt gradually decreased but was sustained above control throughout the course (Table 1).

EARLY STUDIES AFTER RELEASE OF CUFF

Immediately after release of the cuff LVSP dropped to normal; EDD further decreased to 2% less than control and was smaller by 1% 24 hours later. There was slight but not significant improvement in percent shortening compared to values prior to constriction, the average values immediately and at 24 hours being 4% above the control values. Resting heart rates were 80 ± 4 beats/min immediately and 79 ± 5 beats/min at 24 hours after cuff release; paced heart rates were 99 ± 2 beats/min and 98 ± 2 beats/min, respectively.

There were no significant changes in WTh or the average CSA early after release. Immediately after cuff release, peak WSt dropped to 8% less than control, and after 24 hours it remained at 11% below control. Immediately after cuff release, mean $V_{CF}$ increased to 16% above control; at 24 hours after cuff release it was 12% above control, but not significantly different (Fig. 3).

Peak dP/dt immediately and at 24 hours after release averaged 3,585 and 3,325 mm Hg/sec, respectively, values that were not significantly different from the control before aortic constriction (3,290 mm Hg/sec) (Table 1).

REGRESSION LATE AFTER CUFF RELEASE

Three dogs were followed for 6 to 7 days after release of the cuff (Fig. 4). The follow-up studies were terminated by loss of signals, sudden death by aortic rupture, or development of arrhythmias. Following the cuff release, LVSP dropped to near control (Table 1), but one dog (dog R, in Fig. 4) retained a pressure 25% higher than control even after cuff release; this was due to residual supravalvular stenosis caused by an organic deformity of the aortic wall.

LVSP before the release had been elevated to 274 mm Hg and at 1 week after release it was 222 mm Hg (control value, 162 mm Hg); CSA, which had been increased by 21% above control, fell to 17% above control during this 1-week period. In the two other dogs LVSP was at or near control values for the 1-week period after cuff release. In these two animals, regression of hypertrophy during this period was more rapid, CSA decreasing from 13% to 7% above control in one dog, and from 18% to 7% above control in the other (Fig. 4).

Discussion

It is generally agreed that myocardial hypertrophy with increased contractile element mass constitutes one of the principle compensatory mechanisms whereby the heart adapts to a chronically increased afterload. However, despite many investigations, there still is no uniform agreement concerning the functional responses that accompany hypertrophy of the whole heart, and whether or not in-

![Figure 4](http://circres.ahajournals.org/)

**Figure 4** Time course of left ventricular systolic pressure (LVSP) and cross-sectional area of the ventricular wall (CSA) following aortic cuff release in three dogs. C = control; I = late study after cuff release; 24H = 24 hours after cuff release; R = late study after release. Time intervals in days (d) after constriction (left) and late release (right) are shown below.
creased muscle mass is associated with a change in myocardial inotropic state remains controversial. The major reason for these divergent views would appear to relate partly to the lack of a suitable experimental model and in part to differences in the methods by which inotropic state has been assessed.

In our present study, the ultrasonic dimension gauge used appears to provide a highly suitable approach for the serial evaluation of wall motion in intact animals because of its long-term stability and accuracy, its applicability to measurement of absolute WTh without damaging tissue between the crystals, and its minimal constraining or tethering effects on the subtended myocardium. In combining this method with the use of high fidelity pressure recordings and a model for the production of LV hypertrophy in the conscious dog, we have been able to document the sequential effects of chronically increased afterload on LV function. To assess the basal level of myocardial inotropic state we used indices derived from both the isovolumic (dP/dt) and ejection phases of LV systole; the relative superiority of the latter (such as mean VCF) in many conditions has been recently discussed. Thus, ejection phase indices are not dependent on a particular muscle model, function is expressed per unit of muscle, and the usefulness of their greater sensitivity to afterload in defining basal contractility after the occurrence of chronic adaptations has been suggested.

Observations in chronic volume overloading have indicated that diastolic sarcomere lengths in chronic ventricular dilation and hypertrophy are similar to those in the acutely dilated heart, suggesting that additional sarcomeres were developed in series, and it was observed that the increased stroke volume several weeks after chronic volume overloading was attained by normal extent and velocity of shortening per unit of myocardium; thus, normal VCF values were observed when corrected to per unit of circumference. The increase in muscle mass in chronic pressure-overloaded ventricles is also related to an increased number of sarcomeres within cells. Again, since the chronic adaptation to elevated afterload appears to be an increased number of sarcomeres, we have assessed cardiac function in terms of mechanical performance per unit of circumference (percent shortening and normalized VCF) related to wall CSA (peak WSt), with the view that such measures should detect a depressed basal level of inotropic state after the adaptation to chronically increased afterload has occurred.

The immediate response to sudden, severe elevation of aortic pressure consisted of compensatory augmentation of LVEDP and EDD. The relatively small change in EDD may be related to the LVEDP being near the upper limit of normal during control (Table 1) (hence a relatively steep passive LVEDP-EDD relation), as well as to the mild tachycardia that occurred. This slightly increased resting fiber length only partially maintained the stroke excursion in the face of the markedly augmented afterload, due to increased intracavitary pressure with associated wall thinning (Fig. 2). Under these acutely changing conditions, we do not consider Vcf to be a useful index of inotropic state, but have used it rather to define a basal level of contractility. In isolated muscle or controlled experiments in the isolated heart, progressive sudden elevations of afterload with the preload constant cause the stroke excursion and velocity to diminish progressively. However, in the conscious state the response to increased afterload is modified by changes in the preload, venous tone, and heart rate, and by reflex changes in cardiac contractile state. Un doubtedly, the tachycardia that we observed acutely was related to hypotension in the carotid sinuses occurring as the aortic cuff constricted the ascending aorta, and other peripheral and cardiac adjustments also occurred. It might be expected that the Anrep effect also had a role in these early responses. The Anrep effect has been related to the recovery from subendocardial ischemia by vascular autoregulation of the coronary bed, and the extent of the Anrep effect in conscious dogs at slow heart rates was demonstrated to be less marked than at rapid heart rates, or after general anesthesia. Studies of regional myocardial blood flow after sudden supravalvular aortic constriction have shown reversal of the epicardial to endocardial flow ratio associated with reduction in the diastolic pressure time per minute. Thus, subendocardial ischemia could also have contributed to the reduced ejection phase indices that we observed acutely.

At an average of 9 days after pressure overload the chamber diameter was larger than that of the control. However, early hypertrophy was already evidenced at this stage by increasing WTh and CSA despite mild dilation. Meerson defined the first 5-10 days of increased resistance to ventricular ejection, as the "damage state" of isotropic hyperfunction, which was characterized by breakdown of myocardial proteins with concomitant activation of protein and nucleic acid synthesis. Recently it has been suspected that cardiac dilation could give rise to hypertrophy by increasing intramural stress, to which myocardium may respond by hypertrophy to maintain stress within certain limits. According to studies of Streeter et al., the circumferential WSt is higher near the endocardium and decreases toward the epicardium. Under circumstances in which the LV chamber dilates in the face of chronically increased afterload, one would expect greater increases in WSt at the inner layers of the myocardium; more severe myocardial hypoxia due to increased oxygen consumption and reduced coronary blood flow might also contribute to the development of hypertrophy. This possibility was recently supported by morphological findings of Bishop et al., who described the most prominent ultrastructural alterations in the subendocardial region of the hypertrophy ing left ventricle of dogs with aortic constriction. Greater hypertrophy near the endocardium could explain the tendency for concentric hypertrophy to occur with pressure overload; such concentric hypertrophy has a favorable effect on ejection by reducing the chamber size and increasing WTh, hence decreasing WSt, or afterload (Fig. 3). This gradual decrease in stress was accompanied by progressive restoration of the mean Vcf toward normal.

In the present experiments a relatively stable, compensated state was reached at an average of 2½ weeks after aortic constriction. At that time, CSA was shown to have increased by 15% above control, implying increased muscle mass, and initially depressed shortening characteristics recovered gradually as peak WSt progressively decreased.
The time interval studied was relatively short although, as shown in Figure 3, hypertrophy began to develop early. It has also been shown in other species that experimental hypertrophy induced by chronic pressure overload may be apparent within 3 days and may remain relatively constant after 7 days. In experiments in which LV hypertrophy was produced by banding the ascending aorta in puppies 7 weeks old, subsequently followed for 9 to 18 months, the LV to body weight ratios (6.4 g/kg) indicate that sufficient time had elapsed for substantial hypertrophy to occur. The functional responses in the stable, compensated state in our present experiments indicate that the degree of hypertrophy was appropriate to the level of increase in LVSP, and that this adaptation allowed the heart to regain normal wall shortening characteristics without increase in end-diastolic dimensions and at a normal basal level of contractive state.

The performance of the hypertrophied ventricle was also studied after cuff release, under normal loading conditions. Under these conditions when end-diastolic dimension (preload), resistance to ejection (afterload), and heart rate are unchanged, measures such as percent shortening, shortening velocity, and peak dp/dt should reflect the inotropic state of the ventricle. Even if the immediate release data are discounted because of possible reflex effects or acute catecholamine release, 24 hours after relief of pressure load the peak stress was not significantly different from the control value (although the average value was slightly subnormal) and measures of contractility were the same or slightly above control. These data suggest strongly that in this conscious animal model, when sufficient time for compensation had elapsed, moderate ventricular hypertrophy due to pressure overload was not accompanied by intrinsic depression of inotropic state.

In two of the three dogs studied considerable regression of hypertrophy occurred quite rapidly within 1 week after the release of the cuff (from 17% to 7% above control over 7 days and from 13% to 7% above control over 6 days). In a third dog so studied, however, because of a residual stenosis of the aorta the LVSP was not reduced completely and there was little regression. Cardiac hypertrophy established in rats due to pressure overload was not accompanied by intrinsic shortening characteristics without increase in end-diastolic dimensions and at a normal basal level of contractive state.

Acknowledgments

We acknowledge the excellent assistance of W. Scott Kemper, Daniel McElwain, and Fred Werner. We also thank Hazel Wills and Ruth Lerner for their invaluable secretarial assistance.

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Circ Res. 1976;38:172-178
doi: 10.1161/01.RES.38.3.172

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