SUMMARY This study examined the recuperative potential of cat hearts subjected to experimental right ventricular pressure overload (for a 10- to 14-day period) which provoked hypertrophy with and without congestive heart failure. Five groups of cats were studied: normal controls; one group with 70% pulmonary artery constriction which produced right ventricular hypertrophy (RVH); one group with an 87% constricted valve which also produced right ventricular hypertrophy but with congestive heart failure (CHF); and two groups which had been similarly subjected to pressure overload but which had been allowed a recovery period of 30 days after relief of the pressure overload. Both the 70% and 87% pulmonic constrictions were associated with extensive right ventricular hypertrophy, depression of myocardial contractile function, and severe reduction of cardiac norepinephrine stores (normal, 1.42 μg/g; RVH, 0.11 μg/g; CHF, 0.01 μg/g). After a 30-day period of relief from the pulmonic constriction normal hemodynamic function returned. In cats in which RVH had been relieved, right ventricular weight and contractile function were normal but catecholamine depletion persisted. Cats with relieved CHF showed depressed contractile function and depleted myocardial norepinephrine, and the right ventricular weight did not return to normal. Cardiac muscle of all pressure-overloaded nonrelieved hearts showed depressed velocity of shortening and depressed ability to sustain load. Cats with RVH alone regained normal muscle shortening velocity and load-bearing ability after relief. However, cardiac muscle from the CHF-relieved group recovered only unloaded shortening velocity while the ability to sustain load remained depressed. We conclude that the recuperative potential of myocardium damaged by pressure overload is adequate provided congestive heart failure has not occurred. Heart failure produces a persistent reduction in force-generating ability of the myocardium. Hypertrophy due to pressure overload, with or without CHF, leads to cardiac catecholamine depletion which is not readily reversed by relief of the overload.

MYOCARDIAL contractile function and function of the cardiac sympathetic system are impaired when ventricular hypertrophy and congestive heart failure result from a pressure overload on the heart. There is well established therapy to relieve the pressure overload; for example, systemic hypertension can be treated by pharmacological means and aortic stenosis can be relieved by cardiac surgery. However, relatively little is known of the potential for recovery of contractile function and repletion of myocardial catecholamine stores following relief of a pressure overload, despite the clinical relevance of such information for the correct timing of therapeutic interventions. Even less is known of factors that may determine the potential for return of contractile function and norepinephrine stores. A recent study has established that the contractile defect of hypertrophy due to pressure overload without heart failure, produced by experimental pulmonic constriction, is totally relieved after relief for approximately 4–5 weeks from the pulmonic stenosis.

The mechanics of cat papillary muscle can be described in a manner similar to that employed for skeletal muscle. It has been shown that the variation in mechanical muscle function is small within different groups of cats, thus functional parameters from different groups can be compared quantitatively. Since it is possible by constriction of the pulmonary artery in the cat to produce right ventricular hypertrophy with and without overt congestive heart failure, a source of myocardium from hypertrophied and failing hearts is available. In addition, surgical reversal of

30. Romero JC, Strong CG, Torres VE, Ott C, Knox FG: Plasma prosta-
the pressure overload is possible. In the present study, in addition to examining the reversibility of right ventricular hypertrophy and depressed myocardial function, the potential for repletion of depleted norepinephrine stores was investigated.

Methods

Hemodynamics of the intact cat, contractile performance of isolated right ventricular papillary muscles, and ventricular norepinephrine concentrations were assessed in five groups of cats: normal nonoperated controls (C); cats with pulmonic constriction of a degree which produced right ventricular hypertrophy without congestive heart failure (RVH); cats prepared as in RVH but with the constriction removed for 30 days (RVHR); cats with severe pulmonic constriction producing congestive heart failure as well as hypertrophy (CHF); and cats prepared as in CHF but with the pulmonic constriction removed for 30 days (CHFR). An additional group of cats received a pulmonic constriction as in RVHR but did not have the stenosis relieved after 2 weeks as in the RVHR group. This group remained constricted for an additional period which was approximately equal to the relief period accorded to the RVHR group.

Cats of either sex, weighing 1.7-3.5 kg, were anesthetized with intravenous sodium pentobarbital (25 mg/kg). Succinylcholine (1 mg/kg) was injected intravenously and ventilation was supported by endotracheal positive-pressure ventilation. Circular clips were placed around the proximal main pulmonary artery under aseptic conditions through a left intercostal thoracotomy. The lumina of the constricted portion of the pulmonary arteries averaged 30% and 13% of normal, with clips having average diameters of 3.5 mm and 2.8 mm, respectively. The clips with smaller diameters produced CHF and the larger clips produced RVH. It has been shown previously by histological examination that this method of producing right ventricular hypertrophy also causes hypertrophy of the associated papillary muscles. Regular diet was maintained postoperatively. After 10-14 days the cats were again anesthetized with sodium pentobarbital (25 mg/kg). Cannulas were placed in the descending aorta through a femoral artery and in the right ventricle through the right external jugular vein. Right ventricular and aortic pressure was measured by a widely used method which has never been described in the literature. The method of producing right ventricular hypertrophy also causes hypertrophy of the associated papillary muscles. Regular diet was maintained postoperatively. After 10-14 days the cats were again anesthetized with sodium pentobarbital (25 mg/kg). Cannulas were placed in the descending aorta through a femoral artery and in the right ventricle through the right external jugular vein. Right ventricular and aortic pressure was measured with Hewlett-Packard (1280 series) pressure transducers. The zero reference point was taken at the midchest position with the cats supine. All signals were recorded on a multichannel Hewlett-Packard (7888A) pressure ink oscillograph. A cardiac index (defined as cardiac output/body weight) was measured by the indicator-dilution technique employing thermal dilution. Saline (1 ml) at room temperature was injected into the right ventricle and temperature was sampled in the proximal aorta with a thermocouple introduced through the left carotid artery.

Following the hemodynamic study, if the pulmonic band was to be removed, the left chest was opened at the 4th intercostal space and the pulmonary arterial constriction was relieved. Any intrapleural fluid was withdrawn with a syringe. The chest was closed and the cat was allowed to recover for 30 days. For cats from the nonrecovery (RVH and CHF) and the control (C) groups the hearts were rapidly excised and a papillary muscle from the right ventricle was removed and transferred immediately to a myograph containing oxygenated Krebs' solution. The myograph has been described in detail previously. The papillary muscle was held at its nontendinous end by a clip attached to a rigid pin. The pin penetrated the bottom of the myograph bath through a silicone grease seal and was fixed to a Statham force transducer (GI4-25). The upper, tendinous, end of the muscle was attached to an isotonic lever for the measurement of muscle shortening. The isometric lever, mounted on an adjustable Palmer stand, could be clamped in a fixed position, allowing the force of isometric contraction to be measured. Muscle length could be controlled by adjusting the elevation of the fixed lever with the adjustable Palmer stand. When the lever was unrestrained and an appropriate load applied, the extent and velocity of shortening of the muscle could be determined at various preloads and afterloads.

Thus both the length-tension and force-velocity relations of the papillary muscle were assessed. Force, muscle length, their time derivatives, and the stimulus artifact were recorded on a Hewlett-Packard (7888A) multichannel oscillograph. Muscles were stimulated by an AEL stimulator with square wave pulses 5 msec in duration and with voltage limited to 15-25% above threshold; stimuli were delivered through field electrodes placed parallel to the vertical axis of each muscle. The limited stimulus strength prevented augmentation by release of catecholamines from the papillary muscle stores. Muscle bath temperature was maintained at 30°C and contraction frequency was 12/min. All studies were conducted after the muscle had contracted for at least 1 hour in the myograph and performance had become stable. Preparations remained stable for a period exceeding that necessary for all studies (at least 3 hours). Effects of paired stimulation, including peak tension, maximum isometric dP/dt, and the time from stimulus to peak tension, were examined for the first contraction following the cessation of paired stimulation which had produced 12 augmented contractions in which the interpulse-stimulus interval did not exceed by more than 20 msec the point at which the tension response changed from a simple augmented contraction to a double-bumped biphasic response. Muscle length was determined at a preload approximately equal to that of the control group at an absolute load of 0.4 g and at the apex of the length tension curve. The latter length was used to calculate cross-sectional area and the former to express contraction velocity in muscle lengths per second.

Force-velocity curves representing a mean for each group were obtained by a widely used method which has never been described in the literature. The method of averaging shortening velocities at normalized loads of 0.5, 1.0, 1.5 (etc.) g/mm² consists of plotting for each papillary muscle in a given group the force-velocity curve at the actual loads employed. The abscessae are then altered to reflect load normalization with respect to muscle cross-sectional area. The curves are drawn through the experimentally obtained points and the velocities at the desired loads are read off the curves to obtain the average for the group. An analogous procedure was employed for obtaining the mean length-tension curves.
In consideration of the fact that preload determines $P_a$ (the minimum load which just precludes muscle shortening) in the force-velocity relationship, and since muscle cross-sectional area is not measured until after the experiment, the actual area-normalized preloads are not known until after the experiment. To allow for variability arising in this manner, force-velocity curves were obtained at absolute preloads of 0.2, 0.4, 0.6, and 0.8 g and the specific curves used were selected for the area-normalized preload which most nearly approximated the preload of the control group at an absolute preload of 0.4 g.

After removal of the papillary muscle the free wall of the ventricle was removed, blotted dry, and weighed; the interventricular septum was weighed together with the left ventricle. Within 2 minutes after excision of the heart, approximately one-half of each ventricle, cut from base to apex and including half of the septum in the case of the left ventricle, was frozen in liquid nitrogen for norepinephrine assay by a modified trihydroxyindoleacetic acid method. The percentage of water in the ventricles was determined by weighing a portion of tissue before and after drying at 60°C for 72 hours. Left and right ventricular weights were expressed as ratios of the body weight at the time of papillary muscle study.

At the time of heart excision the 5-mm section of pulmonary artery immediately above the pulmonic valves in the C, RVHR, and CHFR groups was removed, cut longitudinally and flattened under a microscope slide. The width dimension which previously had been the circumference was measured and the luminal cross-sectional area was calculated according to a right cylindrical model. In the two groups which still had bands on at the time of study (RVH and CHF) the area was determined by inserting a succession of cylindrical metal probes of known dimensions through the arterial segment with the band still in place. The diameter of the largest probe which just fit was taken as the pulmonary arterial diameter. Since the size of great vessels varies somewhat with body size, all cross-sectional areas were normalized with respect to body weight (Table 1).

**DEFINITION OF EXPERIMENTAL GROUPS**

**Congestive Heart Failure (CHF)**

In this group of cats the lumen of the pulmonary artery was reduced to 13% of normal and the heart was studied 10-14 days after constriction. In recognition of the difficulty of defining congestive heart failure in absolute terms, and because animal models of heart failure mimic but are not necessarily identical to clinical heart failure, the following criteria were selected to define the presence of CHF: pleural effusion; ascites; abnormally elevated right ventricular end-diastolic pressure (>7 mmHg). All cats in this group satisfied all criteria. Cardiac index as already defined was measured for three cats from each group and was low (<50 ml/min per kg) in the three CHF cats for which it was determined.

**Right Ventricular Hypertrophy without Heart Failure (RVH)**

This group of cats had the pulmonary arterial lumen reduced to 30% of normal for 10-14 days prior to study. Cats were included in this group only if they could be excluded from the category of failure by the criteria outlined above. All cats in both CHF and RVH groups exhibited right ventricular systolic hypertension when compared to normal controls (Tables 1 and 2).

**Pure Control vs. Sham-Operated Controls**

Spann et al. found no significant differences in the mechanical properties of papillary muscles from sham-operated guinea pigs when compared to normal. Thus, unoperated cats were considered suitable for control of experimental mechanical properties in our investigation. Consideration was given to the question of myocardial norepinephrine concentration since an earlier study re-

### Table 1 Hemodynamic Parameters of All Groups of Cats; Comparison of Experimental Groups with Normal Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>No. of cats</th>
<th>Heart rate (beats/min)</th>
<th>Aortic pressure (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
<th>Cardiac index (ml/min)</th>
<th>Pulmonary artery cross-sectional area (mm²/kg wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>±193</td>
<td>5</td>
<td>239 ±13</td>
<td>199/149 ±12/9</td>
<td>32.4 ±1.8</td>
<td>2.6 ±0.6</td>
<td>68.9 ±0.2</td>
<td>10.1 ±0.7</td>
</tr>
<tr>
<td>CHF</td>
<td>±113</td>
<td>5</td>
<td>182 ±120 ±5/6</td>
<td>148/107 ±5.6</td>
<td>79.0 ±1.6</td>
<td>15.2 ±1.6</td>
<td>48.0 ±1.0</td>
<td>1.30 ±0.13</td>
</tr>
<tr>
<td>CHFR</td>
<td>±112</td>
<td>5</td>
<td>231 ±14</td>
<td>178/134 ±10/7</td>
<td>30.6 ±3.7</td>
<td>2.5 ±0.7</td>
<td>72.8 ±2.2</td>
<td>9.85 ±0.53</td>
</tr>
<tr>
<td>RVH</td>
<td>±157</td>
<td>6</td>
<td>272 ±8</td>
<td>174/127 ±8/8</td>
<td>61.7 ±6.2</td>
<td>3.4 ±0.9</td>
<td>56.6 ±2.6</td>
<td>3.04 ±5.3</td>
</tr>
<tr>
<td>RVHR</td>
<td>±28</td>
<td>4</td>
<td>248 ±18</td>
<td>192/133 ±12/3</td>
<td>28.4 ±1.4</td>
<td>2.0 ±0.9</td>
<td>70.4 ±5.3</td>
<td>9.94 ±0.54</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM. Cardiac index was determined in three cats in each group. See Methods for determination of pulmonary artery dimensions normalized with respect to body weight. RVSP = right ventricular systolic pressure; RVEDP = right ventricular end-diastolic pressure. C = controls; CHF = congestive heart failure; CHFR = congestive heart failure-relief group; RVH = right ventricular hypertrophy; RVHR = right ventricular hypertrophy-relief group.

* $P < 0.01$, significantly different from control group.

† $P < 0.05$, significantly different from control group.
ported that regional neural ablation resulted in depleted norepinephrine stores in the dog heart. However, sham-operated controls in the studies of Cooper et al.\(^{15}\) and Chidsey et al.\(^{16}\) showed no significant differences in cardiac norepinephrine concentration from that found in normal dogs. The same observation has been made in the guinea pig.\(^4\) In view of these findings and in recognition of the fact that effective, deliberate surgical cardiac sympathectomy is achieved only with virtual autotransplantation,\(^{15}\) the unoperated cat was considered to be adequate for control experiments on myocardial catecholamine concentration.

**Attempted Regression of Right Ventricular Hypertrophy (RVHR) and Congestive Heart Failure (CHFR)**

These two groups of cats met the same criteria and were treated exactly as their corresponding nonrecovery groups except that after 10-14 days of pulmonic constriction they were studied hemodynamically, then had their constricting clips removed and were allowed to recover for 30 days, at which time they were studied as the other groups. An additional group, prepared initially as the RVH and RVHR groups, was studied. In this extra group, however, after the 10- to 14-day period of constriction the group was neither killed nor studied as in the RVH group nor after the 10- to 14-day period of constriction the group was provided in order to control for the contingency of regression of hypertrophy without relief of the stenosis.

**Results**

**BODY WEIGHTS**

The weights of the cats in the RVH and RVHR groups were matched at the onset and remained stable, exhibiting no significant \((P > 0.1)\) gains or losses during the experiment. Similarly, the body weights of the CHF and CHFR groups were matched initially and also did not develop differences \((P > 0.1)\) during the experiment. Body weight values of cats in the RVH and RVHR groups were intermediate between C group and those of the CHF and CHFR groups. There was no significant change in weight of cats within any group during the course of the experiment although there were differences between groups (Table 1). Pleural and ascitic fluid, withdrawn with a syringe from the CHF group at the time of the study and from the CHFR groups at the time of band removal, was responsible for less than 10% of total body weight.

**HEMODYNAMICS**

Hemodynamic values for the two reversal groups, obtained just before removal of the clip, were comparable to the data for corresponding RVH and CHF groups as shown in Table 2 with the exception that before relief of stenosis the right ventricular systolic pressure of the CHFR group was less than the corresponding pressure in the CHF group. It was, however, significantly higher (almost double) than the control value (Tables 1 and 2).

Table 1 summarizes and compares the hemodynamic parameters of all five groups of cats at the time of final study. Comparisons were made with an unpaired Student's \(t\)-test for populations with essentially similar variance \((F\)-test). Both the RVH group and the CHF group exhibited right ventricular systolic hypertension. The CHF group had depressed systemic blood pressure when compared with the C group. The values of systemic pressure in the RVH group were less than control, although the difference was not significant. The CHF group exhibited an elevation of right ventricular end-diastolic pressure as well as a depressed cardiac index. Both recovery groups, RVHR and CHFR, had normal hemodynamic parameters 30 days following band removal.

**VENTRICULAR WEIGHT AND TISSUE WATER**

Right ventricular weight always increased after the constricting operation (Table 3), whereas left ventricular weight was unaltered. The CHFR cats continued to exhibit abnormally high right ventricular weight after the relief period. Ventricular weight in the CHFR group was less than that found in the CHF group. Cats from the RVHR group had normal right ventricular weights.

Left ventricular tissue water did not vary from normal in any of the experimental groups. Right ventricular tissue water was normal except for group with congestive heart

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**Table 2. Hemodynamic Comparison of Relief Groups (CHFR and RVHR) prior to Relief of Stenosis with Corresponding Nonrelieved Groups (CHF and RVH)**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats</th>
<th>Heart rate (beats/min)</th>
<th>Aortic blood pressure (mm Hg)</th>
<th>RVSP (mm Hg)</th>
<th>RVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
<td>182 ±20</td>
<td>148±107</td>
<td>79.0 ±5.6</td>
<td>15.2 ±1.6</td>
</tr>
<tr>
<td>CHFR before relief of</td>
<td>5</td>
<td>195 ±14</td>
<td>160±117</td>
<td>59.4* ±7.7</td>
<td>13.4 ±2.4</td>
</tr>
<tr>
<td>stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVH</td>
<td>6</td>
<td>272 ±8</td>
<td>174/127</td>
<td>61.7 ±6.2</td>
<td>3.4 ±0.9</td>
</tr>
<tr>
<td>RVHR before relief of</td>
<td>4</td>
<td>228 ±18</td>
<td>186/141</td>
<td>67.3 ±4.0</td>
<td>5.25 ±0.5</td>
</tr>
<tr>
<td>stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM.

RVSP = right ventricular systolic pressure; RVEDP = right ventricular end-diastolic pressure; group identifications as in Table 1.

* \(P < 0.05\), significantly different from CHF group.
† \(P < 0.05\), significantly different from RVH group.
Table 3  Heart Weight (HW)-Body Weight (BW) Ratios and Percentage Water of Left and Right Ventricles

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of cats</th>
<th>Left ventricle</th>
<th>Right ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HW/BW (g/kg)</td>
<td>% H2O</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>2.06 ±0.13</td>
<td>76.3 ±0.5</td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
<td>2.41 ±0.09*</td>
<td>78.5 ±0.50</td>
</tr>
<tr>
<td>CHFR</td>
<td>5</td>
<td>2.56 ±0.21</td>
<td>76.7 ±0.5</td>
</tr>
<tr>
<td>RVH</td>
<td>6</td>
<td>2.07 ±0.18</td>
<td>79.0 ±3.03</td>
</tr>
<tr>
<td>RVHR</td>
<td>4</td>
<td>2.27 ±0.16</td>
<td>75.20 ±0.6</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. Group identification as in Table 1. *P < 0.01, significantly different from normal, by unpaired r-test. †P < 0.05, significantly different from normal.

In the left ventricle of hypertrophied nonfailing hearts (RVH) were 0.11 ± 0.03 μg/g and 0.72 ± 0.14 μg/g for the right and left ventricles, respectively. Cats recovered from hypertrophy without failure (RVHR) had right and left ventricular norepinephrine concentrations of 0.21 ± 0.09 μg/g and 0.61 ± 0.14 μg/g, respectively.

MYOCARDIAL ISOMETRIC LENGTH-TENSION RELATIONSHIPS

The length of the papillary muscle at the apex of the length-tension curve was defined as Lmax, and changes in length were expressed as percentages of Lmax. Tension (force) was calculated as force per unit of cross-sectional area of muscle. The cross-sectional areas of normal (C) papillary muscle averaged 0.94 ± 0.17 mm². The CHF group was not significantly different from control (P > 0.10) and averaged 1.25 ± 0.29 mm². The RVH muscles were significantly larger than control (P < 0.01) and averaged 1.93 ± 0.26 mm². The CHFR group had muscles significantly larger than control (P < 0.05), averaging 1.62 ± 0.28 mm². The RVHR group had papillary muscles not significantly different from control (P > 0.10) and averaged 0.84 ± 0.11 mm² in cross section.

Figure 1 illustrates the active and resting length-tension (mean ± SEM) relationships of the various groups. Resting tensions were not significantly altered from normal in any group. While resting tension in the CHF and RVHR groups appears high and that of the CHFR group appears low, within group variation precludes definition of a significant difference between the means of these groups and the C group. Active tensions were depressed at all lengths along the curves in both the CHF and RVH groups. The CHFR group continued to exhibit a depressed length-active tension relationship but the RVHR group was found to have a normal length-active tension relationship.

The isometric tension developed actively at the apex of the papillary muscle at the apical end of the length-tension curve was defined as Lmax, and changes in length were expressed as percentages of Lmax. Tension (force) was calculated as force per unit of cross-sectional area of muscle. The cross-sectional areas of normal (C) papillary muscle averaged 0.94 ± 0.17 mm². The CHF group was not significantly different from control (P > 0.10) and averaged 1.25 ± 0.29 mm². The RVH muscles were significantly larger than control (P < 0.01) and averaged 1.93 ± 0.26 mm². The CHFR group had muscles significantly larger than control (P < 0.05), averaging 1.62 ± 0.28 mm². The RVHR group had papillary muscles not significantly different from control (P > 0.10) and averaged 0.84 ± 0.11 mm² in cross section.

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the length-tension curve was 6.06 ± 0.86 g/mm² in the normal cats (C). In the CHF group this was reduced from the value of C group to 2.78 ± 0.33 g/mm² (P < 0.01). The CHFR group continued to exhibit reduced (from the value of C group) developed tension at the apex of the length-tension curve and averaged 2.17 ± 0.29 g/mm² (P < 0.01). This value in the RVH group was reduced from the value of C group to 3.58 ± 0.49 g/mm² (P < 0.01). The RVHR group averaged 5.87 ± 0.31 g/mm², a value which was not different from C group (P > 0.1). The tensions of the RVH and CHF groups were not different from each other (P > 0.1).

EQUIVALENT PAPILLARY MUSCLE CROSS-SECTIONAL AREAS

Because the cross-sectional areas of the papillary muscles from the RVH and CHFR group were significantly greater than those found in the other three groups, the significance of the depressed isometric maximum tension in these two groups warranted further examination. Subgroups from these two experimental groups, selected specifically for small cross-sectional areas, were compared with a randomly selected subset obtained from the normal control group. The subset selected from the normal (C) group included muscles whose cross-sectional area averaged 1.21 mm² and which developed peak isometric tension that averaged 5.74 ± 0.65 g/mm² (n = 3). The RVH group subset had papillary muscle cross-sectional areas that averaged 1.26 ± 0.12 mm²; this value was not significantly different (P > 0.10) from that of the control subset but peak isometric tension, the average value of which was 3.70 ± 0.25 g/mm² (n = 2), was nonetheless significantly less (P < 0.05) than that of the normal subset. Similarly, a CHFR subset (n = 2) with papillary muscle cross-sectional areas averaging 1.11 ± 0.25 mm² [not significantly different (P > 0.10) from the normal subset] had a peak isometric tension of 2.08 ± 0.77 g/mm², a value significantly less (P < 0.05) than the normal subset value. The RVH subset tension was not significantly different from that of the CHFR subset (P > 0.1).

FORCE-VELOCITY RELATIONS

Figure 2 illustrates the force-velocity (mean ± SEM) curves for the various groups. Maximum velocity of shortening was assessed at 0.5 g/mm² (Vmax.5) in order to avoid extrapolation of the curves to zero load. Velocity was expressed in muscle lengths per second (L/sec). L was the length of the muscle at the preload closest to that of control muscles at an absolute preload of 0.4 g. Force was expressed in g/mm² of cross section. The values of the area-normalized preloads for the various groups were: C, 0.43 ± 0.06 g/mm²; CHF, 0.48 ± 0.09 g/mm²; CHFR, 0.49 ± 0.07 g/mm²; RVH, 0.41 ± 0.05 g/mm²; and RVHR, 0.48 ± 0.05 g/mm². None of these values was significantly different from control or any other group (P > 0.1). Mean velocities were obtained by averaging velocities at specific levels of area-normalized load. For the normal group (C) Vmax.5 was 0.90 ± 0.07 L/sec. In the CHF group Vmax.5 was reduced to 0.30 ± 0.02 L/sec (P > 0.01). The CHFR group exhibited a normal Vmax.5 of 0.82 ± 0.18 L/sec (P > 0.25). In the RVH group Vmax.5 was reduced to 0.50 ± 0.07 L/sec (P < 0.01). Vmax.5 in the RVHR group was a value not different from normal controls and averaged 1.12 ± 0.13 L/sec (P > 0.10).

The lightest load at which the muscle failed to shorten

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**Figure 2** Force-velocity relationships of right ventricular papillary muscles. Points on curves are means and error bars are ± 1 SEM. Velocity is in muscle lengths per second (L/sec). Load (force) is normalized for cross-sectional area. The left panel compares C group with the CHF and CHFR groups. The right panel compares the same C group with the RVH and RVHR groups. Note the CHFR curve which has depressed isometric load but normal unloaded velocity of shortening (see text for detail). Abbreviations as in Figure 1.
(P₀) for the normal muscles (C) was 4.64 ± 1.29 g/mm². In the CHF group P₀ was reduced to 2.04 ± 0.28 g/mm² (P < 0.05) as it was for the RVH group, 2.00 ± 0.25 g/mm² (P < 0.05). The CHFR muscles demonstrated severely reduced values of P₀, 1.22 ± 0.16 g/mm² (P < 0.025) despite the return of Vmax.5 to normal. Conversely, the RVHR muscles demonstrated P₀ values unchanged from control, 5.14 ± 1.07 g/mm² (P > 0.10), in concert with the return of Vmax.5 to normal.

**AUGMENTATION OF MYOCARDIAL CONTRACTILE FUNCTION—PAIRED ELECTRICAL STIMULATION**

Table 4 compares peak isometric tension (Pₛ), maximum dP/dt, and time from stimulus to peak tension (TTPₚ), all of which varied from the normal control values in every group except the RVHR group. In the CHFR group, the TTPₚ for a single stimulus was not significantly increased over the normal (P > 0.1) although the time to peak tension after paired stimulus was still prolonged (P < 0.01).

The difference between single and paired stimulation values for Pₛ and maximum dP/dt, respectively, produced by paired stimulation, were significantly reduced from the normal (C) values of 3.25 ± 0.39 g/mm² and 30.70 ± 6.22 g/mm² per sec in both the CHF group [2.06 ± 0.43 g/mm² (P < 0.01), and 16.45 ± 4.34 g/mm² per sec (P < 0.01)] and the RVH group [1.40 ± 0.42 g/mm² (P < 0.05), and 11.35 ± 4.31 g/mm² per sec (P < 0.01)]. For the CHFR group, the increments were only 0.88 ± 0.39 g/mm² (P < 0.01) and 9.03 ± 4.19 g/mm² per sec (P < 0.05). The increments for the RVHR group were normal [3.76 ± 0.86 g/mm² (P > 0.1) and 23.32 ± 8.25 g/mm² per sec (P > 0.1)]. The normal (C) decrement in the time from stimulus to peak tension (TTPₚ) produced by paired stimulation was 58 ± 15 msec. The decrement in TTPₚ did not differ significantly from control at the P = 0.05 level in any of the other groups: CHF, 85 ± 18 msec; CHFR, 42 ± 11 msec. RVH, 79 ± 21 msec; RVHR, 67.5 ± 8 msec.

**CONDITION OF RELIEF GROUPS PRIOR TO RELIEF OF STENOSIS**

Consideration was given to the question of the similarity of condition between the RVH and the CHF cats and their corresponding relief groups (RVHR and CHFR). Table 2 shows for cats in the CHFR group just prior to band removal, hemodynamic parameters that were not significantly different from those of the CHF cats. Similarly, the cats in the RVHR group, at the time of relief, had hemodynamic parameters that were not significantly different from those of the RVH group, with the exception of heart rate, which was lower in the RVHR group. The right ventricular systolic pressure of the CHFR group before relief of stenosis was less than the corresponding pressure in the CHF group. It was, however, significantly higher (almost double) than the control (Table 2).

**COMPARISON BETWEEN CONTRACTILE PARAMETERS OF PAPILLARY MUSCLES OF RVHR GROUP AND A GROUP NOT RELIEVED OF PULMONIC STRESS FOR A TOTAL TIME SIMILAR TO THE SUM OF THE CONSTRICTED PERIOD PLUS THE RECOVERY PERIOD**

Table 5 illustrates that contractile function, characterized by the parameters of Pₛ, dP/dt, and Vmax.5, was depressed in a group of muscles obtained from cats treated similarly to the RVHR group but in which the pulmonic constriction remained in place for an additional period similar in duration to the relief period of the RVHR group.

**Discussion**

Little is known of the factors that influence the degree of return to normality following relief of pressure overload. It would be helpful to know whether there is a gradual decrease in the recuperative potential of depressed pressure-overloaded ventricular muscle as severity of overload increases or whether there is a sudden "break point" beyond which recovery is minimal. The studies described in this paper indicate that the mechanically depressed, hypertrophied, but nonfailing right ventricle recovers normal mechanical function and weight after relief of pressure overload. This finding confirms the work of Cooper et al. The extension of this study to the failing, hypertrophied right ventricle, however, indicates that a more lasting defect occurs when heart failure is a complicating factor.

**SEVERITY OF PRESSURE OVERLOAD STRESS**

In the present investigation the more severe stress (87% constriction of the pulmonary artery), which superimposed congestive heart failure on a background of right ventricular hypertrophy, was not associated with recovery of full contractile function in the 30-day relief period. A period of 30 days, however, was sufficient for full recovery of contractile function in the case of the less severe stress...
(70% constriction of the pulmonary artery) which produced the same degree of right ventricular hypertrophy but not congestive heart failure. A hypertrophy stimulus of 2 weeks' duration was used because, due to permanent vessel scarring, it has not been possible, in this laboratory, to remove a pulmonary artery constriction of greater severity than 70% after more than 2 weeks without some residual stenosis persisting. Cooper et al. have successfully unbanded animals after 3-4 weeks with an experimental stenosis similar to the RVH and RVHR groups in our present work. Their results after 3-4 weeks of banding were essentially identical to those in our present work. However, in their study no attempt was made to produce pulmonic constriction of the severity produced in the CHF and CHFR groups of the present work.

**RECOVERY FROM CONGESTIVE HEART FAILURE AND RIGHT VENTRICULAR HYPERTROPHY**

Despite resumption of normal right heart pressures, recovery of resting cardiac pump function, and absence of residual stenosis (Table 2) after removal of the constricting clip, the mechanical contractile properties of the CHFR group remained severely depressed after the 30-day recovery period. The length-tension curve (Fig. 1), Po (the isometric point in the force-velocity relation), and the isometric parameters (P<sub>k</sub>, dP/dt, and TTP<sub>k</sub>) all remained depressed in the CHFR group (Table 4).

The continued depression of the contractile function in the CHFR group is in marked contrast to the return to complete normality of mechanical contractile function observed in the cats of the RVHR group which had the same degree of right ventricular hypertrophy but in response to a less severe pulmonic constriction and with no CHF.

Since the RVHR cats recovered completely normal heart weight, but those in the CHFR group did not although the degree of initial hypertrophy was the same for both (Table 3), the degree of hypertrophy per se cannot be responsible for the different recuperative performances of the two groups of cats. Since all the RVHR cats resumed normal cardiac function after a relief period of 30 days, it would not be illogical to assume that cats subjected to less severe constrictions would also recover under similar circumstances. Above the 70% constriction there does, however, appear to be a "break point" in reserve and recuperative potential of the muscle, because all cats subjected to the more severe stress of an 87% pulmonic constriction presented with symptoms of congestive heart failure and failed to recover normal contractile function despite identical relief of the experimental damaging stimulus.

In view of an observation that the depressed myocardial contractile function of the pressure-overloaded cat heart recovers with time without relief of the pressure overload or regression of hypertrophy, it was necessary to exclude the possibility that recovery of contractile function in the RVHR group would ultimately have occurred, anyway, without relief of the pressure overload. If the RVHR group had not been unbanded after 14 days, would the recovery of function have occurred nonetheless, after a total of 44 days? Accordingly, a comparison was made between the behavior of muscles from the RVHR group and from a group of seven cats which had been subjected to the same degree of pulmonic constriction as the RVHR group but which had not been relieved of the pulmonary stress after 14 days. The muscles of this group were studied after 7.0 ± 0.43 weeks, a period approximately equal to the 6.3-week total of the constriction and relief periods in the RVHR group. Since the contractile parameters of the unrelieved group remained depressed and those of the RVHR group recovered (Table 5), the possibility mentioned is excluded.

**THE NATURE OF LESIONS DEPRESSING CONTRACTILE PERFORMANCE**

The same depressed contractile parameters characterized the hypertrophied papillary muscles from cats whether they had an 87% pulmonic constriction and congestive heart failure or a 70% pulmonic constriction and no congestive heart failure. The fact that the former group failed to recover and the latter group did recover suggests that the failure group may have been an example of a more advanced depression, similar in nature but resulting from a more severe stress stimulus. However, the return of Vmax<sub>5</sub> to normal in the CHFR group with persistence of depressed P<sub>k</sub> (Fig. 2) is in marked contrast with the complete recovery of the RVHR group which had been depressed but had not presented with congestive heart failure. This observed discrepancy permits some speculation about the lesions which may be involved in congestive heart failure and which could contribute to the poor muscle function.

All the contractile depression observed in both the RVH group and CHF group cats (Table 4) could be

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**Table 5** Comparison between Contractile Parameters of Papillary Muscles of RVHR Group and a Group Not Relieved of Pulmonic Stress for a Total Time Similar to the Sum of the Banded Period plus the Recovery Period

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats</th>
<th>Body wt (g)</th>
<th>RV wt/body wt (g/kg)</th>
<th>Weeks banded</th>
<th>Weeks unbanded</th>
<th>Total weeks after banding</th>
<th>Papillary muscle cross-sectional area (mm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>P&lt;sub&gt;k&lt;/sub&gt; (g/mm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>dP/dt (g/mm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Vmax&lt;sub&gt;5&lt;/sub&gt; (L/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVHR</td>
<td>4</td>
<td>2636±22</td>
<td>0.52±0.03</td>
<td>2</td>
<td>4.3</td>
<td>6.3</td>
<td>0.84±0.10</td>
<td>5.87±0.31</td>
<td>32.17±4.45</td>
<td>1.12±0.13</td>
</tr>
<tr>
<td>Unrelieved group</td>
<td>7</td>
<td>2352±214</td>
<td>1.05±0.07</td>
<td>7.0</td>
<td>0.0</td>
<td>7.0</td>
<td>1.17±0.21</td>
<td>4.41±0.47</td>
<td>16.67±2.90</td>
<td>0.54±0.08</td>
</tr>
</tbody>
</table>

Values are given as means ± SEM.

RVHR = right ventricular hypertrophy-relief group; Vmax<sub>5</sub> = maximum velocity of shortening [in muscle lengths per second (L/sec)] at 0.5 g/mm<sup>2</sup>; P<sub>k</sub> = maximum isometric force.
explained by failure of any of a variety of mechanisms which lead to incomplete activation of the contractile mechanism. In the recent study by Cooper et al. of pure hypertrophy reversal, the depression of contractile function was associated with an observed abnormality of state 4 mitochondrial respiration which has been linked to calcium ion transport. It recently has been demonstrated that rabbit papillary muscles depressed by pressure overload hypertrophy developed the same amount of tension as normal muscles when the sarclemma was rendered permeable by glycerination, and the contractile mechanism was activated by externally applied Ca++. This finding is consistent with a lesion associated with the pressure overload which reduces effective calcium activation of the contractile machinery but does not modify the actual contractile mechanism itself. However, in our present study, the CHFR group had papillary muscles which contracted with normal velocity at low loads (Fig. 4) but had little capability for force development. This is a condition consistent with a reduced number of effective contractile units which are nonetheless adequately activated. In terms of the sliding filament theory of muscle contraction this could represent normal function of contractile machinery with far less than the normal numbers of contractile units operating. The implication is that myocardium from animals with congestive heart failure as well as right ventricular hypertrophy was the subject of a double lesion which reduced both contractile activation and effective numbers of participating contractile units, such that when the recovery period was over (30 days) the activation defect had been corrected but the depleted numbers of effective contractile units had not been restored.

Cooper et al. have also demonstrated that cardiac muscle from cats with right ventricular hypertrophy but no signs of congestive heart failure recovered normal function after a similar relief period. This recovery would not preclude the sort of double lesion invoked to explain the behavior of muscles from the CHFR group if such a double lesion were repaired in less time when the initiating stress had been less severe. The work of Henry et al. provides evidence that the presence of a double lesion affecting both the calcium-activating mechanism and the contractile mechanism is unlikely in hypertrophied but nonfailing heart muscle. In that study hypertrophied muscles biologically activated after experimental electrical stimulation developed subnormal force but exhibited a force development potential equal to that of normal muscles when artificially activated with external calcium. This is in contrast with the muscles of the CHFR group in the present work which appeared to have adequate activation, as evidenced by normal shortening velocity at low loads, but little potential for force development assessed as either P0 or P0. Since the essential difference between the CHFR group and the RVHR group was the presence of congestive heart failure we conclude that in CHF and CHFR before the relief period there was a defect of both the activation mechanism and the contractile machinery while in RVH and RVHR before recovery the activation mechanism was the principal limiting factor.

### DEPLETION OF NOREPINEPHRINE STORES

The catecholamine stores of both the left and right ventricles were depleted in both the RVH and CHF groups. Neither of the corresponding recovery groups (RVHR and CHFR) demonstrated normal norepinephrine stores. Since the left ventricles were never hypertrophied but exhibited a reduction in norepinephrine store, both hypertrophic structural changes and a mass-dilution effect can be eliminated as likely sources of the adrenergic lesion evidenced by catecholamine store depletion. The importance of the persistence of this adrenergic lesion cannot be ignored, since it suggests that an important source of contractile augmentation potential afforded neurogenically by the sympathetic nervous system may be denied the weakened heart during the recovery which is possible after relief of a chronic pressure overload.

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