Left Ventricular Adaptation to Sustained Pressure Overload in the Conscious Dog

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SUMMARY. The early adaptation to aortic stenosis was studied in eight conscious dogs previously instrumented with a left ventricular micromanometer and ultrasonic crystals measuring left ventricular minor equator, left ventricular major axis, and ventricular wall thickness. Data were compared during control, acute inflation of a supravalvular aortic cuff occluder and 24 hours after aortic stenosis with and without β-blockade. Acute aortic stenosis increased peak systolic pressure and end-systolic pressure with a decrease of percent systolic shortening of minor diameter (%ΔL). Twenty-four hours after aortic constriction for heart rates, end-diastolic dimensions, and systolic pressures similar to those measured during acute aortic stenosis, %ΔL was significantly increased, compared with acute aortic constriction, and was close to control values. End-systolic diameter was not significantly different from control during sustained pressure overload, although end-systolic stress was increased by 26.7 ± 6.1% (P < 0.01 with control), representing a leftward shift of the end-systolic stress-diameter relation. Similar results were obtained under β-blockade. We conclude that there is, in this model of moderate pressure overload, a nonsympathetic increased inotropic state very early after aortic constriction. (Circ Res 54: 21–29, 1984)

ALTHOUGH cardiac mechanics has been intensively investigated during chronic pressure overload, there is no general agreement concerning the inotropic state in all phases of development of cardiac hypertrophy. During the phase of stable hypertrophy, some studies described a depressed contractility in papillary muscles (Grimm et al., 1963; Bing et al., 1971; Spann et al., 1972) with abnormal cardiac energetics (Cooper et al., 1973) and depressed calcium and actin-activated ATPase activity of myosin (Maughan et al., 1979). In contrast, papillary muscle performance was also assessed as not reduced despite abnormal excitation contraction coupling (Jouannot and Hatt, 1975) or even normal (Fisher and Kavaler, 1971; Pannier, 1971; Williams and Potter, 1974) or above normal (Kerr et al., 1961). In conscious animals, a ventricular hyperfunction with a normal inotropic state has been described (Sasayama et al., 1977) in the stable hypertrophy stage. During the early phase of cardiac hypertrophy, results are also contradictory in in vitro preparations (Bing et al., 1971; Bassett and Gelband, 1973; Jouannot and Hatt, 1975; Coughlin and Gibbs, 1981) and few studies concerned conscious animals (Kraft-Hunter et al., 1971; Sasayama et al., 1976, 1977). These studies were performed 5–9 days after the onset of ventricular overload when some hypertrophy had already developed with a 10% increase of cross-sectional area (Sasayama et al., 1977).

The goal of this study was thus to investigate the early (24 hours) adaptation to sustained pressure overload produced by a hydraulic cuff occluder placed around the aorta of conscious dogs instrumented with ultrasonic crystals measuring left ventricular dimensions.

Methods

Surgical Procedure and Instrumentation

A thoracotomy was performed in the 4th left intercostal space in eight adult beagle dogs weighing 10.5–13.2 kg (average 11.8 kg). Ventilation was maintained with a Harvard respirator delivering room air through an endotracheal cannula. The pericardium was widely opened and a high fidelity micromanometer (Konigsberg P7) was inserted into the left ventricular chamber through the cardiac apex. Ultrasonic crystals measuring the left ventricular major axis were positioned at the base and the apex of the ventricle according to the technique of Rankin et al. (1976); one pair of crystals was positioned for measurement of the internal anteroposterior minor axis diameter and one pair was positioned for the measurement of parietal wall thickness close to the minor axis diameter, according to the technique of Sasayama et al. (1976). A plastic tube filled with heparinized saline solution was placed into the left atrium through the left atrial appendage. An inflatable cuff was placed around the ascending aorta previously dissected. The chest then was closed and experiments were performed after a period of recovery of 7–14 days, the dogs lying quietly on their right side in the conscious state.

Experimental Protocol

Two periods of 24 hours of aortic stenosis were performed. During the first period, after control of the resting state, the aortic cuff was inflated with saline solution in order to produce an increase of about 60% of peak systolic pressure. Data were measured 5 minutes after the infla-
tion. Twenty-four hours later, parameters were measured under sustained pressure overload. In two dogs, systolic pressure was slightly decreased, compared with acute stenosis (20 mm Hg). The cuff was reinflated so that end-systolic pressure was similar to that measured the previous day, and measurements were made 5 minutes after reinflation. The aortic constriction then was released.

The second period of aortic stenosis was performed a similar way at least 72 hours after release of the aortic cuff, but after control of the resting state, the stenosis was slightly more severe (about 70% increase of peak systolic pressure). Instead of releasing the aortic cuff, propranolol (1 mg/kg, iv) was injected 24 hours after aortic constriction and parameters were measured 5 minutes after the injection.

Propranolol (1 mg/kg, iv) was also injected another day without aortic constriction, at least 72 hours after the last intervention before (three dogs) or after (three dogs) the second period of aortic stenosis. The complete β-blockade after propranolol injection was verified by injection of two doses (0.25 µg/kg and 0.50 µg/kg) of isoproterenol, iv.

Figure 1 shows the effect of isoproterenol injection before (marked increase of heart rate and dP/dt) and 5 minutes after propranolol injection (no heart rate or dP/dt changes).

In three dogs, a third period of sustained aortic stenosis was performed. Radiolabeled microspheres were injected in the conscious state through the atrial catheter; myocardial blood flow was measured during sustained (24 hours) pressure overload and 24 hours after release of the occlusion for measurement of control myocardial blood flow. Arterial blood samples were withdrawn from the femoral artery at a rate of about 15 ml/min. After the dogs were killed, ventricular samples were taken in different regions of the heart and divided into epicardial and endocardial zones. Blood and heart samples were weighed and counted in a γ well counter CG 4000 (Intertechnique) and myocardial blood flow (MBF) was obtained (Domenech et al., 1969) as:

$$MBF = \frac{\text{counts/g of tissue}}{\text{counts in reference blood}} \times \text{reference flow rate}.$$
signals were present were considered for hemodynamic, segmental, and wall stress measurements. The same six segments were measured—during the first period of aortic stenosis—and during the second period of aortic stenosis. Myocardial blood flow was measured in three conscious animals (Sasayama et al., 1977); similar results were obtained with this analysis and with the relationship between mean systolic wall stress and mean velocity of systolic diameter shortening (Sasayama et al., 1977). How-ever, there were slight differences in the time occurrence of end-ejection for the different dimensions and different thickness regions (base-to-apex or septum-free wall).

Eight beats were measured and averaged during each intervention to take into account respiratory variations. The position of the crystals was verified at the autopsy. Signals obtained from incorrectly positioned crystals were rejected from the analysis, and only six dogs in which all signals were present were considered for hemodynamic, segmental, and wall stress measurements. The same six dogs were subjected to the two periods of 24-hour aortic stenosis and to the injection of propranolol without aortic stenosis. Myocardial blood flow was measured in three dogs.

**Statistical Analysis**

One-way variance analysis (hemodynamic variables) and two-way variance analysis (dimension data) were used for statistical analysis of different periods and interventions. When a significant trend was found by the F-test (Snedecor and Cochran, 1973) a paired t-test was used to compare two different interventions. Statistical significance was defined by $P < 0.05$. Values are given as mean ± 1 SEM.

**Results**

The aortic constriction did not produce any myocardial ischemia, particularly in the subendocardium, as judged by myocardial blood flow (MBF) measurement using radiolabeled microspheres. In those three dogs in which MBF was measured, the endo:epi ratio was $1.15 ± 0.03$ (transmural MBF $= 1.01 ± 0.16$ ml/min per g) during the control period and it was $1.24 ± 0.03$ (transmural MBF $= 1.19 ± 0.17$ ml/min per g) 24 hours after the inflation of the cuff, which produced an increase of $68.3 ± 12.1$ mm Hg of peak systolic pressure (mean heart rates were $98.2$ beats/min during control and $94.3$ beats/min, 24 hours after aortic constriction). There were no significant variations of myocardial blood flow from one zone to another (base-to-apex or septum-free wall).

**Ventricular Function without /3-Blockade**

Mean hemodynamic and dimensional data are given in Tables 1 and 2, respectively. During the first period of aortic stenosis, peak systolic pressure was $24.2 ± 4.5$ mm Hg, and it was $21.7 ± 4.3$ mm Hg during the second period of aortic stenosis.

### Table 1

**Hemodynamic Data**

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>EDP (mm Hg)</th>
<th>Peak P (mm Hg)</th>
<th>ESP (mm Hg)</th>
<th>dP/dt (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First period of aortic stenosis</strong></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>92.8 ± 8.4</td>
<td>11.7 ± 1.0</td>
<td>129.2 ± 6.3</td>
<td>99.6 ± 5.1</td>
<td>4014 ± 453</td>
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<tr>
<td>Acute stenosis</td>
<td>106.0 ± 7.4</td>
<td>14.2 ± 2.6</td>
<td>208.7 ± 10.3*</td>
<td>117.7 ± 5.0†</td>
<td>3959 ± 308</td>
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<tr>
<td>24-hr stenosis</td>
<td>102.3 ± 9.4</td>
<td>13.4 ± 1.6</td>
<td>218.8 ± 8.7‡</td>
<td>125.5 ± 3.7</td>
<td>4218 ± 250‡</td>
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<tr>
<td>Release</td>
<td>85.2 ± 9.5§</td>
<td>13.0 ± 2.5</td>
<td>142.9 ± 6.5‡</td>
<td>109.6 ± 3.3</td>
<td>4837 ± 402§</td>
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<td><strong>Second period of aortic stenosis</strong></td>
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<tr>
<td>Control</td>
<td>86.0 ± 3.7</td>
<td>14.6 ± 2.6</td>
<td>128.7 ± 7.4</td>
<td>97.3 ± 5.3</td>
<td>3765 ± 363</td>
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<td>Acute stenosis</td>
<td>121.3 ± 3.2‡</td>
<td>17.0 ± 2.8</td>
<td>222.8 ± 10.8*</td>
<td>129.7 ± 7.3†</td>
<td>3744 ± 295</td>
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<tr>
<td>24-hr stenosis</td>
<td>100.5 ± 7.6§</td>
<td>15.6 ± 1.6</td>
<td>229.0 ± 11.8</td>
<td>126.6 ± 9.5</td>
<td>4427 ± 326‡</td>
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<tr>
<td>24-hr stenosis + propranolol</td>
<td>94.6 ± 4.4</td>
<td>16.5 ± 3.3</td>
<td>215.2 ± 9.5</td>
<td>126.9 ± 9.3</td>
<td>3886 ± 258‡</td>
</tr>
</tbody>
</table>

|                |               |             |               |             |                   |
| **/3-Blockade without aortic stenosis** |               |             |               |             |                   |
| Control         | 93.2 ± 5.4    | 12.2 ± 1.9  | 129.9 ± 6.1   | 103.2 ± 5.0 | 3866 ± 327       |
| Propranolol     | 90.1 ± 5.3    | 14.1 ± 2.9  | 138.0 ± 6.6   | 108.3 ± 5.5 | 3427 ± 282‡      |
| $P < 0.025$     | F = 2.69      | F = 0.52    | F = 27.59     | F = 3.92    | F = 10.84         |
| $P < 0.001$     | NS            | $P < 0.001$ | $P < 0.001$   | $P < 0.001$ |                   |

During the first and second periods of aortic stenosis, acute stenosis was compared with the corresponding control resting state, and sustained pressure overload (24 H stenosis) was compared with the acute response to aortic constriction. During the first period of pressure overload, release of aortic stenosis was compared with the control state before aortic stenosis. During the second period of aortic stenosis, data obtained under sustained pressure overload + propranolol were compared with data obtained without /3-blockade. The effect of propranolol injection ('Propranolol') was compared with the third control without aortic constriction. $P < 0.05$; $† P < 0.025$; $‡ P < 0.005$; $* P < 0.001$. HR: heart rate; EDP: end-diastolic pressure; Peak P: peak systolic pressure; ESP: end-systolic pressure; dP/dt: peak of the first time derivative of ventricular pressure. F values were obtained by one-way variance analysis (two-way variance analysis for dP/dt) with their corresponding $P$ value for the number of degrees of freedom.
was increased by 61.5%, with a slight increase of heart rate. End-systolic pressure was significantly increased (18.2%), and the percentages of diameters shortening and wall thickening were decreased. Twenty-four hours after aortic stenosis, for end-systolic pressures and heart rate close to those measured during acute aortic constriction (Table 1), ventricular function was significantly increased, as indicated by a similar percentage of systolic shortening (EDL) and wall thickening (%AL) which returned to a value close to that measured during the control state. Also, after release of aortic constriction, systolic function was found to be increased, compared with the control before aortic constriction, indicated by a significantly increased systolic diameter shortening and wall thickening for a slightly larger systolic pressure (Tables 1 and 2).

This increased ventricular function observed under sustained pressure overload is illustrated in Figure 2, which shows the pressure-minor diameter loops in these six dogs. There was a clear shift to the left of the end-systolic pressure-diameter point 24 hours after aortic stenosis, as compared with acute stenosis, and Figure 3 shows the mean loops in these two conditions. Compared with acute stenosis, end-diastolic dimensions were slightly but not significantly shorter during sustained aortic stenosis, and end-systolic dimensions were significantly shorter, for a slightly larger end-systolic pressure. The systolic diameter measured after the same systolic time as the control ejection time was also significantly shorter during sustained pressure overload than during acute aortic stenosis for a similar systolic pressure (Fig. 3).

Ventricular Function under ß-Blockade

Ventricular function had returned close to control levels immediately before the inflation of the aortic cuff of the second occlusion period, as judged by the comparison of the systolic pressures and diameter shortening or wall thickening during the controls of the first and second periods of aortic constriction (Tables 1 and 2).

During the second period of aortic constriction, which was slightly more severe than during the first period (peak systolic pressure was increased by 73.1% and heart rate was significantly increased during acute aortic constriction as compared with control), ventricular function was significantly increased 24 hours after aortic stenosis, compared with acute stenosis. The injection of propranolol decreased ventricular function, but when ventricular function 24 hours after aortic stenosis under ß-blockade was compared with ventricular function under ß-blockade before aortic stenosis, the function was found to be augmented, as indicated by a similar systolic shortening or wall thickening from a similar end-diastolic diameter or wall thickness, in the presence of an increase in peak systolic pressure by 77.2 mm Hg and end-systolic pressure by 18.6 mm Hg (Tables 1 and 2).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Major axis</th>
<th></th>
<th>Minor axis</th>
<th></th>
<th>Wall thickness</th>
<th></th>
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<tr>
<td></td>
<td>EDL (mm)</td>
<td>%ΔL</td>
<td>EDL (mm)</td>
<td>%ΔL</td>
<td>EDTh (mm)</td>
<td>%ΔTh</td>
</tr>
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<td>First period of aortic stenosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>43.7 ± 2.9</td>
<td>11.4 ± 1.9</td>
<td>24.5 ± 2.1</td>
<td>24.9 ± 2.0</td>
<td>11.1 ± 0.8</td>
<td>24.9 ± 0.8</td>
</tr>
<tr>
<td>Acute stenosis</td>
<td>44.1 ± 3.0</td>
<td>8.9 ± 2.1*</td>
<td>25.2 ± 1.9</td>
<td>22.1 ± 1.4</td>
<td>10.9 ± 0.8</td>
<td>20.8 ± 2.1§</td>
</tr>
<tr>
<td>24-hr stenosis</td>
<td>43.4 ± 3.1</td>
<td>10.5 ± 2.4</td>
<td>24.6 ± 2.0</td>
<td>24.0 ± 1.2§</td>
<td>11.3 ± 0.9</td>
<td>23.0 ± 1.9†</td>
</tr>
<tr>
<td>Release</td>
<td>43.6 ± 3.2</td>
<td>13.4 ± 1.9§</td>
<td>24.5 ± 2.0</td>
<td>27.3 ± 2.3‡</td>
<td>11.2 ± 0.9</td>
<td>29.4 ± 0.8*</td>
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<tr>
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<tr>
<td>Control</td>
<td>43.8 ± 2.8</td>
<td>10.9 ± 1.5</td>
<td>24.3 ± 2.0</td>
<td>26.2 ± 2.2</td>
<td>11.1 ± 0.7</td>
<td>24.9 ± 1.8</td>
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<tr>
<td>Acute stenosis</td>
<td>44.1 ± 3.0</td>
<td>8.0 ± 1.4*</td>
<td>24.7 ± 1.9</td>
<td>21.1 ± 1.6</td>
<td>11.1 ± 0.8</td>
<td>19.0 ± 2.8 §</td>
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<tr>
<td>24-hr stenosis</td>
<td>43.3 ± 3.0</td>
<td>9.6 ± 1.5</td>
<td>24.4 ± 2.2</td>
<td>25.2 ± 1.9‡</td>
<td>11.4 ± 0.8</td>
<td>23.2 ± 2.5§</td>
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<tr>
<td>24-hr stenosis + propranolol</td>
<td>43.6 ± 2.7</td>
<td>7.6 ± 1.5§</td>
<td>24.9 ± 2.0</td>
<td>23.2 ± 1.4‡</td>
<td>11.2 ± 0.8</td>
<td>20.9 ± 2.7</td>
</tr>
</tbody>
</table>

β-Blockade without aortic stenosis

<table>
<thead>
<tr>
<th></th>
<th>Major axis</th>
<th></th>
<th>Minor axis</th>
<th></th>
<th>Wall thickness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>43.8 ± 2.7</td>
<td>11.8 ± 1.9</td>
<td>24.2 ± 2.1</td>
<td>25.9 ± 2.2</td>
<td>11.4 ± 0.8</td>
<td>25.0 ± 2.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>44.2 ± 2.6</td>
<td>9.9 ± 1.5</td>
<td>24.6 ± 1.9</td>
<td>22.5 ± 1.4‡</td>
<td>11.4 ± 0.7</td>
<td>21.0 ± 2.0*</td>
</tr>
</tbody>
</table>

F values were obtained by two-way variance analysis. Interventions were compared the same way as in Table 1, with the same symbols for statistical significance. EDL: end-diastolic length; %ΔL: percentage of systolic shortening; EDTh: end-diastolic wall thickness; %ΔTh: percentage of systolic wall thickening.
End-Systolic Stress-Diameter Relations

Mean normalized values of the end-systolic stress-diameter relations are given in Figure 4. During the first occlusion period, twenty-four hours after aortic stenosis, end-systolic diameter was significantly shorter than during acute aortic stenosis, although end-systolic stresses were similar (left panel). End-systolic diameter was not significantly different from control without aortic constriction, although end-systolic stress was significantly increased during the first and second periods of aortic constriction (left and right panels). Similarly, under β-blockade, end-systolic diameter during sustained pressure overload...
was not different from the value measured before aortic stenosis, whereas end-systolic stress was 18.5% greater than that without the stenosis.

**Discussion**

The increase of ventricular systolic function during a 24-hour period of aortic stenosis is indicated by the increase in the percentage of systolic shortening of minor diameters which returned to control although peak systolic pressure was increased by more than 50%. In the studies of Sasayama et al. (1976 and 1977), systolic function was significantly increased early (5–9 days) after aortic stenosis, compared with acute aortic constriction, but %ΔL of diameter was still reduced compared with control. The degree of increase of peak systolic pressure was similar in both studies. However we found an increase of end-systolic pressure of only 18.1 mm Hg (Table 1); it was increased by 38.0 mm Hg in the study of Sasayama et al. (1977). This difference may be due to a slightly different position of the aortic cuff in the different studies, probably allowing a larger supra-valvular chamber when the cuff was higher on the aortic root in our study. This may explain the response of ventricular function and the absence of dilation of the heart we found 24 hours after aortic stenosis: end-diastolic ventricular dimensions returned to control (Table 2) in contrast to the
ventricular enlargement found in early studies by Sasayama et al. (1976). But one could also expect ventricular function to be different 2 days and 5–9 days after aortic stenosis when some hypertrophy had already developed. Although the degree of pressure overload was thus probably less severe in our study, the calculation of the end-systolic stress-diameter relations allows the study of the inotropic state in acute and sustained pressure overload, since wall stress provides a good description of afterload (Pouleur et al., 1979). The major difference between our results and those previously published (Sasayama, 1977), is the leftward displacement of the end-systolic stress-diameter relationship we found 24 hours after aortic stenosis (Fig. 4). Sasayama et al. (1977) performed early studies 4–16 days after the onset of pressure overload when some hypertrophy had already appeared, which explained an increased ventricular function with a normal inotropic state. Twenty-four hours after aortic constriction, a minimal end-diastolic wall thickening was present, which was taken into account in the calculated wall stress. The leftward displacement of the end-systolic stress-diameter relationship thus represents an increased inotropic state of a myocardium subjected to a sustained pressure overload. The calculated equatorial wall stress has been shown to correlate well with directly measured wall stress when an ellipsoidal model of left ventricular cavity is used (Burns et al., 1971). This formula does not take into account the septum-free wall diameter which is supposed to be equal to the anteroposterior diameter. Although variations of right ventricular filling pressure modify the septum-free wall diameter (Bove and Santamore, 1981), no right ventricular intervention was produced in this study, and ventricular geometry probably was not modified within 24 hours of aortic stenosis.

A reflex from the aortic arch and carotid baroreceptors could have been responsible for the increased inotropic state during aortic stenosis, since aortic pressure was probably decreased below the aortic cuff. However, such a reflex would have produced an acute leftward shift of the end-systolic stress-diameter relationship which, probably, would have disappeared, or at least decreased, 24 hours after aortic stenosis. Studies from Krieger (1970), Coleridge et al. (1981), and Kunze (1981) showed that a substantial amount of threshold resetting of baroreceptors occurs within minutes after they are subjected to acute hypertension or hypotension and proceeds the ensuing hours. This reflex thus would tend to decrease the observed enhanced contractility during sustained aortic stenosis as compared with acute pressure overload observed in our study.

The end-systolic stress-diameter point during sustained aortic stenosis plus propranolol was close to the control line for end-systolic stress-diameter relationship (Fig. 4). This might suggest that increased sympathetic tone could be an explanation for the shift of the relationship to the left 24 hours after aortic stenosis. However, when this point was compared to the propranolol injection before aortic stenosis, end-systolic diameters were similar although end-systolic stress was significantly larger during sustained aortic stenosis (Fig. 4), indicating that at least some part of the increased inotropic state must be attributed to a mechanism other than sympathetic stimulation.

LeWinter et al. (1979) showed an increased ventricular systolic function during the recovery phase of a saline-phenylephrine infusion which produced a large increase of end-diastolic and systolic pressures. This was not attributed to an increased inotropic state, since end-systolic diameter was longer for matched end-systolic pressure. Rather, the increased systolic function was attributed to a change of ventricular viscoelastic properties, as indicated by an increased end-diastolic diameter for matched end-diastolic pressure. Similar patterns had been demonstrated previously in papillary muscles, and were attributed to the presence of viscous elements in series (Sonnenblick et al., 1966). However, the association of major elevation of systolic pressure and end-diastolic pressure is required to observe such a shift (LeWinter et al., 1979). This mechanism cannot be advocated in our results since end-systolic relations were shifted to the left and end-diastolic diameter was not increased 24 hours after aortic constriction, compared with control.

The increased inotropic state we observed might have represented the "Anrep effect" (Sarnoff and Mitchell, 1961) or the "homeometric autoregulation" (Sarnoff et al., 1960), i.e., a rapid return of end-diastolic volume and pressure toward control levels after an abrupt elevation of systolic pressure. Sonnenblick et al. (1966) proposed the viscoelastic properties’ changes to explain this effect, but we excluded them in our preparation. Monroe et al. (1972) and Vatner et al. (1974) demonstrated that this effect could be attributed to the recovery of a subendocardial ischemia induced by an abrupt increase of myocardial oxygen demand. They showed that subendocardial ischemia was dissipated within 1 minute, and we took care measuring parameters at least 5 minutes after aortic constriction. Although this type of effect can thus be excluded in our preparation, the increased inotropic state which persists under β-blockade resembles, in its pattern, the homeometric autoregulation with a longer time constant and an unknown mechanism.

Hemodynamics, muscle mechanics, and energetics have been studied early after the onset of chronic pressure overload with contradictory results. Bassett and Gelband (1973) did not find detectable changes of muscle mechanics obtained from cat right ventricles subjected to 24-hour pulmonary artery banding while parameters decreased in 3-day pressure-loaded ventricles with a change of action potential configuration. Similarly, Bing et al. (1971) and
Jouannot and Hatt (1975) described a depression of isotonic shortening velocity and maximum isometric force of rat ventricular papillary muscles 7 days and 5 days, respectively, after aortic constriction. When muscles were studied 1 day (Bing et al., 1971) after aortic constriction, maximum velocity of shortening was slightly but not significantly increased, compared with control animals. Coughlin and Gibbs (1981) recently described an increased work output and an increased total enthalpy in papillary muscles obtained from rats subjected to 2-4 days of aortic constriction. They interpreted the early increased work and enthalpy to an increased intracellular free calcium level. Early changes in sarcoplasmic reticulum have been shown during chronic pressure overload. Shihafer et al. (1978) described a time-dependent alteration of in vitro ability of Ca++ accumulation in microsomes of feline right ventricles subjected to pulmonary artery constriction. Ca++ accumulation increased 3 days after the onset of pressure overload, returned to control during the stable hypertrophy stage, and decreased when ventricular failure was present. The mechanism of the observed increased inotropic state in the early phase of chronic pressure overload is, however, speculative. It resembles that which we showed in the early phase of volume overload (Crozatier et al., 1982), and it can be postulated that an increased wall stress, whether it is systolic or diastolic, stimulates both cardiac hypertrophy and the inotropic state as a mean of adaptation. Myocardial inotropic state is normal when the ventricle is hypertrophied (Sasayama et al., 1977). It can be assumed that the inotropic state is modulated by wall stress with an increase when afterload is substantially increased, and a return to control with wall stress when hypertrophy has appeared. It remains to be demonstrated whether a larger increase of wall stress could be associated with a similar increased inotropic state. Obviously, when the augmentation of oxygen requirements is very large during severe overloads, or when coronary blood flow is limited (as in the clinical situation where the aortic obstruction is below the origin of the coronary arteries), myocardial adaptation may be impossible. In severe pressure overload, morphological alterations, compatible with cellular damage, were described (Hatt et al., 1982), and such muscles probably would not exhibit an increased inotropic state. Different degrees of stenosis and different models may thus explain different findings in muscle mechanics. Our model does not simulate the clinical situation, but allows an adaptation of myocardial blood flow to metabolic requirements (since no subendocardial ischemia was observed) and demonstrates a possibility of adaptation of the left ventricle to a moderate pressure overload through a modulation of the inotropic state.

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