Physiologic Changes during Chronic Congestive Heart Failure in Dogs with Tricuspid Insufficiency and Pulmonic Stenosis

By NICHOLAS A. YANKOPOULOS, M.D., JAMES O. DAVIS, PH.D., M.D., JAMES A. McFARLAND, M.D., AND JOHN HOLMAN, V.D.M.

With the surgical assistance of Alfred Casper

Chronic congestive heart failure was studied in dogs with surgically-produced tricuspid insufficiency and pulmonic stenosis. Ascites formed in association with an elevation in mean right atrial pressure. The volume of ascitic fluid and the rate of urinary sodium excretion varied greatly in individual dogs during the course of congestive failure and among the different animals. Sodium retention was most common but periods of sodium balance and natriuresis occurred. Comparative data on the right and left ventricles were obtained from determinations of intracardiac pressures, measurements of ventricular muscle mass at the time of sacrifice and studies of the lungs for evidence of chronic passive congestion. There was significant right ventricular hypertrophy but no evidence of left ventricular hypertrophy or failure.

In recent years efforts have been made to define the myocardial changes in experimental heart failure on a biochemical basis.1-4 Before the biochemical changes in the heart can be adequately evaluated in experimental congestive failure, the physiologic changes at an organismal level must be understood. This study on the pathologic physiology of experimental heart failure was undertaken to aid in the interpretation of data on the contractile proteins from the myocardium of dogs with congestive failure produced by the combined lesions of tricuspid insufficiency and pulmonic stenosis.4 This experimental preparation was developed by Barger and co-workers5 who elucidated many aspects of the pathologic physiology. However, available data on left ventricular function and on chronic daily sodium excretion have been inadequate. In this study, evidence of the functional and pathologic changes in both right and left ventricles was obtained from observations of intracardiac pressures, ventricular muscle mass and lung pathology. For comparison, heart weights were obtained from 5 dogs with ascites secondary to constriction of the thoracic inferior vena cava.6 Also, additional observations on left ventricular end-diastolic pressure were made in 7 dogs with right-sided heart failure produced by progressive pulmonic stenosis.7

Methods

Studies were conducted on 15 normal dogs and 16 dogs with experimental congestive heart failure. Heart failure was produced by essentially the same technique that Barger used. Tricuspid insufficiency was produced surgically by cutting the chordae tendineae of the tricuspid valve. During a second operation, a Nylon ligature was loosely placed around the pulmonary artery and, at a later date, progressively tightened under local anesthesia at 1 to 2 week intervals7 until signs of congestive failure appeared.

All animals were trained mongrel dogs weighing 16 to 23 Kg. The dogs in congestive heart failure were kept in metabolism cages and fed a synthetic diet containing 60 mEq. of Na, 18 mEq. of potassium (K) and 9 Gm. of protein nitrogen per day except for the dogs with progressive pulmonic stenosis. Occasionally, Na, K and nitrogen intake was limited by reducing the diet to 1/4 of the daily ration but all balance measurements were made during the described intake.

The amount of ascites during the course of con-
Experimental Chronic Congestive Heart Failure

Congestive heart failure was estimated visually as minimal, moderate or massive, or actually measured at the time of sacrifice. When in doubt during the course of the study, the presence of ascites was checked by paracentesis needle but fluid was never removed. Sodium was measured by flame photometry. Right atrial mean pressure (RAP) and right ventricular systolic and mean pressures were measured through a plastic catheter which was inserted via the femoral vein. Left ventricular mean and left ventricular end-diastolic pressures were measured by direct puncture through the chest wall. All pressures were determined in unanesthetized animals using Statham strain gages with a Sanborn recording system and referred to a level 6 cm. above the table surface. Heart and lung weights were determined at sacrifice. After weighing the entire heart (without pericardium), the atria and visible fat were removed and the ventricles were separated into right and left ventricular walls and septum. The separate weights were referred to body weight before production of the valvular lesions (initial body weight) and to body weight minus ascitic fluid weight at sacrifice (final ascites-free body weight). The lungs of 5 dogs were examined histologically for evidence of chronic passive congestion.

RESULTS

Course and Extent of Ascites. The syndrome of congestive heart failure as evidenced by ascites formation, a high RAP, peripheral venous engorgement, pulsating external jugular veins and hepatomegaly was produced in all dogs with experimental lesions. Of the 16 dogs with tricuspid insufficiency, 2 did not require pulmonary artery constriction in order to develop and maintain ascites. Therefore, these animals were studied without further surgery. Seven dogs formed ascites after the very slight constriction produced by the padding around the pulmonary artery; of these animals, the ligature was constricted in 2 dogs either because ascites disappeared early or in an attempt to increase the amount of ascitic fluid. In the remaining 7 animals, the pulmonary artery was constricted by 1 to 4 tightenings of the ligature until signs of congestive failure occurred.

The average duration of ascites was 2½ months with a range from ½ to 6½ months (table 1). All but 5 dogs (no. 2, 4, 10, 11, 12) were sacrificed; these 5 animals died in severe congestive failure. During the course of chronic congestive failure, the extent of ascites varied greatly among the animals. Although the volume of ascitic fluid was relatively stable in many animals, in others it increased until massive quantities of fluid were present while in other dogs ascites decreased. Neither of the animals with tricuspid insufficiency alone developed massive ascites and in one of them ascites disappeared after 2½ months.

Urinary Sodium Excretion during the Course of Congestive Failure. The daily urinary excretion of Na for 8 dogs is presented in figure 1. In the presence of ascites, sodium excretion was most often low (values below about 40 mEq./day), but occasionally sodium balance was present (values near 50 to 60 mEq./day); less frequently, a negative Na balance was observed.

Intracardiac Pressures. The onset of ascites was associated with an elevation in RAP (fig. 2). After tricuspid insufficiency alone, RAP increased from an average control value of 55 mm. of water to 120 mm. of water. A further increase in RAP was achieved by the addition of pulmonary stenosis (increment of 110 to 120 mm. water) and was associated with the onset of ascites. The dogs with less variation in the volume of ascites had more stable RAP's. A progressive elevation of RAP occurred in a number of dogs and was associated with a further increase in ascites. In 1 animal, ascites disappeared; the RAP associated with the loss of ascitic fluid was higher than the venous pressure present at the onset of ascites. This finding may indicate the development of resistance to ascites formation. It has been suggested that increased resistance to fluid filtration from the liver capsule may result from chronic thickening of the capsule.8

The measurements of right ventricular systolic pressure have the limitation that they were made with a pliable plastic catheter. Right ventricular systolic pressure was not detectably increased in the majority of dogs and no alteration occurred during the course
of congestive failure. A slight elevation in right ventricular mean pressure was frequently present and about half the animals showed a further increase during the study. This increase in right ventricular mean pressure may reflect an undetectable elevation in right ventricular systolic pressure and an increase in filling pressure of the right ventricle.

Measurements of left ventricular end-diastolic pressure (fig. 3) and left ventricular mean pressure showed no change. For comparison, left ventricular end-diastolic pressure was measured in 7 dogs before and after production of right-sided heart failure by progressive pulmonic stenosis—no change occurred.

**Autopsy Data on the Heart and Lungs.** At sacrifice, all 3 cusps of the tricuspid valve were usually found injured; 70 to 80 per cent of the chordae tendineae were cut. There was no evidence of erosion by the pulmonary artery ligature into the vessel lumen. The diameter of the lumen of the constricted area ranged from 10 to 18 mm.

The average normal heart weighed 8.20 ± 1.11 Gm./Kg. body weight (table 1) whereas the average heart weight for dogs with tricuspid insufficiency and pulmonic stenosis was 8.59 ± 2.04 Gm./Kg. initial body weight. The increase was not statistically significant. When the walls of the ventricles were weighed separately, the average weight of the normal right ventricle was 1.62 ± 0.23 Gm./Kg.; the average weight of the right ventricle of dogs with tricuspid insufficiency and pulmonic stenosis was 2.17 ± 0.63 Gm./Kg. initial body weight. The increase was significant (p < 0.01).

The necessity of body weight as a reference can be eliminated by use of the ratio of right ventricular weight to left ventricular weight (RV/LV). For normal dogs the ratio RV/LV was 0.510 ± 0.046 in comparison with 0.915 ± 0.137 for dogs with congestive failure (table 1). The difference was highly significant (p < .001).

**FIG. 1** Top. Urinary Na excretion in the presence of ascites during the course of chronic congestive failure in dogs with tricuspid insufficiency and pulmonic stenosis. Dog no. 5 had ascites secondary to tricuspid insufficiency alone. Large black squares, variation in urinary Na excretion in a dog with massive ascites for 6½ months.

**FIG. 2** Middle. Mean right atrial pressure during the control period, after tricuspid insufficiency alone (T.I.) and during the course of ascites secondary to T.I. (dogs 5 and 10) or to T.I. and pulmonic stenosis (P.S.) in all other animals. Symbols as in figure 1.

**FIG. 3** Bottom. Left ventricular end-diastolic pressure before and during congestive heart failure produced by tricuspid insufficiency and pulmonic stenosis. The necessity of body weight as a reference can be eliminated by use of the ratio of right ventricular weight to left ventricular weight (RV/LV). For normal dogs the ratio RV/LV was 0.510 ± 0.046 in comparison with 0.915 ± 0.137 for dogs with congestive failure (table 1). The difference was highly significant (p < .001).

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**FIG. 3** Bottom. Left ventricular end-diastolic pressure before and during congestive heart failure produced by tricuspid insufficiency and pulmonic stenosis.
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<th>Initial B. W. (Kg.)</th>
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<th>RV weight—LV (Gm./Kg.)</th>
<th>RV weight—final (Gm./Kg.)</th>
<th>LV weight—final (Gm./Kg.)</th>
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<th>Lung weight—initial B. W. ratio (Gm./Kg.)</th>
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*Abbreviations: B.W., body weight; RV, right ventricular; LV, left ventricular; N, number of dogs; S.D., standard deviation.
†Calculated by subtracting the weight of the ascitic fluid removed at sacrifice from the final body weight. Therefore, these values are only approximate.
‡In the Fisher test for significance, comparison is with the equivalent parameter of the normal dogs. Since for normal dogs there is no final ascites-free body weight, the initial body weight is used for comparison.
There was a significant decrease below normal in left ventricular weight per kilogram initial body weight (p < .01) in dogs with tricuspid insufficiency and pulmonic stenosis. It has been shown that starvation in dogs results in almost as great a decrease in heart weight as the decrease in body weight. In order to determine if the decrease in heart weight could be explained on the basis of loss of body weight from protein depletion, the left ventricular heart weight was referred to final ascites-free body weight as an approximation of edema-free body weight; the p value remained < .01. This suggests atrophy in excess of what can be accounted for by protein depletion.

The heart weights of dogs with ascites secondary to thoracic inferior vena cava constriction are of interest. These animals also become protein depleted and the metabolism of salt and water is very similar to that of dogs with congestive failure. The average weight of the right ventricle of the dogs with caval constriction was 0.82 ± 0.08 Gm./Kg. initial body weight (table 1). This was significantly less (p < .001) than the normal right ventricular weight and was also less (p < .05) when calculated on the basis of final ascites-free body weight. Similar changes were found in the left ventricle. The data, therefore, demonstrate atrophy of both ventricles in dogs with thoracic inferior vena cava constriction, possibly to a greater extent than can be accounted for by protein depletion. This finding may be a reflection of decreased work load on the heart in some animals. The atrophy was more marked in the right ventricle (p < .05 for the RV/LV ratio).

The lung weights were not different in normal dogs and dogs with tricuspid insufficiency and pulmonic stenosis (p > .8, table 1). Histologic sections of lungs stained with hematoxylin and eosin and Van Gieson stain showed no chronic passive congestion in the 5 dogs studied.

**DISCUSSION**

These results confirm the previous observations of Barger that chronic congestive failure with ascites is produced by tricuspid insufficiency and pulmonic stenosis. With this technique of progressive pulmonic stenosis, a very high yield of successful experimental preparations was obtained. These animals differ from those with progressive pulmonic stenosis and functional tricuspid insufficiency which in 1 to 3 weeks progressively develop severe failure or undergo cardiac compensation and diuresis. Apparently, removal of the tricuspid valve facilitates the retrograde escape of blood when the right ventricle contracts so that the ventricle contracts against less resistance; the backflow of blood contributes to the increase in central venous pressure. It appears, therefore, that the work load on the right ventricle is less in animals with marked surgically-produced tricuspid insufficiency than in dogs with cardiac failure produced by progressive pulmonic stenosis. This interpretation is supported by the finding of a relatively small increase in right ventricular mean pressure in these dogs with surgically-produced tricuspid insufficiency. There was, however, enough strain on the right ventricle to produce marked hypertrophy. The degree of constriction of the pulmonary artery was less in the present dogs with tricuspid insufficiency and pulmonic stenosis than in dogs with heart failure secondary to progressive pulmonic stenosis.

In studies of dogs with congestive heart failure from tricuspid insufficiency and pulmonic stenosis, Barger et al. provided evidence of a decrease in the Starling curve of the right ventricle in the open chest dog, but the data on left ventricular function were inconclusive. In the present study there was no evidence of failure of the left ventricle in dogs with tricuspid insufficiency and pulmonic stenosis. Left ventricular end-diastolic pressure was not elevated and there was no left ventricular hypertrophy. The lungs did not show chronic passive congestion histologically and the weight of the lungs was not increased. Since there is evidence for impairment of function of the right ventricle only, the findings of Benson et al. of decreased isometric tension developed by gly-
cerol-extracted myocardial fibers and of changes in the actomyosin from both left and right ventricles\(^8\) may be a reflection of factors other than ventricular muscle hypertrophy or ventricular failure per se.

It is interesting that there are times in the course of chronic congestive heart failure during which the dogs were not retaining Na. A dog in congestive heart failure obviously cannot retain Na indefinitely. There must be sufficient space into which to extravasate the retained salt and water. When fluid no longer escapes (mostly from the liver in dogs), salt retention ceases. This was demonstrated by placing a plaster body cast around the trunk of a dog with ascites secondary to thoracic inferior vena cava constriction; urinary aldosterone fell and a natriuresis ensued.\(^11\) If one may generalize from these observations in the dog, patients with congestive heart failure and edema may at times have normal urinary Na excretion. This may be the explanation for the normal urinary Na and aldosterone excretion found in 4 patients with chronic edema by Muller.\(^12\)

**SUMMARY**

The extent and duration of ascites, urinary Na excretion and functional and pathologic changes in the ventricles of the heart were evaluated in dogs with congestive failure secondary to tricuspid insufficiency and pulmonic stenosis. Of 16 dogs with surgically-produced tricuspid insufficiency, 2 formed chronic ascites after this operation alone; all others required some degree of pulmonic artery constriction. Ascites formed in association with a rise in right atrial mean pressure of 110 to 120 mm. of water and was present throughout the course in all but 2 dogs. The volume of ascitic fluid varied greatly among the animals. On a constant Na intake, daily urinary Na excretion varied markedly; there were periods of marked Na retention, Na balance and natriuresis.

There was marked right ventricular hypertrophy demonstrated by a significant increase in right ventricular weight. In contrast, there was no evidence for left ventricular hypertrophy or failure. The left ventricular mean and left ventricular end-diastolic pressures were unchanged; the latter parameter was also measured in 7 dogs with congestive failure produced by progressive pulmonic stenosis without surgical tricuspid insufficiency and found unaltered.

Measurements of left ventricular weight showed a decrease in ventricular mass; in 5 dogs with ascites produced by thoracic inferior vena cava constriction, there was evidence for both left and right ventricular atrophy. Protein depletion accounted for much, but perhaps not all, of this decrease in ventricular muscle mass. Lung weights and lung histology of material from dogs with tricuspid insufficiency and pulmonic stenosis were normal.

**ACKNOWLEDGMENTS**

We are indebted to Dr. Robert Bühn for the histologic observations and to Harry Marshall for able technical assistance.

**SUMMARIO IN INTERLINGUA**

Esseva evolutate le extension e le duration de ascites, de excretion urinari de natrium, e de alterationes functional e pathologic occurrente in le ventriculos del corde de canes con disfallimento congestive secundari a insufficienctia tricuspidie e stenosis pulmonic. Inter 16 canes con insufficiencia tricuspidie de production chirurgie, 2 formava ascites chronic post iste operation sol. Omne le alteres requireva un certe grado de constriccion pulmono-arterial. Ascites se formava in association con un augmento del tension dextero-atrial medie de 110 a 120 mm de aqua e esseva presente usque al fin del curso experimental in omne le canes con 2 exceptiones. Le volumine del liquido ascite variava grandemente inter le animalis, in le presentia de un constante ingestion de natrium, le diurne excretion urinari de natrium variava marcamente. Esseva noteate periodos de marcate retention de natrium, de balancia de natrium, e de natriurese.

Grados marcate de hypertrophia dextero-ventricular esseva demonstrate per un augmento significative in le peso ventriculo dext-
tere. Per contrasto con isto, nulle signo de hypertrophia o de disfallimento sinistro-ventricolare eseva constata. Le tensiones sinistro-ventricolare media e sinistro-ventricolare termino-diastolic monstrava nulle alteration. Le secunde de iste magnitudes eseva etiam mesurate in 7 canes con congestive disfallimento cardiaco producite per progressive stenosis pulmonic sin chirurgic insufficentia tricuspid. Etiam in iste casos illo manifestava nulle alteration.

Mesurationes del pesos sinistro-ventricolare revelava un reduction del massa ventricolare. In 5 canes con ascites produceite per constriction de vena cave infero-thoracic, indicios de atrophia tanto sinistro- como etiam dextero-ventricolare eseva notate. Depletion proteomic eseva responsabile pro un grande parte—ben que probabilmente non le integritate—de iste reduction in le massa del musculo ventricolare.

Le pesos del pulmones e le histologia pulmonar in canes con insufficientia tricuspid e stenosis pulmonic eseva normal.

REFERENCES
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