The Renin-Angiotensin-Aldosterone System in Rabbits with Congestive Heart Failure Produced by Aortic Constriction

Brian J. Morris, James O. Davis, Marvin L. Zatzman, and Gary M. Williams

SUMMARY Severe constriction of the suprarenal abdominal aorta of 3-kg rabbits to 3.7 ± 0.2 mm² and maintenance of a daily sodium intake of 10 mEq by infusion of 0.9% sodium chloride resulted in a progressive increase in central ear arterial pressure to 106 ± 3 (SEM) mm Hg (control = 79 ± 1). This was accompanied by a progressive increase in left ventricular end-diastolic pressure to 22 ± 2 mm Hg (control = 3 ± 1), plasma renin activity to 21 ± 5 ng of angiotensin/hour per ml (control = 5 ± 1), plasma aldosterone concentration to 99 ± 23 pg/ml (control = 14 ± 4), and plasma sodium concentration to 142 ± 1 mEq/liter (control = 136 ± 1). Urinary excretion of sodium decreased to 3.9 ± 0.7 mEq/day and marked fluid retention occurred. We also found that these changes were accompanied by a decrease in hematocrit to 24 ± 2% (control = 40 ± 1), the formation of 36 ± 9 ml of fluid in the thoracic cavity, 33 ± 9 ml of ascites, pulmonary congestion and edema, hepatic congestion, and enlargement and hypertrophy of both the left and right ventricles. All rabbits died of ventricular failure at a time that was partly related to the degree of aortic constriction and that ranged from 2 to 12 days. The model we have established is chronic, highly reproducible, easy to produce, and inexpensive, and resembles the clinical syndrome of right and left congestive heart failure in man. Furthermore, the studies provide evidence for an important role of the renin-angiotensin-aldosterone system in the fluid retention that leads to pulmonary and systemic venous congestion after suprarenal aortic constriction.

STUDIES of the mechanisms for experimental congestive heart failure require an animal model that is chronic, highly reproducible, inexpensive, and comparable to the clinical syndrome in man. Models resembling right1,2 and left3,4 congestive heart failure have been produced previously in this laboratory in the dog by constriction of the thoracic inferior vena cava,1 pulmonary artery stenosis,2 or an aortic left atrial shunt and aortic constriction.3,4 Constriction of the abdominal aorta of the rabbit has been reported to lead to congestive heart failure;5,6 however, little attention was given to the mechanisms for fluid retention that lead to pulmonary edema and heart failure. Therefore, in the present study the mechanisms of fluid retention in congestive heart failure were evaluated in the rabbit after constriction of the abdominal aorta and during maintenance of daily sodium intake by infusion of 0.9% sodium chloride. In attempting to define more completely the pathophysiology of the model, one of the primary aims of this study was to determine the role of the renin-angiotensin-aldosterone system, which has been found to be an important cause of fluid retention in experimental congestive heart failure.1,3 A secondary outcome of these studies was the establishment of a method for the consistent, reproducible production of experimental congestive heart failure that satisfies the criteria stated above; the present model might prove particularly useful in investigating the biochemical defect responsible for failure of the ventricular myocardium.

Methods

Forty-two male New Zealand white rabbits weighing 2.9–3.3 kg (mean = 3.02 ± 0.02) were used. The diet was Purina rabbit chow (120 mEq of sodium/kg of chow) and water was provided ad libitum. The rabbits were housed in a room at 20–22°C and allowed to adjust to their surroundings for at least 5 days before being placed in metabolism cages to monitor sodium balance. The rabbits were fed 80 g of chow (9.6 mEq of sodium) each day for 5–7 days before surgery, and urinary excretion of sodium and potassium was determined daily.

A central ear artery and marginal ear vein were cannulated with PE-50 tubing (Intramedic, polyethylene), and 5 ml of blood were withdrawn through the arterial catheter. The arterial catheter was connected to a Statham pressure transducer (P23Db) and a Hewlett-Packard recorder (model 7702B), and mean arterial pressure was monitored for 60 minutes while the rabbit was resting quietly and unrestrained in a black rabbit box. During this time 2 mg of dexamethasone 21-phosphate (Decadron; Merck Sharp and Dohme) in 5 ml of 0.9% sodium chloride were infused intravenously at a constant rate in groups I and II and then 12 ml of arterial blood were collected for measurement of renin, aldosterone, sodium, potassium, and hematocrit. The stress that accompanies sample collection in the rabbit almost invariably results in release of ACTH from the anterior pituitary; dexamethasone inhibits ACTH release and even at lower doses has been shown to suppress completely ACTH-induced production of aldosterone and other corticosteroids in the rabbit.8 Therefore, treatment with dexamethasone permits evaluation of non-ACTH influences on aldosterone production. After removal of plasma by centrifugation the red blood cells were resus-
pended gently in an equal volume of sterile 0.9% sodium chloride and rein infused intravenously. The rabbits were then infused with 65 ml of 0.9% sodium chloride (10 mEq of sodium), injected intramuscularly (im) with 10,000 IU of procaine penicillin, and returned to their metabolism cages; they were given no food, and surgery was performed 24–27 hours later.

Each rabbit was anesthetized with 2.5% sodium thiopental (Pentothal sodium; Abbott) injected intravenously. The left carotid artery was exposed and a catheter was passed into the left ventricle and exteriorized at the back of the neck. The construction of the catheter system used has been described in detail; the system had a Teflon tube connected to a 11-cm segment of Silastic tubing (0.51-mm inner diameter, 0.94-mm outer diameter) within the vessel. A transducer placed at the level of the left ventricle was connected daily to a sealing device at the back of the neck for subsequent measurements of left ventricular end-diastolic pressure. After laparotomy a Goldblatt clamp (internal width = 3 mm, length = 6 mm) was placed on the abdominal aorta just proximal to the renal arteries. The movable plate was screwed down until resistance was felt as opposite walls of the aorta were pressed together; the plate was then carefully unscrewed 1.5–1.7 turns. This reduced the area of cross section of the aorta to approximately 25% of its original size. The exact dimensions of the clamp were later measured with calipers at autopsy and the cross-sectional area was recorded in square millimeters. After surgery each rabbit was given an intravenous injection of penicillin and infused with 65 ml of 0.9% sodium chloride to maintain sodium balance; this procedure may have enhanced postoperative survival.

The rabbits were weighed each day and sodium balance was monitored by daily measurement of urine electrolytes. Since the rabbits ate less than 80 g of food during the 1st week after surgery, it was necessary to maintain a constant sodium intake of 10 mEq by infusion of an appropriate amount of 0.9% sodium chloride. Left ventricular end-diastolic pressure (LVEDP), mean ventricular pressure, ventricular systolic pressure, and heart rate were measured each morning. Every 2–3 days mean arterial pressure was recorded from the central ear artery for 60 minutes and blood was withdrawn for measurement of renin, aldosterone, sodium, potassium, and hematocrit using the protocol described above. Red blood cells were rein infused, followed by the appropriate volume of 0.9% sodium chloride. Each rabbit was given a daily intramuscular injection of penicillin, and body temperature was measured at intervals with a rectal probe. Autopsies were performed on all rabbits; the amounts of fluid in the thoracic and abdominal cavities were measured and the right ventricle, septum, left ventricle, lungs, liver, adrenals, and kidneys were weighed and placed in 16% formaldehyde solution. Histological examination was performed of lung and liver tissue sections stained with hemotoxylin and eosin, prepared by the Clinical Pathology Laboratory of the University Hospital.

The procedure described above was performed with 15 rabbits which were designated as group I. This protocol was also followed in a sham series of eight rabbits in which the Goldblatt clamp was not tightened (group II). Both group I and group II received daily sodium chloride infusions to maintain a constant sodium intake of 10 mEq/day. In an additional group of 19 rabbits (group III) the clamp was unscrewed 1.6–1.9 turns and the rabbits were not infused with 0.9% sodium chloride, therefore sodium intake was not maintained during the first few days after surgery; left ventricular pressures were not studied in this preliminary group. Normal tissue weights were ascertained for 10 rabbits (group IV).

Plasma renin activity (PRA) was determined by a previously described method. A 5-ml sample of blood was collected and placed in 0.1 ml of 10% (wt/vol) ethylenediaminetetraacetic acid (EDTA) on ice. The amount of angiotensin I formed during incubation of 2 ml of plasma for 90 minutes at 37°C and pH 5.3 in the presence of 0.25 mg of disopropyl fluorophosphate (DFP) was measured by the pressor response of the pentobarbital-anesthetized, pentolinium-blocked rat, with synthetic angiotensin II (Hypertensin, Ciba) as standard. PRA is expressed as nanograms of angiotensin generated in 1 hour per milliliter of plasma.

The concentration of aldosterone in peripheral plasma before and after infusion of dexamethasone was determined by an established radioimmunoassay procedure. A sample of 5 ml of blood was mixed with 0.1 ml of 10% (wt/vol) EDTA on ice; plasma was stored at −20°C and 2 ml were later used for assay. After an extraction step using methylene chloride, other steroids were separated by Celite partition chromatography and aldosterone was quantified by a radioimmunoassay employing [1,2-3H]aldosterone (New England Nuclear; specific activity = 30 Ci/mmol, determined by self-displacement analysis in this laboratory) as tracer, a 1:100,000 dilution of antiseraum (sheep 088, National Institute of Arthritis and Metabolic Diseases), and synthetic aldosterone (Ciba-Geigy) as standard.

The concentrations of sodium and potassium in urine and plasma were determined by flame photometry after collection of 1 ml of blood in 10 U of heparin. Hematocrit was determined by a microhematocrit method.

The concentration of renin substrate in plasma was determined by the amount of angiotensin I produced after complete enzymatic hydrolysis by rabbit renal renin. Plasma was treated and assayed according to the protocol for renin activity except that 0.2 ml of undialyzed plasma was incubated with 0.1 ml of a preparation of rabbit renal renin for 60 minutes in 2 ml of 20 mm sodium phosphate buffer, pH 5.3, containing EDTA and DFP.

Student's paired and nonpaired t-tests were used, where appropriate, in the statistical analysis and each result is expressed as the mean ± SEM.

Results

When the abdominal aorta of each of 15 rabbits was severely constricted by tightening a Goldblatt clamp on the vessel and then unscrewing the movable plate 1.5–1.7 turns, the cross-sectional area of the aorta was reduced to 3.2–4.5 mm² (mean = 3.67 ± 0.16). All of these rabbits (group I) recovered from surgery and were infused with...
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enough 0.9% sodium chloride daily to maintain a constant sodium intake of 10 mEq. Thirteen later died with pulmonary congestion and edema, eight between days 2 and 6, four between days 7 and 12, and one 23 days after constriction of the aorta (mean time of death = 8 ± 2 days); the other two rabbits died in convulsions on days 4 and 6 shortly after clots were flushed from a blocked cardiac catheter and were excluded from subsequent analysis of data from group I. There was a direct correlation between the survival time of the 13 rabbits and the area of cross section of the clamp (r = 0.542, P < 0.01). In contrast, the eight sham-operated rabbits (group II) had none of the changes that were evident in group I and were all normal in appearance at autopsy; five of the sham group were killed 8-27 days after surgery (mean = 19 ± 3 days), two others died on day 12 (one with a bowel obstruction and one with diarrhea), and the eighth died on day 3 from an undetermined cause. In the rabbits in group III the Goldblatt clamp was tightened and unscrewed 1.6-1.9 turns and sodium chloride was not infused after surgery. Of 19 rabbits, eight died overnight and were normal in appearance when autopsied (area of cross section of clamp = 3.1-4.0 mm²; mean = 3.51 ± 0.13) and nine recovered from surgery, returned to eating 80 g of food after 5-12 days, and were killed 8-29 days after surgery (mean = 18 ± 3 days) (clamp area = 2.8-4.9 mm²; mean = 3.73 ± 0.25). The cross-sectional area inside the clamp for group I rabbits was not significantly different from that for group III rabbits. Only two rabbits in group III died with pulmonary congestion and edema, one within a day after aortic constriction (clamp area = 2.8 mm²) and one after 3 days (clamp area = 3.3 mm²); the pathological changes in the two rabbits were similar to those seen in group I. These two rabbits and those that died overnight after surgery were not included in subsequent analysis of data from group III.

In group I, arterial pressure measured from a central ear artery increased from 79 ± 1 mm Hg the day before surgery to a peak of 106 ± 3 mm Hg after aortic constriction (P < 0.0005). The level of arterial pressure achieved was inversely correlated with the area of the aortic constriction (r = -0.651, P < 0.01). The individual responses in blood pressure of the 13 rabbits are shown in Figure 1. In three rabbits (nos. 1, 3, and 12) the last measurement of arterial pressure was made within a few hours before death and marked hypotension (55-64 mm Hg) was noted; this drop in arterial pressure probably reflects a drop in cardiac output from failure of the left ventricle. Daily measurements of LVEDP were made in 11 of the rabbits (Fig. 2). LVEDP increased progressively from 3.0 ± 0.6 mm Hg to a peak of 21.8 ± 1.5 mm Hg after aortic constriction, and in two rabbits (nos. 1 and 3) a further marked decrease in LVEDP was evident within a few hours before death. There was a significant correlation between maximum LVEDP and the degree of aortic constriction (r = 0.520, P < 0.05) and also between the values for arterial pressure and the LVEDP on the same day (r = 0.593, P < 0.001). Sham-operated rabbits (group II) showed no rise in arterial pressure or LVEDP (Table 1). The arterial pressure of rabbits with a constricted aorta but without daily sodium chloride infusions (group III) increased significantly and to a similar degree as the sodium chloride-infused rabbits (group I) (Table 1). However, within 2-3 days after surgery arterial pressure was 105 ± 3 mm Hg in group I compared to 94 ± 5 for group III (P < 0.05), indicating a more rapid rate of increase in arterial pressure in rabbits that died later with heart failure. No correlation was observed between the degree of aortic constriction and the level of arterial pressure attained in group III (r = -0.094, P < 0.1). LVEDP was not measured in these rabbits.

The urinary excretion of sodium in group I decreased to 3.9 ± 0.7 mEq/day after aortic constriction, despite a constant intake of 10 mEq, maintained by daily infusion of 0.9% sodium chloride (Table 1). This was accompanied by a significant increase in the concentration of sodium in plasma (P < 0.0005) and a decrease in hematocrit (P <
The concentration of sodium in plasma on a given day after aortic constriction was inversely correlated with urinary sodium excretion on the same day ($r = -0.322$, $P < 0.025$) but not with hematocrit ($r = -0.120$, $P > 0.1$). The concentration of potassium in plasma did not increase significantly. The renal excretion of sodium by sham-operated rabbits (group II) was similar to the daily sodium intake (10 mEq) and there was no change in plasma sodium concentration (Table 1). Hematocrit did, however, decrease in group II, but not nearly to the same extent as in group I. The aorta-constricted rabbits that were not maintained on a constant sodium intake by NaCl infusions (group III) excreted sodium at a daily rate that was not significantly greater than that of group I. However, the low sodium excretion (5.7 ± 0.7 mEq/day) in group III was due to a reduced sodium intake (5.9 ± 0.8 mEq/day, as food only), and group III rabbits were in sodium balance. The concentration of sodium in plasma of rabbits in group III did not change significantly and hematocrit decreased only to the degree noted in the sham group.

PRA increased progressively after aortic constriction in rabbits that died with pulmonary congestion and edema (group I), and reached a level that was an average of 4 times higher than control ($P < 0.0005$) (Fig. 3). There was an inverse correlation between the daily rate of increase in PRA and the number of days before the rabbit died ($r = -0.468$, $P < 0.05$). In contrast, there was no

**Table 1. Changes in Cardiovascular Function, Electrolytes, and Water Metabolism in Rabbits with Congestive Heart Failure (Group I)**

| Groups          | AP (mm Hg) | LVESP (mm Hg) | HR (min-1) | RR (min-1) | PRA (mEq/day) | Sodium (mEq/L) | Potassium (mEq/L) | Urine sodium (mEq/day) | Urine potassium (mEq/day) | Hematocrit (%) | P < 0.0005
|-----------------|------------|---------------|------------|------------|---------------|----------------|-------------------|------------------------|------------------------|---------------|----------
| 1. Aorta constr. | B          | A             | 79 ± 7     | 109 ± 2    | 124 ± 5      | 22 ± 1         | 88 ± 37           | 3.9 ± 1                | 0.6 ± 0.5               | 4 ± 1          | 0.0005   
| 2. Sham (0.9% NaCl), n = 8 | 7.1 ± 1   | 7.3 ± 1       | 7.5 ± 1    | 42 ± 3      | 7.6 ± 1       | 7.6 ± 1         | 4.1 ± 1          | 4.1 ± 1                | 0.6 ± 0.5               | 4 ± 1          | 0.0005   
| 3. Aorta constr. (no NaCl infused), n = 9 | 7.1 ± 1   | 7.3 ± 1       | 7.5 ± 1    | 42 ± 3      | 7.6 ± 1       | 7.6 ± 1         | 4.1 ± 1          | 4.1 ± 1                | 0.6 ± 0.5               | 4 ± 1          | 0.0005   
| P < 0.001 | NS         | < 0.001       | < 0.001    | < 0.001    | < 0.001       | < 0.001         | < 0.001           | < 0.001               | < 0.001               | < 0.001        | 0.0005   

**Figure 3** The level of plasma renin activity and plasma aldosterone concentration attained after aortic constriction of rabbits that died with pulmonary edema (0.9% NaCl infused daily; group I) and control values. Plasma renin activity before and after placing a clamp on the abdominal aorta is also shown for a sham series of rabbits (0.9% NaCl infused daily, clamp left untightened; group II) and a group that survived with no pulmonary edema (no NaCl infused, clamp tightened; group III). The corresponding concentrations of aldosterone in plasma from the sham group are also shown.
significant change in PRA in sham-operated rabbits (group II) and aorta-constricted rabbits that were not infused with sodium chloride (group III).

The concentration of plasma renin substrate (PRS) on the day before surgery was 516 ± 35 ng of angiotensin/ml in group I and 497 ± 51 in group II. However, in the sample collected after surgery the concentration had risen to 1,249 ± 126 in group I (P < 0.0005) and 1,382 ± 207 in group II (P < 0.0005). Thereafter PRS progressively decreased to 830 ± 206 and to 869 ± 210 in groups I and II, respectively, values which were not significantly different from PRS before surgery. There was no significant difference in the changes in PRS between group I and group II.

The concentration of aldosterone in plasma was measured in groups I and II before and after infusion of dexamethasone to inhibit the secretion of ACTH. In control samples collected the day before surgery the plasma aldosterone level before infusion of dexamethasone was 150 ± 19 pg/ml. Then, after infusion of dexamethasone for 1 hour into the unrestrained resting rabbits, plasma aldosterone decreased to 16 ± 3 pg/ml (P < 0.0005). However, after constriction of the aorta (group I) the concentration of aldosterone in plasma following dexamethasone infusion progressively increased from day to day, reaching 99 ± 23 pg/ml (P < 0.005), a value 7 times greater than control (Fig. 3). There was a direct correlation between the concentration of aldosterone in plasma on a given day after aortic constriction and PRA on the same day (r = 0.820, P < 0.001) (Fig. 4). For rabbits in group I there was also a significant inverse correlation between sodium excretion on a given day and both PRA (r = -0.468, P < 0.001) and the concentration of aldosterone in plasma (r = -0.317, P < 0.025) on the same day in the period following aortic constriction. The change in hematocrit in group I rabbits on successive days after aortic constriction was inversely correlated with the sequential changes in PRA (r = -0.468, P < 0.001) and plasma aldosterone (r = -0.381, P < 0.01). However, no correlation was found between plasma sodium concentration and either PRA (r = 0.196, P > 0.1) or plasma aldosterone (r = 0.067, P > 0.1). Figure 5 shows the decrease in urinary sodium excretion accompanying the progressive rise in plasma aldosterone concentration, PRA, and LVEDP after constriction of the aorta of one of the rabbits in group I that died with pulmonary edema and ventricular failure.

Autopsy of rabbits in group I revealed a large amount of fluid in the thoracic cavity (10-117 ml) and a corresponding amount of ascites (5-115 ml) (Table 1) (r = 0.569, P < 0.01). There was a significant correlation between the volume of pleural fluid and maximum LVEDP (r = 0.469, P < 0.05), ascites and maximum LVEDP (r = 0.569, P < 0.01), pleural fluid and final hematocrit (r = -0.445, P < 0.05), ascites and final hematocrit (r = -0.810, P < 0.001), pleural fluid and maximum plasma aldosterone (r = 0.622, P < 0.01), ascites and maximum plasma aldosterone (r = 0.580, P < 0.05) and maximum PRA and ascites (r = 0.463, P < 0.05). Sham-operated rabbits (group II) had no fluid in the thoracic or abdominal cavities and the aorta-constricted rabbits that did not receive sodium chloride infusions (group III) had no thoracic fluid, although two did have some ascites (8 and 55 ml).

The mean weights of organs and tissues expressed as grams per kilogram of original body weight is shown in Table 2. In rabbits in group I considerable hypertrophy of the left ventricle, septum, and right ventricle was evident. The left ventricle of the aorta-constricted rabbits that were not infused with sodium chloride (group III) was slightly hypertrophied, but not nearly to the extent seen in group I. All rabbits in group I also exhibited marked pulmonary

![Figure 4](https://example.com/figure4.png)  
**Figure 4** The relationship between plasma aldosterone concentration and plasma renin activity determined at intervals after aortic constriction in rabbits that died with pulmonary edema (group I).
congestion and edema; the weights of the lungs were 3 times greater than normal. Moreover, four rabbits in group I contained considerable frothy fluid in the trachea. The livers of rabbits in group I were mottled (“nutmeg liver”) and considerable hepatomegaly was evident. The weights of the adrenals and kidneys of group I were slightly greater than those of sham rabbits (group II) and a group of normal rabbits, and the kidneys were appreciably heavier than those of aorta-constricted rabbits that did not receive sodium chloride infusions (group III).

Histological examination of lung tissue from rabbits in group I revealed marked congestion and disruption of alveoli; those that were not engorged with edema fluid had markedly thickened walls. Distinct red blood cells were seen in some alveoli, suggestive of hemorrhagic lesions, and areas of pink, amorphous infiltrate, often accompanied by alveolar macrophages laden with golden-brown hemosiderin-like pigment (so-called “heart failure cells”), were evident. The pulmonary capillaries were congested and edema fluid was present in the bronchioles. Liver tissue from rabbits in group I was also congested; this was evidenced by dilated sinusoids and, in many rabbits, marked central lobular necrosis. There was minimal evidence of triad involvement. The necrosis surrounding the widened central veins was either focal or irregular, involving 25–50% of the lobule, and was characterized by a change in coloration of the stained tissue section, loss of definition of many cell membranes, and a change to smaller, darker, markedly flattened nuclei; these changes would result if a large increase in central venous pressure had occurred. Polymorphonuclear leukocytes containing hemosiderin-like granules and monocytes were occasionally seen.

Discussion

In 1953 Alexander et al. described the production of experimental congestive heart failure in rabbits by supra-aortic constriction. Evidence for heart failure was obtained from histological studies which showed passive congestion of the liver and lungs; ascites and pleural fluid were observed and heart failure cells were present in rabbits surviving for more than a month. In a subsequent study, Alexander and associates reported measurements to show that plasma volume (T-1824 dye space) and thiocyanate space were increased and sodium balance was positive.

In the present study extensive measurements were made to document the presence of both left and right congestive failure and to define the conditions for production of a useful model for the study of heart failure. Evidence of failure of the left ventricle included a high LVEDP and pulmonary congestion and edema. The weight of the congested lungs was almost 3 times that of lungs from control rabbits. Histological examination of lung tissue revealed findings characteristic of pulmonary congestion and edema. In rabbits with severe pulmonary edema, a pink, frothy fluid was found in the trachea at autopsy. Hyperpnea was also a manifestation of pulmonary congestion and edema. It is suggested that the increase in arterial pressure above the aortic constriction increased the afterload on the left ventricle which led to failure. The impact of this afterload on the left ventricle was manifested by the left ventricular hypertrophy; the weights of both the left ventricular wall and the septum were greater in rabbits with congestive failure than in the normal and sham-operated rabbits. Also, the increases in left ventricular systolic, end-diastolic, and mean pressures reflect the responses to the afterload. The present findings agree with the suggestion of Alexander et al. from studies of a heart-lung preparation of this model that left ventricular failure resulted from the rise in arterial pressure. Apparently, the increase in pulmonary capillary pressure played a key role in leading to pulmonary congestion, to transudation of fluid in the alveolar walls and alveolar cavities, and to frank pulmonary edema.

Evidence of right ventricular failure included a large congested liver with dilated sinusoids and central lobular necrosis and chronic ascites formation. Any substantial amount of retained salt and water is a reflection of right congestive failure; since only a limited volume of fluid can accumulate in the lungs as congestion and edema without death occurring. Pleural fluid is more common in right

Table 2 Weights of Tissues in Rabbits with Congestive Heart Failure (Group I) and Control Groups

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<tr>
<th>Groups</th>
<th>Body wt</th>
<th>Heart</th>
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<th>Adrenals</th>
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<td>Initial</td>
<td>Final</td>
<td>S</td>
<td>LV</td>
<td>R</td>
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<td>I. Aorta constricted (+0.9% NaCl), n = 13</td>
<td>2.97 ± 0.02</td>
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<td>II. Sham (+0.9% NaCl), n = 8</td>
<td>3.10 ± 0.03</td>
<td>2.73 ± 0.03</td>
<td>0.45 ± 0.03</td>
<td>0.46 ± 0.02</td>
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<td>III. Aorta constricted (no NaCl in fused), n = 9</td>
<td>2.99 ± 0.04</td>
<td>2.74 ± 0.05</td>
<td>0.47 ± 0.04</td>
<td>0.56 ± 0.07</td>
<td>1.18 ± 0.10</td>
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<td>IV. Normal, n = 10</td>
<td>3.04 ± 0.05</td>
<td>3.00 ± 0.05</td>
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P values

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Weights of tissues are given in g/kg initial body weight of rabbit. RV = right ventricle; S = septum; LV = left ventricle; R = right, L = left. Each value shown is the mean ± SEM. Statistics were performed with Student’s nonpaired t-test (NS = not significant, >0.05).
heart failure but can also occur as a consequence of left ventricular failure. The decrease in hematocrit in group I was significantly greater than that in groups II or III (P < 0.0025); this is probably a reflection of the increase in plasma volume noted by Alexander et al.2 Hypernatremia occurred in group I only; this response during the acute phase of right heart failure has been reported previously.13 It seems likely that the left ventricular failure preceded the development of failure of the right ventricle. As pulmonary congestion occurred and pulmonary vascular resistance resulted, an extra load was placed on the right ventricle; this could have led to right ventricular failure. Thus, the sequence of changes suggested is (1) elevation in arterial pressure above the constriction with an increased afterload on the left ventricle, (2) an increase in left ventricular filling pressure (and presumably an associated decrease in cardiac output), (3) pulmonary venous congestion, (4) failure of the right ventricle, and (5) systemic venous engorgement as evidenced by a large nutmeg liver. Early in this sequence of changes, the kidney is signaled to secrete renin which increases aldosterone and leads to salt and water retention, ascites formation, and pleural effusion.

The sequence of changes between the failing myocardium and the increase in renin secretion is not well understood. Although cardiac output was not measured here, it seems likely that a decrease occurred because of an afterload on the ventricle and the marked elevation in LVEDP. In this model, the constricting aortic clamp decreased renal perfusion pressure which alone could account for an initial increase in PRA. As the myocardium failed, as evidenced by a rise in filling pressure of the left ventricle, PRA increased further. It is noteworthy that a similar reduction in renal perfusion pressure failed to produce a chronic elevation in PRA in group III; this finding indicates that the chronic increase in PRA observed in group I was secondary to the myocardial failure. Renin substrate was elevated to a similar degree in both group I and group II (sham) in the first plasma sample collected after surgery and thereafter reverted toward control levels. The changes in PRS appear to be caused by surgery per se, especially as a 2- to 3-fold rise has also been found by others after performing quite different surgical manipulations with rabbits.14,15 and may be due to ACTH-induced enhancement of hepatic synthesis of renin substrate.16 Since PRA did not change significantly in the sham group, despite the initial surge of PRS, and since the rise in PRA in group I did not correspond with the acute postsurgical rise in PRS, it is concluded that the progressive increase in PRA in rabbits with ventricular failure was due to increased renal secretion of renin. It is unlikely that dexemethasone contributed to the high PRA in group I because (1) PRA was normal in group II (sham) despite a similar dose of dexamethasone, and (2) PRA in group II was similar to that of group III which did not receive dexamethasone. The increase in PRA provided an explanation for the increase in plasma aldosterone concentration; there was an excellent correlation between the level of PRA and the plasma level of aldosterone. Also, there was a significant inverse correlation between sodium excretion on a given day and the concentration of aldosterone in plasma. It is noteworthy that both PRA and plasma aldosterone were normal in the group II rabbits and PRA was normal in group III rabbits. Others have also found that rabbits made chronically hypertensive by aortic constriction have a normal PRA.17 These findings, considered together with the data from group I rabbits, support the concept of a causal relationship between the renin-angiotensin-aldosterone system and sodium retention. The retained salt and water expanded the plasma volume, as reported by Alexander et al.17 and as reflected in the decreased hematocrit in our present study; the fall in hematocrit was inversely correlated with the increments in PRA and plasma aldosterone. The hypernatremia occurred only in the rabbits with congestive failure. Finally, the high inverse correlation between the level of PRA and the duration of the survival period before death in pulmonary edema is another suggestion of a causal relationship of the renin-angiotensin system to the pathogenesis of heart failure. These findings indicate that the renin-angiotensin-aldosterone system played a key role in the alterations in salt and water metabolism in this model of congestive failure.

In group III there was no evidence for chronic heart failure in the group as a whole although two rabbits, which were excluded from group III for the chronic studies, died in acute pulmonary edema 1–3 days after aortic constriction. Since group I received saline intravenously to maintain salt intake but group III did not, the results suggest that the extra load of salt and water was an important factor in the production of heart failure in group I. Although the peak rise in arterial pressure was essentially the same for groups I and III, the rate of rise in arterial pressure was considerably greater in group I than in group III. This means that the response to the afterload in group I occurred early and before compensatory hypertrophy had developed to any appreciable extent, a finding which helps to explain the development of myocardial failure. The present report provides a detailed description of the methods for production of chronic congestive heart failure in the rabbit by suprarenal aortic constriction with a Goldblatt clamp. The cross-sectional area of the constriction was varied from 3.2 to 4.5 mm2. There was a direct correlation between the area of the cross section of the clamp and the number of days until death, so less constriction produced a more chronic model. The level of arterial pressure above the constriction was inversely correlated with the cross-sectional area of aortic constriction. This model is easily produced and the method provides highly reproducible results in the New Zealand white rabbit. The model has utility for study of various aspects of the syndrome of congestive heart failure.

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Influence of a Prostaglandin Endoperoxide Analogue on the Canine Pulmonary Vascular Bed

PHILIP J. KADOWITZ AND ALBERT L. HYMAN

SUMMARY We evaluated the effects of an analogue of the prostaglandin endoperoxide, PGH_2, in the canine pulmonary vascular bed. The analogue increased pulmonary arterial pressure whereas cardiac output and left atrial pressure were unchanged. Although pulmonary vascular resistance was increased markedly, only small increases in systemic vascular resistance were observed. In experiments in which blood flow to a lobe was maintained constant, the analogue produced dose-related increases in lobar arterial and small vein pressure but little change in left atrial pressure. These data suggest that the analogue increased resistance to flow by constricting intrapulmonary veins and upstream vessels presumed to be small arteries. The increase in resistance was similar when the lung was perfused with dextran or with blood. In addition, the analogue increased inflation pressure; however, similar increments in vascular resistance were obtained in ventilated and nonventilated lung lobes. Indomethacin, in doses which abolished responses to arachidonic acid, did not attenuate the response to the analogue. These results suggest that interaction with formed elements, increases in airway tone, or stimulation of prostaglandin synthesis contribute little if anything to the pressor response to the analogue. These data show that the analogue is far more potent than the biseonomic prostaglandins in the pulmonary vascular bed and suggest that endoperoxides may represent an active form of the prostaglandins in the lung.

PROSTAGLANDINS E_2 and F_6 (PG E_2 and PG F_6) are formed in the lung from the precursor, arachidonic acid, and their effects on the pulmonary vascular bed have been investigated in a variety of species. In dog, cat, sheep, swine, and calf PGF_6 was found to be a potent pulmonary presor substance, whereas in dog, swine, and lamb, PGE_2 elicited small increases in pulmonary vascular resistance. The prostaglandin precursor, arachidonic acid, has been reported to have pressor activity in the canine pulmonary vascular bed and its effects are blocked by inhibitors of prostaglandin synthesis. Direct evidence for the formation of an endoperoxide intermediate during prostaglandin synthesis has been obtained recently and, in the guinea pig lung, the major products of synthesis are metabolites of intermediates rather than the biseonomic prostaglandins. However, the endoperoxides are highly unstable substances with a half-life of less than 10 seconds in platelet-rich plasma. The instability of the endoperoxides made it difficult to investigate their biological activity. The synthesis of stable analogues of the endoperoxide permitted the evaluation of the biological activity of these novel intermediates. Stable analogues that are chemically similar to the endoperoxide, PGH_2, have been synthesized. The purpose of the present study was to investigate the effects of (15S)-hydroxy-11E,9E( epoxy-methano)prosta-S,13E-dienoic acid, a stable PGH_2 analogue, on the canine pulmonary vascular bed. In addition, we evaluated the contribution of changes in bronchomotor tone, interaction with formed elements, and syn-
The renin-angiotensin-aldosterone system in rabbits with congestive heart failure produced by aortic constriction.

B J Morris, J O Davis, M L Zatzman and G M Williams

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