Plasma Renin in Chronic Experimental Heart Failure and during Renal Sodium "Escape" from Mineralocorticoids

By C. I. Johnston, M.B., B.S., M.R.A.C.P., James O. Davis, Ph.D., M.D., Charles A. Robb, Ph.D., and James W. MacKenzie, M.D.

ABSTRACT
A striking increase in the plasma renin level occurred in dogs with low output right heart failure secondary to tricuspid insufficiency and pulmonic stenosis and in three of five animals with high output failure produced by a large arteriovenous fistula. When dogs with a small arteriovenous fistula were given daily injections of DOCA, the renal sodium "escape" phenomenon occurred. In these animals, the level of plasma renin was suppressed during DOCA administration both during the initial period of sodium retention and also later when sodium balance was normal or negative. In contrast, when dogs with a larger arteriovenous fistula but without evidence of cardiac failure were given DOCA, they retained sodium and developed signs of congestive heart failure. However, in these animals with congestion and ascites, in contrast to the dogs that developed spontaneous high output failure, the plasma renin was low. Renin-substrate was unaltered in all of the experimental situations studied except for the decrease observed in dogs with low output right heart failure. In these animals, it seems likely that decreased renin-substrate was secondary to hepatic congestion and liver damage. The renin-angiotensin system does not seem to be related to the "escape" phenomenon, and renin does not appear to be the factor that makes the kidney unusually responsive to mineralocorticoids. Thus, in experimental heart failure the renin-angiotensin system was activated, but in the congestive syndrome produced by DOCA the plasma renin level was suppressed.

ADDITIONAL KEY WORDS
arteriovenous fistula desoxycorticosterone sodium balance renin-substrate tricuspid insufficiency and pulmonic stenosis high output failure conscious dogs

Hypersecretion of aldosterone is common in edematous states (1-12). Many patients with congestive heart failure have increased secretion and excretion of aldosterone (1, 3-7), but patients with edema also have normal rates of secretion of this hormone (8-10). Experimental heart failure in dogs is regularly accompanied by an increase in aldosterone secretion and a high plasma level of aldosterone (2, 11, 12). The increase in plasma aldosterone in heart failure also results from a decrease in the metabolic clearance of aldosterone by the liver (4, 9, 13). The present study relates the participation of the renin-angiotensin system in experimental heart failure to sodium balance and to the known hypersecretion of aldosterone.

This investigation is also concerned with the role of the renin-angiotensin system in the "escape" phenomenon (14-15). Normal humans or animals given large quantities of a mineralocorticoid retain sodium for only a few days and then escape from the sodium-retaining action of the steroid (15-17). Certain
patients and experimental animal preparations, however, when given a mineralocorticoid retain sodium for prolonged periods, do not exhibit this "escape" phenomenon (14, 15). In many of these conditions in which marked sodium retention occurs during mineralocorticoid administration, there is evidence for increased activity of the renin-angiotensin system (2, 12, 14). To determine whether renin or angiotensin II could possibly make the kidney more responsive to the sodium-retaining action of mineralocorticoids, plasma renin was measured sequentially in two groups of dogs. One group, with a small arteriovenous fistula, showed the renal “escape” from the sodium retaining action of desoxycorticosterone acetate (DOCA). The other group, with a large arteriovenous fistula, did not exhibit the “escape” phenomenon during DOCA administration, but the animals retained sodium and developed the signs of congestive heart failure.

Methods

Studies were conducted in conscious trained mongrel dogs weighing 18 to 28 kg. The animals were kept in individual metabolic balance cages and fed a diet containing a constant amount of sodium (30 or 60 mEq per day) and potassium (28 or 56 mEq per day). Urine was collected daily. Urine and plasma were analyzed for sodium and potassium by flame photometry. Arterial pressure was measured by direct percutaneous femoral artery puncture with a no. 20 gauge needle connected to a Statham P23Bd pressure transducer and Sanborn recording apparatus. Right atrial pressure was determined with a water manometer attached to a polyethylene catheter which was passed into the right atrium via the jugular vein. At the same time that the pressure measurements were made, blood was obtained and placed in polycarbonate tubes chilled in ice. Each tube contained 0.1 m of disodium ethylenediaminetetraacetate (EDTA) for each 20 ml of whole blood; EDTA served as an anticoagulant and as an inhibitor of angiotensinase activity. Plasma renin was measured by a modified Helmer method adapted for dog blood (18, 19); all values are expressed in nanograms of angiotensin II formed during a 4-hour incubation period. When synthetic angiotensin

1Supplied by Upjohn and Company.
II was added to plasma which was processed and incubated, 97% of the angiotensin was recovered. When dog renin was added to dog plasma, 94 to 109% was recovered. Evidence for the specificity of the modified Helmer procedure has been presented previously (18, 19). Plasma renin substrate was measured by a method described elsewhere (19). Two or three control plasma renin determinations were made in all dogs, and blood was drawn every second or third day throughout the experimental period for measurement of plasma renin.

Right heart failure was produced in five dogs by tricuspid insufficiency and pulmonary stenosis (20, 21). Aortic-caval fistulas were placed below the kidneys in 14 dogs (12). Sodium pentobarbital anesthesia (30 mg/kg) was used during the surgery. In five dogs the fistula was large enough to produce spontaneous full-blown congestive heart failure. The nine dogs that did not develop heart failure were allowed to recover from the surgery; in these further studies were made of metabolic balances, arterial and right atrial pressures, plasma electrolytes, and plasma renin. After these measurements, the animals were given 15 mg of DOCA intramuscularly per day. Four dogs received DOCA until they died in pulmonary edema after a period of 7 days or more. The other five dogs showed renal sodium "escape" from DOCA, and administration of the steroid was stopped after 12 days; observations were made in four of the animals after recovery.

Results

Dogs with low output heart failure (N = 5).—The average values of each dog for the con-
control and experimental periods for renal sodium excretion, the concentration of plasma sodium, arterial and right atrial pressures, and plasma renin determinations are given in Table 1. An example of the metabolic balance data and the experimental design for an individual animal is presented in Figure 1. All dogs showed the characteristic syndrome of right-sided congestive heart failure with edema and ascites; renal sodium excretion was very low, central venous pressure was elevated, and arterial pressure was reduced. In every animal there was an increase in plasma renin above the control level; the magnitude of this elevation in renin varied among individual animals. In one dog plasma renin declined after 18 days (Fig. 1). The increase in mean plasma renin level (expressed as angiotensin formed during in vitro incubation) from 9 to 29 ng angiotensin/ml of plasma for the group of five dogs is significant \((P<.025)\). In one dog (no. 8 of Table 1), the concentration of plasma sodium fell from 154 to 131 mEq/L although the average value for the period with heart failure was 144 mEq/L.

Dog no. 11 was found to be pregnant; she aborted and died 10 days after development of heart failure. Her control plasma renin levels were not significantly different from those of the other dogs in the series, and the sudden significant increase in the plasma renin in this dog coincided with constriction of the pulmonary artery ligature. This observation suggested that the production of heart failure rather than pregnancy resulted in the increase in plasma renin in this animal. Even when this dog is excluded from the series, the increase in plasma renin is statistically significant.

**Dogs with high output heart failure \((N=5)\).**—The average values for the observations in dogs that developed spontaneous heart failure following placement of an aortic-caval fistula are presented in Table 2. The results in an individual animal are presented in Figure 2. The findings in both Table 2 and Figure 2 demonstrate that after placement of the fistula nearly complete renal retention of so-

---

**Table 2**

| Dog  | Days | Control, MAP | Pk, MAP | RAP, MAP | Plasma Sodium Excretion, Daily, Average | Mean | SEM
|------|------|-------------|---------|---------|----------------------------------------|------|------
| 1    | 6    | 159 13 4.7 | 153 8.5 | 133 16 | 6 (3)                                  | 13  3| 1.2
| 2    | 7    | 156 13 3.9 | 152 3.4 | 134 15 | 8 (3)                                  | 13  5| 1.2
| 3    | 7    | 158 13 4.1 | 153 7.5 | 134 15 | 10 (3)                                 | 13  6| 1.2
| 4    | 8    | 154 13 3.5 | 153 7.5 | 134 15 | 10 (3)                                 | 13  6| 1.2
| 5    | 9    | 155 13 3.9 | 153 7.5 | 134 15 | 10 (3)                                 | 13  6| 1.2
| Mean | 8    | 155 13 4.0 | 153 7.5 | 134 15 | 10 (3)                                 | 13  6| 1.2

*The abbreviations are the same as those used in Table 1.*

---

*Circulation Research, Vol. XXII, February 1968*
Results obtained in a dog that developed high output failure following placement of a large arteriovenous fistula (dog 5 of Table 2).

Dium persisted after the immediate postoperative period and was associated with an increase in plasma renin in three of the five dogs. The average value for the eleven plasma renin determinations during the experimental period (Table 2) in dog no. 23 does not reflect the marked initial increase from 9 to 36 ng angiotensin/ml of plasma which was observed. Dog no. 25 failed to show a rise in plasma renin, and the difference between the mean control level of plasma renin and the average value during heart failure was not significant for the group.

All the dogs developed ascites and peripheral edema and died with pulmonary edema. At autopsy the animals displayed large amounts of ascites and pleural effusion, hepatic congestion, frothy fluid in the bronchi and trachea, and heavy edematous congested lungs. One dog (no. 24) developed marked hyponatremia (from 152 to as low as 118 mEq/L) during the period of congestive heart failure.

Dogs with an arteriovenous fistula given DOCA (N = 9).—In this group of dogs, the arteriovenous fistula was not large enough to produce heart failure. These animals were given 15 mg/day of DOCA intramuscularly and divided into two groups on the basis of their response to the mineralocorticoid.

In the first group of five dogs, after several days of renal sodium retention, renal sodium "escape" from the sodium-retaining action of the DOCA occurred. The response was similar to that observed for normal dogs given DOCA (17), except that occasionally sodium
Retention occurred for a longer period than in normal animals. The data in Figure 3 show the renal sodium “escape” from DOCA in a dog with a small arteriovenous fistula. On a dietary sodium intake of 30 mEq/day, DOCA produced sodium retention for 10 days in this dog before renal “escape” occurred. This was associated with depression of the plasma renin level and the development of hypokalemia. The average values for the findings during the control period after placement of the arteriovenous fistula, for the first 5 days of DOCA administration, and during prolonged DOCA administration are presented in Table 3 (center column). Plasma renin levels were not changed by the placement of a small arteriovenous fistula. However, DOCA suppressed plasma renin levels significantly both during the first 5-day period with renal sodium retention and also after 5 days during the period of renal sodium “escape” (Figs. 3 and 4). The renin values were low both when renal sodium excretion was less than 5 mEq per day and when the renal sodium excretion increased to as high as 75 mEq per day. Slight hypokalemia developed during DOCA administration in this series of dogs; plasma potassium fell from 4.3 ± .2 to 3.7 ± .2 mEq/L.

In the second group of four dogs given DOCA, the renal sodium “escape” phenomenon failed to occur (right column of Table 3). In one dog DOCA was discontinued, and
Average Values for Plasma Renin, Sodium and Potassium Concentrations, Daily Renal Sodium Excretion and Mean Arterial and Right Atrial Pressures in Dogs with Arteriovenous Fistulas Given DOCA

<table>
<thead>
<tr>
<th>Renin Administration</th>
<th>Normal (N = 5)</th>
<th>Normal (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>39 ± 6</td>
<td>43 ± 8</td>
</tr>
<tr>
<td>PN (mEq/L)</td>
<td>154 ± 3</td>
<td>153 ± 1</td>
</tr>
<tr>
<td>PK (mEq/L)</td>
<td>4.2 ± 1</td>
<td>3.7 ± 9</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>131 ± 3</td>
<td>131 ± 9</td>
</tr>
<tr>
<td>RAP (mm water)</td>
<td>58 ± 6</td>
<td>78 ± 6</td>
</tr>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td>17 ± 3</td>
<td>16 ± 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control period (5-20 days)</th>
<th>Small arteriovenous fistula placed (N = 5)</th>
<th>Large arteriovenous fistula placed (N = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>37 ± 4</td>
<td>38 ± 4</td>
</tr>
<tr>
<td>PN (mEq/L)</td>
<td>152 ± 1</td>
<td>151 ± 1</td>
</tr>
<tr>
<td>PK (mEq/L)</td>
<td>4.3 ± 2</td>
<td>4.0 ± 1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>120 ± 6</td>
<td>75 ± 9</td>
</tr>
<tr>
<td>RAP (mm water)</td>
<td>68 ± 5</td>
<td>95 ± 15</td>
</tr>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td>17 ± 4</td>
<td>17 ± 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial 5 days of DOCA</th>
<th>DOCA 15 mg/day</th>
<th>DOCA 15 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>19 ± 2</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>PN (mEq/L)</td>
<td>155 ± 1</td>
<td>154 ± 1</td>
</tr>
<tr>
<td>PK (mEq/L)</td>
<td>3.9 ± 2</td>
<td>4.1 ± 1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>133 ± 5</td>
<td>87 ± 7</td>
</tr>
<tr>
<td>RAP (mm water)</td>
<td>103 ± 12</td>
<td>116 ± 9</td>
</tr>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prolonged DOCA administration (10-25 days)</th>
<th>Renal sodium escape</th>
<th>Congestive syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNaV (mEq/day)</td>
<td>24 ± 3</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>PN (mEq/L)</td>
<td>154 ± 2</td>
<td>151 ± 1</td>
</tr>
<tr>
<td>PK (mEq/L)</td>
<td>3.7 ± 2</td>
<td>4.2 ± 2</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>119 ± 7</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>RAP (mm water)</td>
<td>113 ± 19</td>
<td>162 ± 16</td>
</tr>
<tr>
<td>Plasma renin (ng angiotensin/ml of plasma)</td>
<td>7 ± 1</td>
<td>8 ± 3</td>
</tr>
</tbody>
</table>

U NaV = daily renal sodium excretion, PN and PK = plasma sodium and potassium concentrations, RAP = mean right atrial pressure, MAP = mean arterial pressure, daily Na intake = 30 or 60 mEq/day. Mean values, ±SEM.
On the left, mean plasma renin levels and SEM are presented for five dogs with a small arteriovenous fistula during the control period and after placement of an arteriovenous fistula, for the first five days after DOCA administration (DOCA + Na retention), and during DOCA "escape." On the right data are presented for dogs with a large arteriovenous fistula during the control periods and during the congestive syndrome produced by DOCA administration.

the dogs with an arteriovenous fistula in which spontaneous heart failure developed (Fig. 6). The average plasma renin for the animals with heart failure was significantly higher than that found in the dogs given DOCA \( (P < .001) \). In all other parameters the two groups were similar.

There was an interesting relationship between the mean values for plasma sodium and plasma renin among the 12 groups of animals (Tables 1-3). The highest plasma renins for the dogs with low and high output heart failure (Tables 1 and 2) were associated with the lowest plasma sodiums.

**Plasma renin substrate**—The concentration of renin substrate in plasma was measured in four dogs with low output right heart failure, in three dogs with an arteriovenous fistula that developed high output failure, and in four dogs with an arteriovenous fistula given DOCA. The results are shown in Figure 7. The values represent an average of two control determinations for each dog and two values during the experimental period. Only the dogs with low output right heart failure showed a significant change in the plasma renin substrate level. In these animals renin substrate fell during the period of heart failure.

**Discussion**

The present study suggests that in both low output, right-sided congestive heart failure and in high output cardiac failure produced
Observations in a dog with a large arteriovenous fistula that developed the congestive syndrome following administration of DOCA. Renal sodium excretion remained low throughout the administration of DOCA. The dog died with acute pulmonary edema.

by a large aortic-caval fistula the hyperaldosteroneism is mediated by the renin-angiotensin system. In all of the dogs with low output failure and in three of the five dogs with high output failure, the plasma renin level was elevated; this finding is consistent with the presence of increased activity of the renin-angiotensin system. The result agrees with the earlier observation that the extractable renin content of kidneys from dogs with heart failure was increased (22), and that in dogs with heart failure secondary to an arteriovenous fistula there was frequent hypergranulation and hyperplasia of the juxtaglomerular cells (12). On the basis of available data, it seems likely that hypersecretion of renin occurred in both experimental low and high output heart failure.

In the present experiments each animal served as its own control. This is important because of the variability in the control levels of plasma renin among different dogs. The explanation for these differences is not clear. By utilizing the present experimental design,
statistically significant differences in plasma renin between groups were demonstrable except for the data in Table 2. Two of these dogs with high output heart failure and marked sodium retention failed to show a clear-cut increase in plasma renin. For dog no. 1* of Table 2, several of the experimental values were higher than the average control value of 13, but the difference between the experimental and control values was not large enough to be certain that plasma renin increased. Mechanisms other than the hypersecretion of aldosterone which could have dogs with spontaneous heart failure following placement of an arteriovenous fistula with the level found in those dogs with congested state produced by DOCA. P < 0.001.

**FIGURE 6**
Comparison of the plasma renin level in the group of

**FIGURE 7**
Plasma renin-substrate levels in dogs with right heart low output failure, in dogs with an arteriovenous fistula and high output failure, and in dogs with an arteriovenous fistula given DOCA.

*Control + DOCA*
contributed to the retention of sodium in dogs 1 and 25 of Table 2 include: (1) a sufficient reduction in the glomerular filtration rate reported previously in high output failure (12), and (2) a high circulating level of aldosterone secondary to a decrease in the metabolic clearance rate of this hormone. In dog no. 25 the elevation in venous pressure and associated hepatic venous congestion could have decreased the rate of inactivation of aldosterone by the liver (23).

There are only a few reported studies on the renin-angiotensin system in patients with heart failure. As early as 1946, Merrill, Morrison, and Brannon (24) reported a high concentration of a substance similar to renin in renal vein blood of patients with heart failure. In 1963 DeChamplain, Boucher, and Genest (25) described a series of patients with edema of various etiologies; their results included ten patients with heart failure with an increased circulating level of angiotensin. Their data on angiotensin are suggestive, but additional observations are needed with a highly specific method for angiotensin (26). More recently, DeChamplain and associates (27) found that plasma renin activity was increased in patients with heart failure and fell after therapy and cardiac compensation. Massani et al. (28) also reported high levels of plasma renin in patients with congestive heart failure, but there was a wide scatter in their data, and considerable overlap occurred between normal and experimental values. In a review Brown, Davies, Lever, and Robertson (29) stated that two distinct patterns have been observed in untreated congestive failure; the plasma renin was low and increased with diuretic therapy, or renin was high and fell with treatment. In the present study plasma renin was elevated in experimental heart failure (both low and high output) in all but two dogs with high output failure.

The stimulus for the elevation in plasma renin in experimental heart failure is unknown. The elevation did not correlate with the fall in arterial pressure or the rise in right atrial pressure. Although the average values for arterial pressure in low and high output failure were uniformly low, several individual values for arterial pressure in these animals were at the control level in the presence of very high plasma renins. Similarly, plasma sodium was frequently low in both low and high output failure in the presence of elevated plasma renin, but this relationship was not invariable. A striking inverse correlation between plasma sodium and plasma renin has been reported by Brown, Davies, Lever, and Robertson (30) in a group of hypertensive patients.

The fall in plasma renin-substrate in dogs with right-sided heart failure was probably a consequence of the marked hepatic congestion and liver necrosis that occurs in animals with central venous congestion (2). A parallel functional change which is secondary to decreased hepatic blood flow is the decreased plasma clearance of aldosterone (13). The mechanism for the renal sodium "escape" from mineralocorticoids is unknown (14, 15, 17). However, many clinical conditions and experimental situations, in which failure to "escape" and prolonged sodium retention occur, are associated with increased activity of the renin-angiotensin system and high levels of plasma renin. Gross and co-workers (31) have postulated that the "escape" phenomenon may be mediated by changes in the activity of the renin-angiotensin system; in their experiments depression of kidney and plasma renin induced a natriuresis, whereas high levels of renin favored increased fractional renal tubular sodium reabsorption during mineralocorticoid therapy. Similar to the results of previous studies of the effect of DOCA on normal animals (32, 33), DOCA suppressed the level of plasma renin in the dogs with a small arteriovenous fistula. Furthermore, the lowest plasma renins were observed in the animals that escaped from DOCA or developed the congestive syndrome. This suppression of plasma renin was unrelated to the rate of renal sodium excretion. Renin was significantly decreased during the first five days of DOCA administration, during the period of
maximal fractional renal sodium reabsorption, and later during renal sodium "escape" when urinary sodium excretion was high. Similarly, in the dogs with large arteriovenous fistulas that developed signs of congestive heart failure during DOCA administration, and in which renal sodium excretion was low, there was a sustained decrease in the plasma renin level. Therefore, the results from this study do not support the concept that changes in the renin-angiotensin system are responsible for the "escape" from DOCA or that renin sensitizes the kidney to the action of mineralocorticoids.

Acknowledgments
We are indebted to Mr. Joseph Trigg for capable technical assistance with the electrolyte determinations.

References
RENIN IN HEART FAILURE AND DURING DOCA ADMINISTRATION


Plasma Renin in Chronic Experimental Heart Failure and during Renal Sodium "Escape" from Mineralocorticoids

C. I. JOHNSTON, JAMES O. DAVIS, CHARLES A. ROBB and JAMES W. MACKENZIE

Circ Res. 1968;22:113-125
doi: 10.1161/01.RES.22.2.113

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/22/2/113

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/