Cardiac Myosin and Congestive Heart Failure in the Dog

By Robert E. Olson, Ph.D., M.D., Eric Ellenbogen, Ph.D.,* and Raja Iyengar, Ph.D.

Chronic congestive heart failure has been produced in dogs by surgical induction of valvular disease. Cardiac myosin was isolated from the normal dogs and from dogs with congestive heart failure and characterized. Physicochemical properties of the cardiac myosins were determined by measurements of velocity sedimentation, partial specific volume, rate of diffusion, limiting viscosity number, light-scattering behavior, and ATPase activity. The measurements show that normal cardiac myosin (myosin C) has a molecular weight of 225,000, whereas myosin from the failing heart (myosin F) has a molecular weight of 690,000. This change in molecular weight occurs without a marked alteration in amino acid composition and suggests that end-to-end trimerization of normal cardiac myosin occurs in association with congestive heart failure in the dog. There was no significant change in ATPase activity.

For the past several years our laboratory has been engaged in the systematic study of cardiac metabolism in the dog in various conditions of malnutrition, endocrine imbalance, and surgically induced valvular heart disease. Of particular interest has been the study of the contractile proteins of the heart in various states, including experimental chronic congestive heart failure. This study was undertaken because of the inability of many investigators, including ourselves, to discover in either dogs or man with heart failure any evidence of a biochemical defect in the uptake of substrates from the coronary blood, the oxidation of these substrates to carbon dioxide and water, or in the process of oxidative phosphorylation. The shortening of the myofibril in the contractile process involves the interaction of at least 2 contractile proteins, myosin and actin, with ATP. Hence, in view of the above negative evidence, it seemed important to study the properties of these proteins in hearts of animals in various states of cardiac compensation. Since appropriate samples of cardiac muscle from human subjects are very difficult to obtain immediately after death, it was necessary to study this problem in an experimental animal. This report presents the results of studies of the physicochemical properties of cardiac myosin isolated from normal dogs, from dogs with sodium retention after ligation of the inferior vena cava, and from dogs with chronic congestive heart failure from valvular disease. More detailed reports of these findings have appeared elsewhere.

Methods

Normal mongrel dogs, immunized upon arrival from the kennel and known to be in good health through observations in our animal colony over several weeks, served as the normal control group for this study. Dogs with inferior vena cava ligation (ICL) having marked sodium retention and ascites served as the second control group. This ICL group was a particularly good control group because these animals possessed normal cardiac contractility in the presence of sodium retention and altered aldosterone metabolism.

In the first experimental group, congestive heart failure was produced in a series of animals by surgical avulsion of the tricuspid valve and stenosis of the pulmonary artery, essentially by the method of Barger, Roe, and Richardson. This combination of surgical lesions, which was accomplished in 2 stages at 3-week intervals, produced congestive heart failure in 60 per cent of the surviving dogs, with an operative mortality of less than 15 per cent. These animals began to show clinical signs of congestive heart failure within 1 to 4 weeks after constriction of the pulmonary artery. These signs included oliguria, marked sodium retention, an increase in body weight with the appearance of ascites, and reduced exercise tolerance.

Ventricular end-diastolic pressures in dogs operated upon to produce tricuspid insufficiency and pulmonary stenosis. The time of each operation is noted. The end-diastolic pressures were measured in nonanesthetized dogs. The solid symbols are right ventricular pressures; the open circles are left ventricular pressures. The lower set of curves represents the pressures in animals that did not develop congestive heart failure.

In the second experimental group of dogs, primary left heart failure was produced by creating a mitral insufficiency followed by 1 of 2 aortic lesions. Aortic stenosis was produced by resecting the noncoronary aortic cusp and adjacent aorta with the formation of a bicuspid valve along the lines suggested by Carmella, Andersen, and Oropeza. A constriction in the lumen of about 60 per cent was achieved. Aortic insufficiency was induced by punching holes in the noncoronary cusp with a circular valvulotome through the aorta according to Roshe and Morrow. Postoperatively, the intraventricular pressures of many of these dogs were measured through the chest wall at intervals to determine the time of onset of failure. Statham gauges and a Sanborn viscoardiette were employed to record the pressures. Minimal morphine sedation was used to facilitate the procedure so that the dogs were quiet but awake and responsive. All of the animals sacrificed for characterization of cardiac myosin had been in failure for at least 6 weeks, as evidenced by elevated end-diastolic pressures.

In order to describe the hemodynamic status of these animals prior to sacrifice, a light plane of anesthesia was induced in each animal by the intravenous administration of Nembutal : Dial-Urethane (1 : 1/v/v). Cardiac catheterization of the right heart and coronary sinus was accomplished, a femoral artery was cannulated, and pressure measurements were made in the femoral artery, right atrium, right ventricle, and pulmonary artery, by means of Statham gauge transducers with either a Sanborn twin viscoardiette or a Medical Electronics recorder. In some instances simultaneous tracings in right ventricle and left ventricle were recorded using a direct puncture of the left ventricle through the chest wall (see figure 2.). Myocardial oxygen and carbon dioxide exchange and substrate extraction were measured by sampling simultaneously from the coronary sinus and the femoral artery. Coronary flow was measured by the nitrous oxide method. Blood gases and substrates were measured by methods previously described and the results of studies of the metabolic activity of the failing heart are reported elsewhere.

At the conclusion of the physiologic measurements the plane of anesthesia was deepened by administration of additional Nembutal to permit a thoracotomy and institution of artificial respiration. The pericardium was opened and the animal sacrificed by rapid excision of the beating heart. The organ was immediately chilled in deionized water in 1 C. Generally, a ventricular ectopic rhythm persisted until the heart had been immersed in the cold water for a few seconds. After being fully chilled to 1 C, the heart was dissected in a cold room to remove fat and connective and atrial tissue. Both right and left ventricular tissue were combined and minced in a meat grinder at 4 C, and the myosin was isolated by the method previously described.

Cardiac myosin was isolated from dogs in the 2 control and in the 2 experimental groups and characterized by a study of velocity sedimentation, partial specific volume, rate of free diffusion, limiting viscososity number, light-scattering behavior, and ATPase activity. Partial specific volumes were determined by pyknometry. ATPase activity was determined at 25 C. on samples dialyzing against veronal buffer (pH 8.6) in order to remove phosphate ions. The method of Gergely was employed and the ATPase activity expressed as Q,(microliters of phosphorus liberated per milligram of myosin per hour). Sedimentation-velocity measurements were carried out in a Spinco Model E analytical ultracentrifuge. Solutions above 0.2 per cent protein were analyzed in the conventional manner from schlieren patterns. More dilute solutions were
analyzed by measurement of ultraviolet absorption, using a Spinco analytrol to plot the density of the absorption bands. Sedimentation runs were carried out both at 24 and 4 C.; no dependence of sedimentation constant upon temperature or speed of rotor was noted. Diffusion constants were estimated both from boundary spreading observed in the ultracentrifuge and from free diffusion in the Spinco Model H electrophoresis apparatus. Diffusion constants were calculated from schlieren patterns and from Rayleigh fringes respectively employing the method of second moments. The boundary-spreading coefficients were corrected for the concentration dependence of the sedimentation constant. Light-scattering measurements were carried out in a Brice-Phoenix light-scattering photometer equipped with a Brown recorder. The wave length chosen was a mercury blue line (436 mµ). The refractive index increment was determined at the same wave length in a Phoenix differential refractometer and found to be 0.206 on a weight fraction basis. The solutions were clarified and measurements were carried out at 0, 45, 90, and 135 degrees at a temperature of 15 C. or less. The limiting viscosity number was obtained by measurement of the viscosity of solutions of different concentrations in an Oswald viscometer with a water time of about 180 seconds mounted kinematically in an unsilvered Dewar flask at 2 C. Triplicate determinations were obtained with a maximal deviation of ± 0.3 second. Further details of these methods have been published.6

Three preparations of normal cardiac myosin and the myosin obtained from the failing heart were hydrolyzed in 6N HCl, and their amino acid was analyzed by the method of Moore and Stein.16, 17

Results

Physiologic Studies

All the animals in this series with valvular disease showed generalized congestive heart failure at the time they were sacrificed for the study of cardiac myosin. Both the normal animals and the controls with inferior vena cava ligation showed no evidence of congestive heart failure.

In several of the animals operated upon, the development of failure was followed by measurements of end-diastolic pressures in the right and left ventricles. Results of a typical series of animals is presented in figure 1. After production of tricuspid insufficiency, end-diastolic filling pressure in the right heart was elevated from 2 to approxi-
mately 6 mm. of Hg. After pulmonary stenosis was established, certain of the animals demonstrated a further rise in right ventricular end-diastolic, followed in 2 weeks by an elevation in left ventricular end-diastolic, filling pressure. The changes in the left heart followed the appearance of ascites. In the animals unsuccessfully operated upon (lower curve in figure 1) the end-diastolic pressures on the right side remain only moderately elevated and the pressures on the left side remain normal. Some of these later animals had transient ascites. Simultaneous left and right ventricular pulse tracings for a control dog and for 1 whose congestive heart failure was due to TI/PS are shown in figure 2.

The net body weight, amount of ascites, cardiac index, coronary flow, and oxygen usage by the myocardium for the 2 control and 2 experimental groups are shown in table 1. Both the animals with inferior vena cava ligation and those with tricuspid insufficiency showed a below-normal reduction in cardiac output, whereas those with left heart disease showed an increase in cardiac output. Coronary flow was not significantly changed from normal in any of the groups, and the oxygen usage by the myocardium was likewise within normal limits.

The evidence for congestive heart failure in these animals may be seen by examining table 2 in which the atrial and ventricular pressures are reported. Both the normal control animals and those with inferior vena cava ligation controls showed essentially normal pressures in both chambers of the heart and no evidence of regurgitation into the right atrium. The animals with tricuspid insufficiency and pulmonary stenosis had a moderate right ventricular systolic hypertension (44 mm. vs. 30 mm. for the normal) and markedly elevated end-diastolic filling pressures. Regurgitation into the right atrium was marked in these animals, with the atrial systolic pressure reaching an average of 30 mm. of Hg. The left ventricle of these animals was also failing, indicated by the elevation of end-diastolic pressures in that chamber. In the 2 animals with left heart disease, there was evidence for left ventricular failure in terms of a marked elevated end-diastolic filling pressure. Some elevation of filling pressure was also noted in the right ventricle.

**Physiochemical Studies**

Results of the physiochemical studies are shown in figures 3, 4, 5, and 6, and are summarized in table 3. The data in figure 3 show the dependence of sedimentation constant (upon concentration) for myosin isolated from the control dogs (normal and ICL) and from those with congestive heart failure. The $s^2_{20,w}$ for the control animals was 6.16 ± 0.13 and for the animals in failure was 6.50 ± 0.01, a difference that is on the borderline of significance ($p = 0.05 > 0.01$). The concentration dependence of $s_{20,w}$ is linear. The slopes of the sedimentation curves from normal and failing myosin are significantly

### Table 1

**Hemodynamic Findings in Control and Experimental Dogs**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>Body* weight Kg.</th>
<th>Ascites L.</th>
<th>Cardiac index L./min./M.²</th>
<th>Coronary flow Ml/100 Gm./min.</th>
<th>Oxygen usage Ml/100 Gm./min.</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>12</td>
<td>±1.1</td>
<td>—</td>
<td>±0.18</td>
<td>±6</td>
<td>±1.0</td>
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<tr>
<td></td>
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<td>16.9</td>
<td>7.0</td>
<td>1.68</td>
<td>115</td>
<td>12.3</td>
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<tr>
<td>ICL</td>
<td>5</td>
<td>±1.8</td>
<td>±2.0</td>
<td>±0.12</td>
<td>±12</td>
<td>±1.1</td>
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<td></td>
<td></td>
<td>18.8</td>
<td>6.0</td>
<td>1.89</td>
<td>75</td>
<td>10.0</td>
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<tr>
<td>TI/PS (CHF)</td>
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<td>±1.1</td>
<td>±1.4</td>
<td>±0.24</td>
<td>±9</td>
<td>±1.0</td>
</tr>
<tr>
<td>MI/AI or AS (CHF)</td>
<td>2</td>
<td>21.3</td>
<td>—</td>
<td>3.36</td>
<td>119</td>
<td>14.5</td>
</tr>
</tbody>
</table>

*Ascites-free
different. The calculated slope for the normal control group was $-3.10 \pm 0.16$, whereas for the dogs with heart failure it was $-6.66 \pm 0.84$ ($p = < 0.01$). The diffusion measurements for normal cardiac myosin and myosin isolated from dogs with heart failure are shown in figure 4. The concentration dependence of $D_{20,w}$ was more marked with normal cardiac myosin than with myosin from the failing heart. On extrapolation to zero protein concentration the value for $D_{20,w}$ for the normal dogs was found to be $2.46 \times 10^{-7}$ cm$^2$/sec., whereas that for the dogs with heart failure was $0.82 \times 10^{-7}$ cm$^2$/sec. The molecular weight calculated for normal cardiac myosin from sedimentation constant, diffusion constant, and partial specific volume was 226,000; for myosin from the failing heart it was 680,000.

In figure 5 are plotted the turbidities uncorrected for dissymmetry at 90 degrees against protein concentration obtained in the light-scattering experiments for myosin from normal and failing hearts. The zero intercept of $H \times c$ is proportional to the reciprocal of the molecular weight. After applying correction factors for dissymmetry to the respective intercepts, the molecular weight for normal cardiac myosin was found to be 270,000, whereas that for failing cardiac myosin was 760,000.

The changes in intrinsic viscosity are presented in figure 6. The shape of the plots

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*Sedimentation constants of dog heart myosin as a function of concentration. The panel on the left shows the values for control animals. The open circles are animals with ascites resulting from inferior vena cava ligation. The panel on the right shows the values for animals with congestive heart failure. The solid circles are from animals with primary right heart failure and the open circles are from animals with primary left heart failure. Conditions: 56,100 rpm; temperature 4 C.; 0.6 M KCl; pH 6.8.*
(1/\ln \eta/\eta_0 \text{ vs. concentration}) are markedly different for the 2 proteins. Normal cardiac myosin appears to disaggregate in very dilute solution and extrapolates to a limiting value of 50 c.g.s. units. On the other hand, myosin isolated from the failing heart shows a reciprocal behavior and appears to undergo aggregation in dilute solution to a high limiting viscosity number of 363 c.g.s. units. This behavior has also been noted by Davis et al.\textsuperscript{18}

The ATPase activity of the myosins from normal and failing heart muscle were not significantly different. The value for normal myosin was 382 ± 68 microliters P/mg./hr. vs. 424 ± 112 for the myosin from the failing heart.

From analyses carried out thus far, it would appear that the amino acid composition of myosin from normal heart, failing heart, and rabbit skeletal muscle are essentially indistinguishable on the basis of moles/100,000 Gm. protein. Representative data are shown in table 4. These data strongly suggest that the changes in molecular weight and other properties noted among the myosins represent changes in secondary and tertiary structure.

Discussion

The studies demonstrated conclusively that generalized cardiac failure can be induced in the dog by surgical production of tricuspid insufficiency and pulmonic stenosis. Elevation of end-diastolic filling pressures in the left heart as well as the right heart were noted in most of the dogs that have developed heart failure in our laboratory and all of these ani-
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Figure 5
Light-scattering measurements on dog heart myosin as a function of concentration. The values in the left panel were obtained on preparations from control animals. The values in the right panel were obtained on preparations from animals with congestive heart failure. Conditions: temperature 12 to 15 C.; 0.6M KCl; pH 7.2.

mals selected for the study of cardiac myosin from the failing heart. This finding supports the studies of Barger, Roe, and Richardson of heart-lung preparations made from hearts obtained from animals whose clinical cardiac failure was due to TI/PS. They observed that such hearts failed quickly in vitro in a Starling heart-lung circuit. Not only were the hearts unable to maintain normal output when the right atrial venous supply was increased, but also they were unable to maintain a normal output when the "Starling resistance" was increased. These authors concluded that "On the basis of two experiments, it would appear that as in cardiac failure in the human, the involvement of one chamber may predominate early in the disease, but with the progression of the disease decompensation of both chambers becomes apparent."

Our studies are in contrast to those of Davis et al. in which the surgical production of tricuspid insufficiency and pulmonic stenosis lead to an elevation of right ventricular, but not left ventricular, end-diastolic pressures. These workers concluded that they had isolated right ventricular failure in their preparations. We can only conclude that the preparation they obtained was somewhat different from ours. They report that right ventricular systolic pressures were rarely increased in their animals, whereas these pressures were uniformly increased in ours. It is conceivable that the valvular dis-
ease was more severe in our animals with extension of the defect in contractility to the opposite side, a phenomenon frequently seen in man21 and expected on the basis of the anatomy of the heart.22

The molecular weight of normal canine cardiac myosin appears to be about 226,000 from data based on 3 independent methods carried out in our laboratory.6 The value obtained from light-scattering is slightly higher (270,000), but this is typical of a technic that estimates weight-average rather than number-average molecular weight. On the other hand, the molecular weight obtained from studies of myosin from the failing heart is 690,000 from D, s, and v and 760,000 from light-scattering measurements. The ratio of corresponding molecular weights for normal and failing myosin is 1:3. Since the amino acid composition is essentially identical it appears that the myosin from the failing heart is a trimer of that from the normal heart. If we designate normal cardiac myosin as myosin C (for cardiac) and myosin from the failing heart as myosin F (for failure), the transformation may be summarized as follows:

3 myosin C→myosin F
The stimulus for this transformation seems to be chronic stretch. It may be that distortion of the myosin rodlet (thick filaments) in the chronically stretched myofibril may be instrumental in stimulating mild denaturation of normal myosin, which, in turn, results in polymerization. Since the ATPase activity of myosin F is not altered, the association apparently does not involve the active site of this enzyme. Evidence for alteration in the myosin filaments in the failing heart are now being sought in our laboratory by electron microscopy.

It seems clear that the change observed represents an acquired molecular disorder that may account for the decrease in contractility of the failing heart. The phenomenon of polymerization of myosin has been observed to occur in vitro23 during denaturation. The myosin of rabbit skeletal muscle may, furthermore, represent a polymer of a monomer of approximately the size of normal cardiac myosin. Kielley and Harrington24 found that guanidine salts will depolymerize rabbit skeletal myosin to a monomer of molecular weight 219,000.

Benson25 studied the effect of heart failure in dogs with tricuspid insufficiency and pulmonary stenosis upon the properties of actomyosin. The animals with experimental heart failure possessed a cardiac myosin with reduced ATP sensitivity, that is, a reduced change in the specific viscosity of actomyosin after addition of ATP. These investigators also found that the cardiac myosin peak from experimental dogs seemed to be more prominent in velocity sedimentation studies of actomyosin than in normals. They suggested that the combination of actin with myosin was less stable in the experimental dogs as compared with the controls.

Davis and his group26 attempted to verify these findings but were unable to; they observed no difference in the ATP sensitivity

Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>No.</th>
<th>Syst.</th>
<th>Mean</th>
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<tr>
<td>Normal</td>
<td>12</td>
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<td>±0.7</td>
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<tr>
<td>ICL</td>
<td>5</td>
<td>±0.4</td>
<td>±1.1</td>
</tr>
<tr>
<td>TI/PS (CHF)</td>
<td>11</td>
<td>±3.4</td>
<td>±0.1</td>
</tr>
<tr>
<td>MI/AI or AS (CHF)</td>
<td>2</td>
<td>6.5</td>
<td>5.0</td>
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<table>
<thead>
<tr>
<th>Right atrial pressure (mm. Hg)</th>
<th>Ventricular pressures (mm. Hg)</th>
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</thead>
<tbody>
<tr>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>29.4</td>
<td>2.1</td>
</tr>
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<td>32.0</td>
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<tr>
<td>44.2</td>
<td>13.6</td>
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<td>38.0</td>
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Circulation, Volume XXIV, August 1961
of actomyosin from normal heart muscle and heart muscle obtained from dogs with right heart failure resulting from tricuspid insufficiency and pulmonic stenosis. They did observe, however, that certain preparations of actomyosin from the failing right ventricle heart muscle did show a slow component (probably myosin) present in the sedimentation pattern that was not present in controls. In other words, the behavior of actomyosin from the failing heart was not identical with that from normals. Nevertheless, these investigators concluded that "these data do not support the concept that the contractile proteins are altered in experimental heart failure."

With regard to the work on actomyosin, it is probable that actomyosin formed during extraction of cardiac muscle by saline phosphate solution is a physiologic artifact. The electron microscopic studies of intact muscle fibers\(^8\) suggest that actin and myosin are segregated in a particulate structure involving the thick and thin filaments in the living cell.\(^8\) They appear to make contact only in a highly oriented manner during the contractile cycle. For this reason the studies of actomyosin, although controversial as noted, probably are not too informative about the state of the contractile proteins in the intact heart.

In the study reported more recently,\(^18\) Davis and his co-workers undertook the characterization of cardiac myosin from normal dogs and from dogs with chronic congestive heart failure caused by tricuspid insufficiency and pulmonic stenosis. Their basic data are in fairly good agreement with ours as reported
above. They employed a narrower range of physicochemical methods to characterize the myosins, from normal and failing heart muscle than have been employed in the present study. For example, they did not carry out equilibrium sedimentation or light-scattering measurements on their preparations. Davis and co-workers did measure sedimentation coefficients over a reasonable range of concentration and their $s_{20,w}$ intercepts are in reasonable agreement with ours. We find a higher mean slope with the preparations from the failing heart, although the scatter is greater than with the normals. It is to be noted, however, that the sedimentation behavior is a relatively insensitive parameter for distinguishing normal and failing myosin because the sedimentation behavior is relatively unaffected by end-to-end aggregation.

Davis et al. admit, furthermore, the presence of impurities in some of their preparations stating that "in a few instances a very small boundary which sedimented faster than the principal myosin component was observed." If this is true, other impurities not distinguishable from the main peak, which could have modified sedimentation behavior at higher concentrations of the preparations from the failing heart, could have been present. 29

The measurements of the diffusion con-

stant by Davis et al. were not carried out over a sufficient range of concentration to detect the concentration dependence in very dilute solution. 6

The changes in intrinsic viscosity observed and described by us were also observed by Davis and co-workers. They were particularly notable in observations made by them on myosin from right ventricular tissue from dogs in congestive heart failure. An elevated intrinsic viscosity was consistently found. In a few preparations a high intercept was noted for the normals, although this was not as frequent nor as marked as in the animals with failure. Davis and co-workers choose to ignore these viscosity findings, which are in good agreement with ours, and concluded that their viscosity measurements were unreliable. "The possibility must be considered," Davis states, "that viscosity measurements at very low concentrations do not represent the true viscosity of the solution." The fact that their viscosity measurements were carried out at room temperature rather than at 1 C. makes it likely that denaturation of their normal preparation would occur with a higher frequency, which could account for the occasional higher intercepts noted in control preparations.

Without the additional support of measurements of light-scattering and equilibrium sedimentation behavior of these myosins, Davis et al. drew the conclusion that the molecular weight of cardiac myosin was in the range of $5 \times 10^5$ and that there were no

Table 3

<table>
<thead>
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<th>Constants</th>
<th>Cardiac Myosin</th>
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<tr>
<td></td>
<td>Normal</td>
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<tr>
<td>$s_{20,w}$</td>
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</tr>
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<td>$d_s/dc$ (weight %)</td>
<td>-3.10</td>
</tr>
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<td>$\bar{V}$</td>
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<td>$[\eta]$ (c.g.s. units)</td>
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<tr>
<td>$t/fo$</td>
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<td>ATPase ($\mu$L.P./mg./hr.)</td>
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Table 4

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<th>Rabbit skeletal muscle</th>
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<td>Kominz, 1945</td>
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<td>Aspartic</td>
<td>83</td>
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differences between the normal and failing heart. We do not believe these conclusions are tenable in view of Davis’s own data and particularly in view of the extensive work reported in this communication.

Whether or not there are differences in the animal preparations must be considered. Davis’s animals were sacrificed without the benefit of an open chest and artificial respiration. Whether or not the degree of failure is different in the 2 groups of animals as evidenced by the apparently normal end-diastolic filling pressures on the right side in the Davis series can be resolved only by further experimentation. It is hoped that some reconciliation of these differences will be ultimately effected.

With regard to the question of generalized cardiac failure in dogs with TI/PS valvular disease, Benson30 found that in vitro contractility of glycerol-extracted muscle strips from both the right and left ventricles of dogs with heart failure resulting from TI and PS was markedly reduced, as a depressed ventricular function curve similar to that observed in vivo could be constructed from the data. Since glycerol-extracted muscle retains little else than the basic contractile system and responsiveness to ATP, it seems reasonable to assume that the defective contractility observed by Benson and co-workers must be due to altered contractile proteins. Kako and Bing31 observed a similar decrease in contractility of actomyosin bands prepared from failing human heart muscle post mortem when compared with control preparations.

It appears from these studies and ours reported herein that cardiac myosin is altered in physicochemical properties in association with congestive heart failure in the dog. The extent to which this is etiologic is not at this moment determined. Also, the extent to which this system is a model for the human with valvular disease is an interesting subject for speculation.

Acknowledgment

The authors are indebted to Drs. Dorothy Piatnek and Maria Liang for the hemodynamic measurements; to Drs. Albert Marranoni and Robert Pontius for performance of the surgical procedures; and to Mrs. Virginia Bartlebaugh for assistance in other laboratory procedures.

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Circulation, Volume XXIV, August 1961
Cardiac Myosin and Congestive Heart Failure in the Dog
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*Circulation*. 1961;24:471-482
doi: 10.1161/01.CIR.24.2.471
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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