Hypersecretion of Renin in Dogs with a Chronic Aortic–Caval Fistula and High-Output Heart Failure (37347)

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Previous work has shown hypersecretion of aldosterone in dogs with high-output heart failure secondary to a large arteriovenous (A-V) fistula (1). Concomitant with the increase in aldosterone secretion, there is an elevation in plasma renin activity (PRA). In a study by Schneider *et al.* (2), it was demonstrated that in dogs with high-output failure, the hepatic clearance of renin was significantly reduced, and that this decrease in renin metabolism contributes substantially to the elevation in PRA. The present experiments were undertaken to investigate the possibility that an increase in the rate of renin secretion by the kidney also contributes to the elevated PRA in experimental high-output heart failure.

Materials and Methods. Experimental high-output heart failure was produced in seven female mongrel dogs weighing 16–23 kg. Under sterile conditions, an A-V fistula was constructed by performing a side to side anastomosis of the abdominal aorta and inferior vena cava midway between the renal arteries and the iliac bifurcation; an opening of about 17 mm (15–22 mm) was produced. Seven normal female mongrels served as the control group. The animals were placed in metabolism cages to measure the daily excretion of sodium and potassium. Each dog received 65 mEquiv of sodium and 60 mEquiv of potassium daily in the diet and had free access to tap water. One day was allowed for recovery from the surgery, after which arterial pressure was measured daily by direct femoral arterial puncture. Mean right atrial pressure was measured every other day by passage of a polyethylene catheter to the right atrium via percutaneous femoral venipuncture. After demonstration of salt and water retention and signs of cardiac failure, the animals were unilaterally nephrectomized and measurements of renin secretion and other physiological functions were made the following day.

Experimental procedures. Following sodium pentobarbital anesthesia (30 mg/kg), a catheter was placed in the carotid artery for measurement of arterial pressure as well as for arterial blood sampling. Through a small flank incision the left ovarian vein was cannulated with a small polyethylene catheter. The catheter was passed into the left renal vein for sampling the renal venous effluent. A noncannulating electromagnetic flow probe (Carolina Instrument Co.) was placed around the left renal artery for measurement of renal blood flow. The ureter was cannulated for urine collection. Arterial blood pressure was determined with a Statham P23Db pressure transducer. Both renal blood flow and arterial blood pressure were recorded on a Sanborn model 7700 recorder. Measurements of glomerular filtration rate were done by a standard renal clearance technique for creatinine (C_{CR}). Urine was collected and analyzed by flame photometry to determine the excretion rates of sodium and potassium. After completion of all surgical and preparatory procedures, the dog was allowed to recover for one hour before beginning the experimental protocol.

After this stabilization period, 10-ml samples of renal venous and arterial blood were collected simultaneously at 15, 30, and 45 min for analysis of plasma renin activity. Blood samples were collected in chilled test tubes containing 10 mg EDTA, centrifuged and the plasma withdrawn for analysis.

Analytical methods. Renin was determined by the method of Schneider *et al.* (2). This consisted of dialyzing 2 ml plasma against

0.22 *M* phosphate buffer (pH 5.3) for 18 hr. After adding sodium chloride and diisopropylfluorophosphate, the samples were incubated for 3 hr at 37°. Following enzyme inactivation in a boiling water bath for 10 min, each sample was diluted to 4 ml with a phosphate buffer solution, and the supernatant was frozen until assayed. Samples were assayed in the pentobarbital-anesthetized pentolinium-blocked vagotomized rat and synthetic angiotensin II (Hypertensin, Ciba) was used as a standard. All renin values are expressed as nanograms of angiotensin II formed per milliliter of plasma for a three-hour period of incubation. The rate of renin secretion was calculated as the product of renal plasma flow and the difference in PRA across the kidney (*i.e.*, renal venous PRA minus arterial PRA).

Results. Marked sodium retention and elevated mean right atrial pressure as well as peripheral edema and ascites were signs of congestive heart failure. Urinary sodium excretion (E_{Na}) fell markedly and was less than 5.0 mEquiv/day for all dogs with an A-V fistula and cardiac failure the day prior to experimentation (Fig. 1). Normal control dogs had a mean E_{Na} of 54.8 ± SEM 2.7 mEquiv/day. Mean right atrial pressure

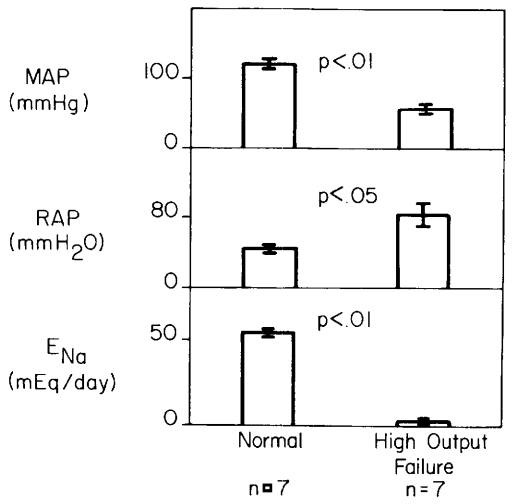

FIG. 1. Means (± SEM) for arterial pressure (MAP), mean right atrial pressure (RAP), and sodium excretion (E_{Na}) obtained the day before the acute experiment in normal dogs and in dogs with experimental cardiac failure secondary to an A-V fistula.

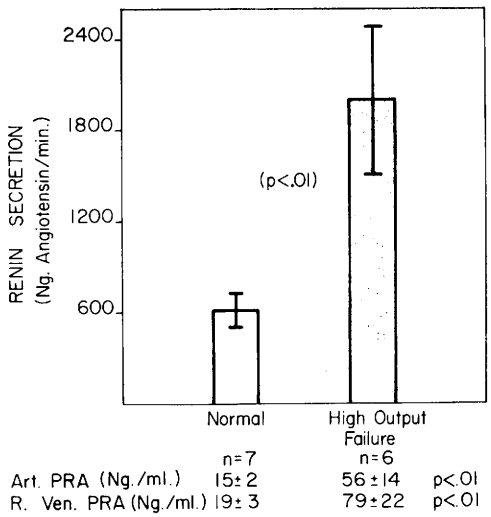

FIG. 2. Means (± SEM) for arterial plasma renin activity (PRA), renal venous PRA and renin secretion in normal dogs and in dogs with experimental heart failure secondary to an A-V fistula.

(RAP) was significantly ($p < 0.05$) elevated (83.5 ± 15.3 mm water) when compared with the normal group (47.1 ± 3.0 mm water). Placement of the fistula also produced a decrease in the mean femoral arterial pressure from a mean of 123 ± 5 mm Hg in normal dogs to 59 ± 3 mm Hg in the group with high output failure ($p < 0.01$).

Figure 2 shows the results of the renin secretion data. The arterial PRA in the group with high output failure was 56 ± 14 ng angiotensin/ml plasma, a value three-fold greater than that for the control group of 15 ± 2 ng angiotensin/ml ($p < 0.01$). Renal venous PRA in the dogs with heart failure showed a four-fold increase over normal dogs, 79 ± 22 ng angiotensin/ml as compared to 19 ± 2 ng angiotensin/ml ($p < 0.01$). The rate of renin secretion was 1978 ± 495 ng angiotensin/min for the dogs with high output heart failure. This was more than three times greater than the renin secretion in the normal control animals (607 ± 101 ng angiotensin/min) ($p < 0.01$).

Dogs with high output failure showed a decrease in renal blood flow (170 ± 32) as compared with normal control animals (300 ± 24 ($p < 0.001$) (Fig. 3). C_{Cr} was not significantly different ($p > 0.05$) between

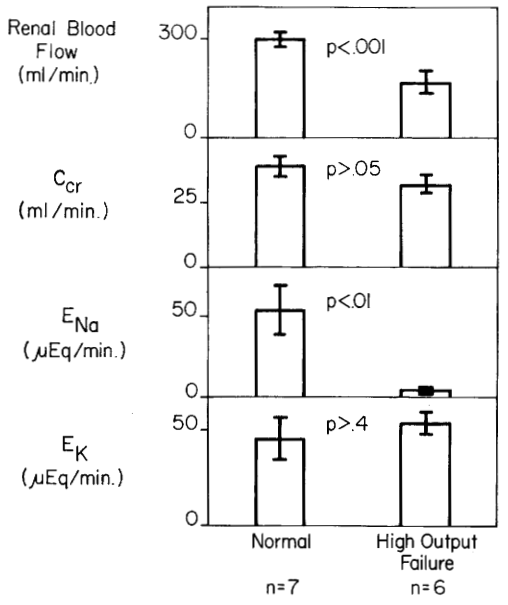

FIG. 3. Means (± SEM) for renal blood flow, clearance of creatinine (C_{CR}), sodium excretion (E_{Na}), and potassium excretion (E_K) obtained during the studies of renin secretion in normal dogs and in dogs with experimental heart failure secondary to an A-V fistula.

the two groups. Sodium excretion measured during the acute experiment was markedly reduced (3.5 ± 1.0 μEquiv/min) as compared to normal animals (53.7 ± 15.8 mEquiv/min) ($p < 0.01$), whereas no significant difference in potassium excretion was detected ($p > 0.4$).

Discussion. The present study confirms the observations reported by other workers (1, 3) that dogs develop congestive heart failure secondary to a large A-V fistula. Evidence of actual impairment of cardiac performance was demonstrated by Ferguson *et al.* (3), by the infusion of whole blood or saline into dogs with large A-V fistulas. They observed that a progressive increase in left ventricular end diastolic pressure was associated with an increase in cardiac work in normal dogs, but in dogs with a large A-V fistula, cardiac work remained unchanged or actually declined.

In the dog with an A-V fistula, signs of both right and left ventricular failure are exhibited. Typically, the increased venous return imposed by the fistula leads to an elevated right atrial pressure, right ventricular hypertrophy, tachycardia, sodium retention, and the formation of ascites and peripheral edema which is the syndrome of right heart failure.

In high-output failure, retention of sodium and water has been associated with an increase in the secretion of aldosterone, concomitant with an elevation in the PRA (1, 4). In a study by Schneider *et al.* (2), dogs with high-output failure showed a significant decrease in the hepatic clearance of renin.

In the present study, a marked elevation in both arterial and renal venous PRA was observed. It was demonstrated earlier (4) that plasma renin substrate is not altered in this type of experimental high-output failure. While an increase in the renal venous PRA suggests an increase in release of renin by the kidney, it might merely reflect a decrease in the renal plasma flow. To show that renin release actually increased, the rate of renin secretion was calculated as the product of renal plasma flow and the difference in PRA across the kidney. Renin secretion in the high-output failure group was observed to be elevated threefold over the control group. These results demonstrate that hypersecretion of renin is a major factor in the hyperreninemia observed in experimental high-output heart failure.

Summary. The rate of renin secretion was measured in six dogs with large aortic–caval fistulas and evidence of cardiac failure. At the time of the study, the dogs showed a decrease in mean femoral arterial pressure, increased mean right atrial pressure, marked sodium retention, edema and ascites. Renin secretion was measured by determining renal blood flow with an electromagnetic flowmeter and the renal venous–arterial difference in plasma renin activity. Renin secretion was elevated to 1978 ng angiotensin/min in the six dogs with an aortic–caval fistula and cardiac failure in comparison with a value of 607 ng angiotensin/min for seven normal dogs studied similarly ($p < 0.01$).

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