Contractile State of Cardiac Muscle Obtained from Cats with Experimentally Produced Ventricular Hypertrophy and Heart Failure

By James F. Spann, Jr., M.D., Robert A. Buccino, M.D., Edmund H. Sonnenblick, M.D., and Eugene Braunwald, M.D.

ABSTRACT
The contractile state of papillary muscles from hypertrophied and from failing right ventricles of cats with pulmonary artery constriction was studied. In muscles from failing hearts, the maximum velocity of shortening, active length-tension curves, and maximum rate of tension development were decreased, while the passive length-tension curves and the time from stimulation to peak tension were normal. The augmentation of isometric tension achieved by paired electrical stimulation, increasing frequency of contraction, and strophanthidin was reduced. In muscle from hearts without failure but with ventricular hypertrophy, there were qualitatively similar depressions of contractile function, although of lesser magnitude. It is concluded that congestive heart failure is associated with extreme quantitative abnormalities of the intrinsic contractile state of each unit of heart muscle, which reflect a depression in the intensity of the active state. Further, ventricular hypertrophy in the absence of failure is associated with a depression of the contractility of each unit of myocardium, while cardiac compensation is maintained by the increase in muscle mass.

ADDITIONAL KEY WORDS intensity of active state duration of active state force-velocity relation papillary muscle norepinephrine digitalis

There is general agreement that when an abnormally high load is imposed on the ventricle, the development of myocardial hypertrophy provides one fundamental mechanism that permits the heart to compensate. Also, it is clear that when the ventricle is subjected to an extremely high load, compensation may no longer be adequate despite the presence of ventricular hypertrophy, and the ventricle fails as a pump. Certain important questions remain unanswered: (1) What is the contractile state of each unit of myocardium in the hypertrophied ventricle that has compensated? Is overall compensation in the hypertrophied heart maintained by an increased muscle mass, each unit of which has a normal or even increased contractile function, or is the function of each unit of hypertrophied muscle depressed while overall compensation is maintained by an increase in the contractile mass? (2) What is the contractile state of each unit of myocardium in the hypertrophied ventricle that has failed? (3) Does failure of the ventricle as a pump occur in the presence of an inadequate contractile mass, although the contractile function of each unit is normal or even supernormal, or does failure result as a consequence of a depression of contractility of the myocardium that is not compensated for by the increase in muscle mass?

Several recent developments have made it possible to examine these questions. The mechanics of papillary muscles isolated from the normal cat heart have been described in a manner similar to that employed for skeletal muscle (1). Further, it has been shown that these mechanical functions can be measured and normalized, that the variation of

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function is small among muscles from groups of similar animals, and that the function of muscles from groups of different animals can therefore be compared quantitatively (2). In addition, a preparation has been devised for producing right ventricular hypertrophy with and without overt congestive heart failure in the cat (3), thus providing a source of cardiac muscle from hypertrophied and failing hearts.

The basic experimental plan was to compare, under controlled conditions, the function of isolated papillary muscles obtained from the right ventricles of three groups of cats: (1) normal controls, (2) cats with pulmonic constriction and right ventricular hypertrophy but without congestive heart failure, and (3) cats with pulmonic constriction which, despite the development of right ventricular hypertrophy, developed heart failure. Prior to removal and study of the papillary muscles, the circulatory dynamics in each animal was evaluated to provide a basis for comparing it with muscle function in vitro.

**Methods**

Papillary muscles were obtained from 24 normal cats and 30 cats with right ventricular hypertrophy with or without overt congestive heart failure produced by chronic constriction of the main pulmonary artery, a procedure described in detail previously (3). Adult cats weighing 1.8 to 2.4 kg were anesthetized with intravenous sodium methohexitol, 15 mg/kg. Succinylcholine (1 mg/kg) was injected intravenously, and respiration was supported by intermittent endotracheal positive pressure. Circular clips were placed around the proximal main pulmonary artery under sterile conditions. The lumina of the constricted portion of the pulmonary arteries averaged 20 and 10% of normal with clips having diameters of 3.5 mm and 2.8 mm, respectively. The animals were maintained on a regular diet postoperatively. One to 90 days after the constriction, the cats were anesthetized lightly with a dose of sodium pentobarbital (20 mg/kg) that allowed them to breathe spontaneously. A cannula was placed in the descending aorta via the femoral artery, the electrocardiogram was monitored, and a no. 5 birds-eye catheter was placed in the cavity of the right ventricle via the right external jugular vein. Right ventricular and aortic pressures were measured by Statham pressure transducers (P23AA). All signals were recorded on a multichannel Sanborn oscillograph.

The zero reference point was taken as the mid-chest position. Cardiac output was determined by the indicator dilution technique with the injection of 1.25 mg indocyanine (1 ml) into the right ventricle and sampling from the abdominal aorta. Mixed venous and arterial blood samples were obtained from the right ventricle and aorta respectively and analyzed for oxygen content by the Van Slyke technique.

Following this study, a tracheostomy was performed and the animals were placed on intermittent positive pressure ventilation. The chest was opened and small samples of the right and left ventricles were taken for determination of myocardial high energy stores (4). The heart was then rapidly excised and one or two papillary muscles from the right ventricle were removed and transferred immediately to a myograph containing oxygenated Krebs solution. The myograph has been described previously in detail (5). The papillary muscle was held at its lower, nontendinous end by a clip attached to the end of a rigid pin. The pin, in turn, penetrated the bottom of the bath and was fixed to a Statham force transducer (G1-4-250). The upper tendinous end of the muscle was attached to an isotonic lever for the measurement of muscle shortening, and the lever itself was mounted on a Palmer stand. With this arrangement, when the position of the lever was fixed, the force of isometric contraction at any desired muscle length could be measured. 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. In this manner, using the same lever, one could describe both the length-tension and force-velocity relations of the papillary muscle. Force, muscle length, the first derivatives of these variables, and the stimulus artifact were recorded on a multichannel oscillograph. The muscles were stimulated by an American Electronic Stimulator (Model 104 A) with square-wave DC impulses of 9 msec and a voltage 10 to 25% above threshold delivered through field electrodes placed parallel to the long axis of each muscle.

To maintain metabolic integrity and stability of performance of the muscles for prolonged periods, the bath temperature was kept at 30°C, and the frequency of contraction was set at 12/min, except when the effects of changes in frequency were specifically studied. When the effects of paired electrical stimulation were determined, 12 pairs of stimuli/min resulting in 12 effective contractions/min were employed; the interstimulus interval did not exceed the muscle's effective refractory period by more than 20 msec. Studies were not done before 1 hr after muscles were placed in the myograph; the function remained
stable for at least 3 to 4 hr. Muscle length was determined both at a preload of 0.4 g and at the apex of the length-tension curve; the latter length was used to calculate the cross-sectional area.

After removal of the papillary muscle and atria, the free wall of the right ventricle was removed and weighed; the interventricular septum was then weighed together with the left ventricle. A portion of each ventricle was frozen rapidly for norepinephrine determination by a modification of the trihydroxyindole acetic acid method (6). The percentage of water in the right ventricle was determined by weighing the tissue before and after heating for 18 hours at 100°C in a partial vacuum. This percentage averaged 72 ± 2% (SEM) in the normal cats and 71 ± 1% in those subjected to chronic constriction, values which did not differ significantly from one another. However, the percentage of water in the right ventricle was increased significantly in the animals studied 24 and 48 hr after constriction, averaging 79 ± 2% and 80 ± 1% respectively (P < 0.05). All heart weights were expressed as a ratio of the preoperative body weight, which did not differ from the weight at the time the experiments were performed. There was no marked loss of body tissue weight in the animals with congestive heart failure, since the pleural and ascitic fluid they accumulated represented less than 10% of total body weight.

To prove that the papillary muscles participated in the hypertrophy of the right ventricle, papillary muscles from 4 normal cats and papillary muscles from 3 with right ventricular hypertrophy were fixed at the apex of the active length-tension curve by rapid substitution of buffered 6.25% glutaraldehyde for the bath fluid. The muscles were then imbedded in Araldite, and thick sections were prepared in the longitudinal axis of the fibers. They were then examined at a magnification of 400 X, and the width of 20 fibers was determined in each muscle by a calibrated reticule in the eyepiece. The average diameter of the myocardial fibers in the 4 normal papillary muscles was 7.8 ± 0.2 μ; in each of the papillary muscles from the 3 hypertrophied right ventricles, this value was significantly increased (P < 0.01) (10.9 ± 0.5, 12.0 ± 0.5, and 12.4 ± 0.4 μ).

**Results**

**DEFINITION OF GROUPS AND HEMODYNAMIC FINDINGS**

The animals with pulmonary artery constriction were separated into 3 groups.

**Congestive Heart Failure (CHF)**—This group of 11 animals in which the lumen of the pulmonary artery had been reduced to 10% of normal or less was studied 21 to 90 days (average 43) after constriction. We realize that the state of congestive heart failure cannot be defined in absolute terms and that experimentally produced heart failure mimics but is not identical to clinically occurring

![Figure 1](http://circres.ahajournals.org/)

Relation between right ventricular weight and the time at which pulmonary artery was banded. Average normal right ventricular weight and standard error are represented by the sawtooth line. Circles and triangles = animals with a 2.8-mm clip. Squares = animals with a 3.5-mm clip. The abscissa represents days after pulmonary artery was constricted.

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cats</th>
<th>Right ventricle weight (g/kg body wt)</th>
<th>Peak pressure (mm Hg)</th>
<th>End-diastolic pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Femoral artery pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13</td>
<td>0.55 ± 0.02</td>
<td>31 ± 3</td>
<td>2 ± 0.6</td>
<td>208 ± 10</td>
<td>185/146 ± 6/7</td>
</tr>
<tr>
<td>RVH</td>
<td>11</td>
<td>1.05 ± 0.08*</td>
<td>60 ± 3*</td>
<td>5 ± 0.7*</td>
<td>178 ± 7</td>
<td>175/135 ± 8/8</td>
</tr>
<tr>
<td>CHF</td>
<td>11</td>
<td>1.33 ± 0.10†</td>
<td>82 ± 8†</td>
<td>13 ± 2.0†</td>
<td>195 ± 10</td>
<td>186/143 ± 8/6</td>
</tr>
</tbody>
</table>

Mean values ± 1 SEM are shown. RVH = right ventricular hypertrophy; CHF = congestive heart failure.

*Significantly different (P < .01) compared to normal.

†Significantly different (P < .01) compared to cats in the normal and RVH groups.

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heart failure. Nonetheless, for the purposes of the present investigation, we considered that right ventricular failure had occurred when one or more of the following was present: pleural effusion, ascites, an abnormally elevated right ventricular end-diastolic pressure (>7 mm Hg) in combination with either an abnormally low cardiac index (<76 ml/min per kg) or a high arteriovenous O\textsubscript{2} difference (>7.0 ml O\textsubscript{2}/100 ml blood). The limits for normal values were set by measurements in 13 normal cats. In 9 of these 11 animals, two or more of the three criteria for heart failure were present; 9 had pleural fluid, ascites, or both; 3 had abnormally elevated arteriovenous O\textsubscript{2} differences; 7 had elevated right ventricular end-diastolic pressures; and 2 had reductions of the cardiac index.

**Right Ventricular Hypertrophy without Heart Failure (RVH).**—This group of 11 animals, in which the lumen of the pulmonary artery had been reduced to 20% of normal, were studied 24 to 85 days (average 52) following constriction. Cats were included in this group only if there was no pleural fluid or ascites and if values for right ventricular end-diastolic pressure, cardiac index, and arterio-mixed venous O\textsubscript{2} difference were within the range of normal, as defined above.

All animals in the CHF and RVH groups had right ventricular systolic hypertension (Table 1). Although the average right ventricular end-diastolic pressure in the RVH group was higher than the average normal value, by definition, none was outside the normal range. Systemic arterial pressure, heart rate and hematocrit did not differ among the normal, RVH and CHF groups.
CONTRACTILITY IN CARDIAC HYPERTROPHY AND FAILURE

Short-Term Constriction.—To examine the early effects of pulmonary artery constriction, cats with a 2.8-mm clip about the pulmonary artery were studied 24 and 48 hr after operation; 4 cats were studied at 24 hr and 4 at 48 hr. These animals were not selected for early study because of any particular clinical or laboratory finding. The right ventricular systolic pressure was not elevated (<35 mm Hg) in the 4 cats studied 24 hr after operation. However, two of them were in heart failure, as defined above. All 4 animals studied 48 hr after constriction were in heart failure and 3 of them had moderately severe right ventricular systolic hypertension (>45 mm Hg).

VENTRICULAR WEIGHT

Right ventricular weight increased promptly after the constricting operation and then rose less rapidly, as shown in Figure 1. The right ventricular weights in 11 normal cats averaged 0.55 ± 0.02 g/kg body weight. These weights were significantly increased above normal 1 and 2 days after constriction, averaging 0.70 ± 0.04 and 0.94 ± 0.05 g/kg respectively (P < 0.02). In the cats in the RVH and CHF groups the right ventricular weights were considerably increased (Table 1). There were no significant differences in left ventricular weights among any of the groups; these values averaged 2.21 (normal), 1.98 (RVH), 2.10 (CHF), 2.24 (24 hr post-constriction) and 2.35 (48 hr post-constriction) g/kg.

MYOCARDIAL MECHANICS

Isometric Length-Tension Curves.—The length of the muscle at the apex of the active length-tension curve was defined as L_max, and changes of muscle length were expressed as percentages of L_max. Tensions were calculated as force per unit of cross-sectional area of each muscle. The cross-sectional areas of the normal papillary muscles averaged 0.88 ± 0.06 mm², while the RVH and CHF groups, muscle areas were larger, averaging 0.99 ± 0.16 mm² and 1.30 ± 0.15 mm², respectively.

In both the RVH and CHF groups the actively developed tension was less than normal at all muscle lengths along the length-tension curve (Fig. 2). Maximum active tension in the RVH group was slightly, but not

![Figure 3](image_url)

**Figure 3**

Left, maximum rate of isometric force development shown for the three groups of muscles in g/mm²/sec. All muscles were studied at the apex of their length-tension curves. Right, time from stimulation to the peak of developed isometric tension in milliseconds. All muscles were studied at the apex of their length-tension curves. Numbers in parentheses = number of animals. Vertical lines with cross bars = ± 1 SEM.

![Figure 4](image_url)

**Figure 4**

The force-velocity relations of the three groups of cat papillary muscles. Average values with ± SEM are given for each point. Velocity has been corrected to muscle lengths per second (L/sec). Numbers in parentheses = number of animals.
significantly reduced, averaging 5.3 ± 0.6 g/mm², compared with the normal value of 6.2 ± 0.7 g/mm², while the maximum isometric tension of the muscles from the cats in the CHF group was markedly below normal, averaging 2.4 ± 0.4 g/mm² (P<0.01). The maximum active tension was not significantly reduced in muscles from animals studied 1 day after constriction, averaging 5.4 ± 1.4 g/mm², while it was below normal in muscles from the 4 cats studied 2 days after constriction, averaging 2.8 ± 0.5 g/mm² (P<0.01). There were no significant differences among the average resting length-tension curves in any of the groups of muscles.

The course of isometric tension was also analyzed in terms of the maximum rate of tension development and the time from stimulation to peak tension. The rate was significantly reduced, while the time to peak tension was unchanged in muscles from cats of both RVH and CHF groups (Fig. 3).

**Force-Velocity Relations.**—Initial muscle length was set by a small preload which was constant for each force-velocity curve, and the effects on the velocity of shortening of progressively increasing afterload were then determined. Velocity of shortening was corrected for muscle length and was expressed in muscle lengths per second (L₀/sec), while the force (or load) was expressed in grams per square millimeter. The velocity of shortening at the smallest load (0.5 g/mm²) was used to approximate the maximum velocity of shortening (Vₘₐₓ) to avoid errors that might result from extrapolation of the curve to zero load.

Similar inverse relationships between force and velocity were found in all three groups (Fig. 4). At each load the velocity of shortening was less in muscles from cats of both RVH and CHF groups, thus shifting the entire force-velocity curve downward and to the left. Vₘₐₓ at a load of 0.5 g/mm² averaged 0.90 ± 0.08 L₀/sec in normal muscles and was significantly lower (P<0.01), averaging 0.65 ± 0.06 L₀/sec in the muscles from cats of the RVH group. Vₘₐₓ was significantly lower in the muscles from the CHF group than in muscles from either of the other two groups (P<0.01), and averaged 0.34 ± 0.06 L₀/sec. Vₘₐₓ was also significantly depressed below normal in the muscles obtained from animals studied shortly after constriction and averaged 0.56 ± 0.04 L₀/sec and 0.44 ± 0.06 L₀/sec 1 and 2 days after operation, respectively (P<0.05).

**RESPONSES TO PROCEDURES THAT AUGMENT MYOCARDIAL CONTRACTILITY**

**Paired Electrical Stimulation.**—The effects of the sustained postextrasystolic potentiation produced by paired electrical stimulation on the maximum active tension of the three groups of muscles are shown in Figure 5. The increments in tension produced by paired electrical stimulation were significantly reduced from the normal value of 3.8 ± 0.3 g/mm² to 2.2 ± 0.4 g/mm² in the muscles from cats of the CHF group (P<0.01) and were lowered, although not significantly, to an average value of 2.8 ± 0.6 g/mm² in the muscles from the cats of the RVH group. On the other hand, the average maximum tensions achieved were significantly reduced in muscles from cats of both RVH and CHF groups,

![Figure 5](http://circres.ahajournals.org/)

Effects of sustained postextrasystolic potentiation produced by paired electrical stimulation on the maximum isometric force of contraction at Lₘₐₓ in the three groups of muscles. The hatched area represents control force with single electrical stimulation; the clear area above represents the augmentation with sustained paired electrical stimulation. Numbers in parentheses = number of animals. Vertical lines with cross bars ± 1 SEM.

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averaging $8.5 \pm 1.0$ g/mm$^2$ and $4.9 \pm 0.7$ g/mm$^2$, respectively, compared to the value of $10.6 \pm 0.4$ g/mm$^2$ observed in normal muscles (RVH vs. normal, $P < 0.05$; CHF vs. normal $P < 0.01$; RVH vs. CHF $P < 0.01$).

Changes in Frequency of Contraction.—When the frequency of contraction was increased in muscles obtained from cats of the normal, RVH, and CHF groups (Fig. 6), there was a progressive elevation in both the rate of tension rise and tension, while the time from stimulation to peak tension was shortened. However, the increments in the rate of rise and tension in response to changes in frequency were clearly depressed in the abnormal muscles. Thus, the increase in the rate of rise per unit increment in frequency per minute averaged 0.43 g/mm$^2$ per sec, 0.13 g/mm$^2$ per sec and 0.07 g/mm$^2$ per sec in the normal, RVH, and CHF groups, respectively.

Strophanthidin.—With the muscle contracting isometrically at the apex of the length-tension curve, 1.0 $\mu$g/ml of strophanthidin was added to the bath, and the maximum effect, which occurred 20 min later, was recorded. The average increment in maximum tension did not differ significantly among the 3 groups, averaging $2.2 \pm 0.3$ g/mm$^2$ in muscles from normal cats, $2.6 \pm 0.5$ g/mm$^2$ in muscles from cats of the RVH group and $1.8 \pm 0.4$ g/mm$^2$ in muscles from cats with heart failure (Fig. 7). Following strophanthidin, the maximum tension achieved by the muscles from cats of the RVH group averaged $8.4 \pm 1.0$ g/mm$^2$, a value equal to...
FIGURE 7

Effects of the addition of 1.0 mg/ml strophanthidin on maximum isometric force of contraction at L\textsubscript{max} in the three groups of muscles. The hatched area of each bar represents the average control force, the clear area represents the average increment following strophanthidin; the upper limit of each bar indicates the average maximum isometric tension achieved following strophanthidin. Vertical lines with cross bars = ±1 SEM; numbers in parentheses = number of animals in each group.

FIGURE 8

The average norepinephrine concentration of the right and left ventricles of cats in the normal, RVH and CHF groups. Vertical lines with cross bars = ±1 SEM. Numbers in parentheses = number of animals in each group.

that observed in normal muscles, 8.4 ± 0.5 g/mm\textsuperscript{2}. The muscles from the cats in the CHF group, however, achieved an average maximum force following the digitalis glycoside of only 4.6 ± 0.7 g/mm\textsuperscript{2}, a value significantly less than normal (P < .01).

**NOREPINEPHRINE CONCENTRATION AND RESPONSES**

Marked depressions of the cardiac norepinephrine concentration were observed in both the right and left ventricles, in both the RVH and CHF groups (P < 0.01). The extent of the depression was comparable in both of these experimental groups (Fig. 8). Neither the right nor left ventricular norepinephrine concentrations were significantly depressed in the animals studied 1 day after constriction. In those studied 2 days postoperatively there was significant depletion of right ventricular norepinephrine.

FIGURE 9

Effects of exogenous norepinephrine on isometric tension of papillary muscles of cats in the RVH and CHF groups. 1-norepinephrine was added to the muscle bath at 5-min intervals in increasing concentrations starting at 10\textsuperscript{-10}M, while isometric tension achieved at each concentration was recorded at L\textsubscript{max}. The increment in isometric tension is shown on the ordinate and the concentration of added norepinephrine (NE) on the abscissa. Solid circles = muscles from normal hearts; solid triangles = muscles from the norepinephrine-depleted hearts of animals in the RVH and CHF groups. Vertical lines with cross bars = ±1 SEM.
norepinephrine concentration, which averaged 0.41 ± 0.09 compared to the normal value of 2.13 ± 0.30 μg/g (P < 0.01) and moderate, but not significant, depletion of left ventricular norepinephrine concentration which averaged 0.92 ± 0.30 μg/g compared to the normal value of 1.49 ± 0.23 μg/g.

The inotropic effect of l-norepinephrine was studied in the muscles from 8 normal cats and 6 cats with pulmonary artery constriction. Four of these were in the RVH group and the other 2 in the CHF group, but because of the small size of these two groups and the fact that all 6 hearts showed depletion of right ventricular norepinephrine to a concentration of 0.39 μg/g or less (average concentration in these right ventricles = 0.18 ± 0.12 μg/g), they were analyzed as a single group and compared to the normal.

All muscles responded to norepinephrine with an increase in tension, and the increments were greater in muscles from the cats in the RVH and CHF groups (Fig. 9). For example, at a concentration of 10^{-7} M l-norepinephrine, the increment in isometric force averaged 1.47 ± 0.23 g/mm^2 in muscles from the RVH and CHF groups, a value significantly greater than that observed in the normal muscles, 0.84 ± 0.20 g/mm^2 (P < 0.05). Thus, the dose-response curve was shifted upward, signifying an increased response to norepinephrine while the initial response occurred at the same concentration.

**Relation of Cross-Sectional Area to Muscle Performance**

In view of the observation that muscles from cats with heart failure were, on the average, thicker than muscles obtained from normal animals, it was necessary to exclude the possibility that the depressed contractile state of muscles from animals with heart failure was due to this increased muscle thickness (and inadequate diffusion of materials to and from the bath) rather than to an intrinsic abnormality of contractile state. Accordingly, a comparison was made between the behavior of 6 muscles from normal animals with widely varying cross-sectional areas with that of 6 muscles from animals with heart failure that were matched for cross-sectional area. These 6 pairs of muscles were the only ones in which such matching of cross-sectional areas was possible. The results, shown in Table 2, indicate that in each instance, the V_{max} and the maximum isometric tension before and during paired electrical stimulation were strikingly depressed in the muscles from animals with heart failure, regardless of the cross-sectional area.

### Discussion

Although knowledge of the intrinsic con-

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**Table 2**

<table>
<thead>
<tr>
<th>Papillary muscle area, mm²</th>
<th>V_{max}* (cm/sec)</th>
<th>Tension† (g/mm²)</th>
<th>Augmented tension‡ (g/mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CHF</td>
<td>Normal</td>
<td>CHF</td>
</tr>
<tr>
<td>1.29</td>
<td>1.33</td>
<td>0.90</td>
<td>0.44</td>
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<td>1.23</td>
<td>1.09</td>
<td>1.02</td>
<td>0.16</td>
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<td>1.50</td>
<td>1.52</td>
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<td>1.40</td>
<td>1.40</td>
<td>0.89</td>
<td>0.03</td>
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<td>0.45</td>
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<td>.95</td>
<td>0.49</td>
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<tr>
<td>0.85</td>
<td>0.76</td>
<td>1.14</td>
<td>0.21</td>
</tr>
<tr>
<td>AVERAGE</td>
<td>1.12</td>
<td>1.09</td>
<td>0.93</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure.

*Maximum velocity of shortening (V_{max}) expressed in length-tension curve (L_{max}) with normal stimulation.

†Actively developed tension at the apex of the active length-tension curve (T_{max}) with normal stimulation.

‡Actively developed tension at I_{max} with sustained postextrasystolic potentiation due to sustained paired electrical stimulation.
tractile properties of the myocardium in hypertrophied and failing hearts is essential to an understanding of the basic processes underlying ventricular compensation and failure, relatively few experimental data concerning this problem have previously been available. Furthermore, there is little agreement among the conclusions derived from the studies of this problem. Two general approaches have been employed by previous investigators: (1) determination of the maximum contractile response of the hypertrophied heart in the intact ventricle and (2) determination of the maximum force developed by isolated preparations of cardiac muscle obtained from hypertrophied hearts.

A number of investigators have concluded that ventricular performance is not depressed in the presence of cardiac hypertrophy. Beznak (7) measured the maximum cardiac output that followed the infusion of fluid into the central venous bed in normal rats and rats with left ventricular hypertrophy due to aortic constriction. Since the latter had normal resting outputs and even greater than normal increments in output in response to infusion, she concluded that the hypertrophied heart is stronger than normal and has a greater "reserve force." Alexander et al. (8) determined the maximum pressure developed by the contracting left ventricle when the aorta was occluded in heart-lung preparations of rabbits with left ventricular hypertrophy due to aortic constriction. Since the latter had normal resting outputs and even greater than normal increments in output in response to infusion, she concluded that the hypertrophied heart is stronger than normal and has a greater "reserve force." Alexander et al. (8) determined the maximum pressure developed by the contracting left ventricle when the aorta was occluded in heart-lung preparations of rabbits with left ventricular hypertrophy and found that the peak pressures achieved by the hypertrophied ventricles were greater than those achieved by normal animals. Geha et al. (9) measured maximum work performance of the right ventricles with right ventricular hypertrophy, found that it was not depressed, and suggested that it might even be increased. Bretschneider et al. (10), who corrected cardiac work per gram of heart weight, observed no differences in cardiac work per unit weight between normal canine heart-lung preparations and those obtained from animals with ventricular hypertrophy.

On the other hand, Meerson and Pshennikova (11) described a depression of function of hypertrophied intact hearts in the absence of congestive failure. They determined the maximum left ventricular pressure developed after aortic occlusion in normal rabbits and in rabbits with left ventricular weights that exceeded the normal by 75%, as a result of chronic constriction of the aorta. Although the absolute level of pressure that the ventricle developed increased in the hypertrophied hearts, there was a significant reduction of developed intraventricular pressure per gram of hypertrophied muscle.

Several limitations are inherent in studies performed on intact hypertrophied ventricles. Among these are the lack of measurements of tension actually developed by the myocardial fibers and the lack of corrections for wall thickness, for changes in geometry of the ventricle, for variations in initial length of the fibers, and for the extrinsic inotropic effects on the heart.

The second experimental approach, i.e. studies of isolated muscle removed from hypertrophied hearts, has also led to divergent conclusions. Grimm and co-workers (12) studied the length-tension relationships of left ventricular papillary muscles of rats with moderate left ventricular hypertrophy produced by exercise or aortic constriction, and found that the maximum isometric tension developed per gram of tissue was unaltered. On the other hand, Kerr et al. (13) found an increase in the isometric force developed per unit of muscle weight in papillary muscles obtained from rats with hypertrophied ventricles due to constriction of the abdominal aorta.

In many of the earlier studies in which the function of the hypertrophied heart was described as normal or augmented, the extent of hypertrophy was relatively slight, and this fact may account, at least in part, for the lack of depression of contractility. Linzbach (14) has pointed out that the "physiologic hypertrophy" of the athlete's heart rarely exceeds 500 g while the "pathologic hypertrophy" of heart disease usually results in heart weights of 600 to 1,000 g, at least a doubling of the normal heart weight.
doubling of right ventricular weight in the current study is comparable to the pathologic hypertrophy of the human heart as described by Linzbach and contrasts with the milder degrees of hypertrophy studied by earlier investigators. It must also be appreciated that all of these earlier studies were carried out only on animals with compensated hypertrophied ventricles not in failure, while in the present investigation, cardiac muscle from both failing and compensated hypertrophied hearts was characterized. In addition, in earlier investigations major emphasis was placed on the peak force developed by heart muscle or the ventricle. However, it is now appreciated that peak force is inadequate as the sole indicator of the contractile state of heart muscle (1); accordingly, in the present study a more comprehensive analysis of myocardial function was carried out. This included the force-velocity relation, determination of the velocity of shortening of the unloaded muscle, the rate of tension development, the time to peak tension, the response to alterations in frequency and the maximum tension developed following various procedures.

A major finding of the present investigation was an extreme depression of the intrinsic contractile state of cardiac muscle removed from the hearts of animals with overt congestive heart failure. This depression was characterized by a downward shift of the force-velocity curve with substantial reduction of the intrinsic speed of contraction ($V_{\text{max}}$). That the intrinsic speed of contraction was reduced was further manifested by a decrease in the rate of force development. These findings indicate that the intensity of the active state is depressed, and can be interpreted as a reduction in the rate of interactions at contractile sites in these muscles (15). However, the time to peak tension was not altered in the isometrically contracting muscles. This latter finding suggests that, although the maximum intensity of the active state is reduced, its duration remains unchanged (16). Had the time to peak tension been increased in the face of a reduction of the rate of development of tension, the maximum force the muscle was capable of developing might have been preserved, at least in part. Since this potential compensatory mechanism was not utilized, the maximum isometric force developed by the muscles from the cats with failure was markedly reduced. Furthermore, the finding that the time to peak tension was normal indicates that the depression of force in the failing muscle does not result from an abbreviation of the duration of active state, but only from a depression of the maximum intensity of the active state. It must be emphasized that these abnormalities were intrinsic to the cardiac muscle of the failing heart, since they were present in vitro, where the chemical and physical conditions were controlled in an identical manner for all the groups of muscles studied.

The present observations also allow elimination of the possibility that the decrease in developed force in failing heart muscle is due to the disengagement of actin and myosin filaments known to occur on the descending limb of the Frank-Starling curve (active length-tension curve) (17). Specifically, it was noted that the tension at all points along the ascending limb of the active length-tension curve was depressed in the failing muscles (Fig. 2). Thus the decreased tension developed by failing and hypertrophied heart muscle can be related to an intrinsic weakness of the muscle rather than an abnormal position on a basically normal length-tension curve. These data allow one to reject the hypothesis that the decreased contractility of failing heart muscle is due to its operation on the descending limb of the Frank-Starling curve. Also, the depression of the active length-tension curves could not be attributed to a change in compliance, since the resting length-tension curves of the hypertrophied, nonfailing, and failing hearts were normal when corrected per unit of muscle.

The possibility was considered that the depressions of contractility in the failing heart could be related to the increased thickness of these muscles, and that this increased thickness resulted in inadequate oxygenation of the muscles, a concept which is suggested.
by the recent observations of Fisher et al. (18). However, a number of factors strongly militate against this possibility. First, as shown in Table 2, comparisons of the contractile state of muscles from cats with heart failure with that of muscles from normal cats with matched cross-sectional areas showed that the contractility of muscles from cats with heart failure was strikingly reduced. Second, an analysis of maximum isometric tensions developed by 23 muscles from normal cats ranging in cross-sectional area from 0.41 mm$^2$ to 1.40 mm$^2$ showed that absolute tension (uncorrected for cross-sectional area) was directly proportional to the cross-sectional area of the muscles ($r = 0.9; P < 0.01$) (Sonnenblick et al., unpublished observations). Third, other studies have recently shown that the total high energy phosphate stores (the sum of ATP and creatine phosphate) in papillary muscles having a cross-sectional area averaging 1.21 mm$^2$ and contracting isometrically at the peaks of their length-tension curves, at a frequency of 12/min, and a temperature of 37°C for 60 min were actually higher than the levels in the intact cat heart (Pool et al., unpublished observations). Finally, and perhaps most significant, it should be noted that the high energy phosphate stores in papillary muscles obtained from cats with hypertrophy and heart failure and studied under in vitro conditions similar to those in the present investigation were identical to those of muscles obtained from normal cats (4) and considerably higher in these muscles than in the right ventricular high energy phosphate stores in animals with heart failure in vivo.

In addition to depressions in the functional level of the contractile state of muscles obtained from animals with heart failure, these muscles also had depressions in the increments in contractility produced by various types of procedures. Thus, the absolute increases in force and rate of force development produced by paired electrical stimulation, strophanthidin, and increased frequency of contraction were less in muscles from failing hearts than in muscles from normal hearts. Furthermore, although the absolute levels of force and rate of force development in the muscles from failing hearts were augmented by these procedures, they did not reach even the basal levels observed in the isolated normal muscles. Thus, it would appear that the contractile state is reduced even in the presence of potentiation, and that the intrinsic defect in heart failure can only be partially corrected by these procedures. On the other hand, the absolute increments in tension produced by paired electrical stimulation and strophanthidin in the muscles from the hypertrophied but nonfailing hearts were not significantly less than normal and the maximum average tension achieved in the hypertrophied muscles after strophanthidin was, in fact, the same as that in normal muscles.

In contrast to the response to the three inotropic procedures just discussed, the response to norepinephrine in muscles from hypertrophied and failing hearts exceeded that observed in normal muscles. Since norepinephrine stores were markedly reduced in the right ventricles of the hypertrophied and failing hearts, this increased response to norepinephrine may represent supersensitivity, as seen in denervated, norepinephrine-depleted heart muscle (2). The decrease in left ventricular norepinephrine in the cats with right ventricular failure is consistent with previous observations of its depletion in the nonfailing ventricles of guinea pigs and dogs with experimentally produced left (6) and right (19) ventricular failure. Norepinephrine depletion also occurred in both right and left ventricles of the hypertrophied but nonfailing heart. Surprisingly, the degree of norepinephrine depletion was as extreme in the hypertrophied nonfailing ventricles as in the hypertrophied failing chambers. These findings allow the previously described concept of cardiac norepinephrine depletion in the failing heart (6, 19, 30) to be extended to the overloaded, hypertrophied, but nonfailing heart as well. The extent of these decreases of norepinephrine concentrations were proportionally much greater than the increases in ventricular weight, thus indicating that there was a true depletion of the adrenergic neu-
rotransmitter rather than mere dilution of a normal complement of nerve endings within the hypertrophied myocardium.

Conclusion.—We realize that the present investigations were carried out on isolated muscle under conditions quite different from those existing in the intact animal. Accordingly, the relevance of these findings to the intact heart must be interpreted with appropriate caution. However, we have recently studied the mechanics of the intact right ventricles of cats in which hypertrophy and heart failure were produced in a manner identical to that used in the present investigation, and have found depressions of the contractile state per unit of muscle similar to those in the present report (21). From this investigation it would appear that when the ventricle is chronically stressed by an increase in the impedance to emptying, its initial response is to increase the total muscle mass. This increase in muscle mass, operating perhaps in conjunction with the Frank-Starling mechanism and increased sympathetic stimulation, maintains overall circulatory compensation despite depression of the intrinsic contractile state of each unit of myocardium. This depression is manifested, in the mildest form, by a reduction in the intrinsic velocity of shortening of each myocardial fiber but only a minimal decrease in the isometric force development. In muscles from such hearts, inotropic stimuli are normally operative and capable of augmenting the isometric contractile force to a normal extent. As the intrinsic contractile state of each unit of myocardium is further depressed, a more extensive reduction in \( V_{\text{max}} \) occurs, and this is now accompanied by a decrease in maximal isometric force. At this point, circulatory compensation can no longer be maintained, despite maximal utilization of the compensatory mechanisms provided by cardiac dilatation and increases in muscle mass; overt congestive heart failure then occurs. The marked reduction in norepinephrine stores impairs the potential support available to the myocardium from sympathetic stimulation (22), but is not responsible for the intrinsic depression of myocardial contractile state (2). Furthermore, while an improvement in function in response to positive inotropic stimuli, such as digitalis, can occur in failing muscles, the augmentation is decreased and the resultant level of contractility remains less than normal.

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