Plasma Renin Activity and the Effects of Deoxycorticosterone Acetate in Dogs with Chronic Left Ventricular Overload

By John S. Baumber, Ph.D., M.D., James O. Davis, Ph.D., M.D., Edward G. Schneider, Ph.D., and J. Alan Johnson, Ph.D.

ABSTRACT

Chronic left ventricular overload and left heart failure were produced by an aortic-left atrial shunt and superimposed aortic constriction. With the shunt alone, plasma renin activity and sodium balance were normal. Superimposed aortic constriction produced a further elevation in left ventricular end diastolic pressure (LVEDP), increased plasma renin activity and sodium retention occurred. Seven dogs died in pulmonary edema within a week, but nine others recovered with a return in plasma renin activity and sodium excretion to normal. Five of these nine dogs that survived the acute effects of aortic stenosis developed pulmonary edema at least 7 days after aortic constriction; LVEDP was markedly elevated, plasma renin activity was high and sodium retention occurred. Six other dogs with chronic left ventricular overload, but not retaining sodium, were given deoxycorticosterone acetate (DOCA), 15 mg/day, to study the response in renal sodium excretion. In two of the dogs, LVEDP was below 35 mm Hg and the normal "escape" pattern, characterized by return of sodium excretion to the normal control level, was observed. However, in the other four animals, LVEDP was above 35 mm Hg, escape failed to occur and marked sodium retention resulted; a further elevation of LVEDP was observed and pulmonary edema occurred on four occasions. The failure of dogs with marked elevation of LVEDP to escape from DOCA indicates that other factors in addition to the renin-angiotensin-aldosterone system are involved in the sodium retention of left ventricular failure.

ADDITIONAL KEY WORDS renin-angiotensin system left heart failure renin-angiotensin-aldosterone system left ventricular failure mineralocorticoid excess "escape" phenomenon pulmonary edema sodium retention aortic-left atrial shunt aortic constriction

A method of producing chronic experimental left heart failure in the dog has recently been described (1). This was achieved by suturing a Teflon graft between the first part of the descending aorta and the left atrium in dogs. To increase further both the flow through the shunt and the afterload on the left ventricle, slight constriction of the descending thoracic aorta was superimposed. This procedure resulted in an additional elevation of left ventricular end diastolic pressure (LVEDP) with the subsequent development of pulmonary edema which was often associated with marked sodium retention. Some animals also showed moderate sodium retention with high levels of LVEDP (over 35 mm Hg) without clinical signs of pulmonary edema (1). There is a paucity of data on plasma renin activity in patients with left ventricular failure. Furthermore, the relationship of LVEDP to activation of the renin-angiotensin system has not been investigated in either experimental left heart failure or in failure of
the left ventricle in man. The importance of mineralocorticoid excess in the pathogenesis of sodium retention has been studied thoroughly in right heart failure (2) but little is known about this relationship in left heart failure. The purpose of the present study was twofold: first, to investigate the role of the renin-angiotensin system in experimental left heart failure in the dog; and second, to study the response in renal sodium excretion to deoxycorticosterone acetate (DOCA) administration in this experimental model.

Methods

Under sterile conditions an 8-mm diameter Teflon graft was sutured between the aorta and left atrium in 16 mongrel dogs and a packed nylon ligature was placed loosely around the lower part of the descending thoracic aorta (1). The entire study was performed on the conscious, trained animal and began 2 to 3 weeks after recovery from surgery. The dogs were kept in metabolic cages and were fed a constant diet containing 66 mEq of sodium and 55 mEq of potassium per day; water was allowed ad libitum. Daily total urine output was collected and potassium balance. The average plasma renin activity was 5.3 ±0.3 (SE) ng angiotensin formed per ml of plasma compared to a normal value in our laboratory of 5.1 ± 0.5. The average values for mean femoral arterial blood pressure and LVEDP were 109 and 26 mm Hg, respectively. Right ventricular pressures, plasma sodium and potassium concentrations, and hematocrit were within normal limits. Effects of Superimposed Aortic Constriction.—Table 1 also summarizes the data on cardiovascular measurements and plasma renin activity determinations were continued at intervals of 2 to 3 days following aortic constriction. In some dogs, further tightening of the aortic ligature was necessary to elevate LVEDP to a critical level before pulmonary edema occurred.

Results

Effects of Aortic-Left Atrial Shunt.—(n = 16) The results obtained after 4 to 5 weeks from the time of the placement of an aortic to left atrial shunt are summarized in Table 1 and depicted in Figures 1 to 4. At this time, the animals were in sodium and potassium balance. The average plasma renin activity was 5.3 ± 0.3 (SE) ng angiotensin II formed per ml of plasma compared to a normal value in our laboratory of 5.1 ± 0.5. The average values for mean femoral arterial blood pressure and LVEDP were 109 and 26 mm Hg, respectively. Right ventricular pressures, plasma sodium and potassium concentrations, and hematocrit were within normal limits.
LEFT HEART FAILURE AND PLASMA RENIN ACTIVITY

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TABLE 1

Effects of an Aortic-left Atrial Shunt, Aortic Constriction and DOCA in Dogs

<table>
<thead>
<tr>
<th></th>
<th>Right ventricular systolic (mm Hg)</th>
<th>Right ventricular diastolic (mm Hg)</th>
<th>Mean femoral artery (mm Hg)</th>
<th>Left ventricular end-diastolic (mm Hg)</th>
<th>Plasma renin activity (mEq/liter)</th>
<th>K (mEq/liter)</th>
<th>Hematocrit (%)</th>
<th>Plasma renin activity in normotensive dogs (mEq/liter)</th>
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<tbody>
<tr>
<td><strong>Effects of an Aortic-Left Atrial Shunt (n = 16)</strong></td>
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<td></td>
<td>44 ± 2.2</td>
<td>2 ± 0.6</td>
<td>109 ± 2.0</td>
<td>29 ± 1.0</td>
<td>144 ± 1.0</td>
<td>3.9 ± 0.1</td>
<td>40 ± 1.9</td>
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<td></td>
<td>(30 – 60)</td>
<td>(0 – 7)</td>
<td>(80 – 130)</td>
<td>(8 – 38)</td>
<td>(140 – 160)</td>
<td>(3.7 – 4.5)</td>
<td>(35 – 47)</td>
<td>(2.0 – 7.8)</td>
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<td><strong>Effects 24 Hours following Aortic Constriction Superimposed on Shunt (n = 12)</strong></td>
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<td></td>
<td>45 ± 3.4</td>
<td>3 ± 0.4</td>
<td>88 ± 3.5</td>
<td>35 ± 2.9</td>
<td>143 ± 1.1</td>
<td>4.1 ± 0.1</td>
<td>34 ± 3.6</td>
<td>14.5 ± 1.9</td>
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<td></td>
<td>(30 – 70)</td>
<td>(0 – 5)</td>
<td>(80 – 130)</td>
<td>(8 – 38)</td>
<td>(140 – 160)</td>
<td>(3.8 – 4.3)</td>
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<td><strong>Effects 7 to 14 Days following Aortic Constriction (n = 8)</strong></td>
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<td></td>
<td>45 ± 3.3</td>
<td>4 ± 0.7</td>
<td>89 ± 5.4</td>
<td>29 ± 3.0</td>
<td>145 ± 0.5</td>
<td>4.8 ± 0.3</td>
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<td>(140 – 160)</td>
<td>(3.8 – 4.9)</td>
<td>(30 – 44)</td>
<td>(3.0 – 8.0)</td>
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<td><strong>Effects of Pulmonary Edema in Dogs which Died over 7 Days Following Aortic Constriction (n = 9)</strong></td>
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<td></td>
<td>59 ± 5.1</td>
<td>6 ± 1.1</td>
<td>65 ± 6.8</td>
<td>28 ± 1.1</td>
<td>146 ± 3.3</td>
<td>4.0 ± 0.2</td>
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<td><strong>Effects of Desoxycorticosterone Acetate (15 mg/day) in Dogs with Chronic Left Ventricular Overload</strong></td>
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<tr>
<td>Group 1§</td>
<td>59 ± 4.8</td>
<td>4 ± 0.8</td>
<td>94 ± 6.0</td>
<td>23 ± 4.1</td>
<td>146 ± 3.2</td>
<td>3.2 ± 0.1</td>
<td>30 ± 1.6</td>
<td>1.6 ± 0.2</td>
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<td></td>
<td>(30 – 50)</td>
<td>(2 – 6)</td>
<td>(80 – 100)</td>
<td>(16 – 31)</td>
<td>(140 – 160)</td>
<td>(1.0 – 2.8)</td>
<td>(10 – 30)</td>
<td>(1.0 – 2.8)</td>
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<td>&lt;0.01</td>
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<td>Group 2†</td>
<td>60 ± 6.1</td>
<td>3 ± 1.0</td>
<td>94 ± 6.2</td>
<td>23 ± 4.1</td>
<td>146 ± 0.5</td>
<td>4.5 ± 0.1</td>
<td>43 ± 2.0</td>
<td>1.4 ± 0.7</td>
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<td></td>
<td>(46 – 74)</td>
<td>(0 – 6)</td>
<td>(76 – 115)</td>
<td>(17 – 52)</td>
<td>(140 – 160)</td>
<td>(4.4 – 4.5)</td>
<td>(0 – 3.1)</td>
<td>(0 – 3.1)</td>
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<tr>
<td>F2</td>
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<td>&gt;0.1</td>
<td>&lt;0.02</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.01</td>
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The mean weight of the dogs was 17.9 ± 0.9 (SE) kg and the range was 14.0 - 26.3 kg.

*P2 = level of significance compared with the effects of the aortic-left atrial shunt.

fP2 = level of significance compared with the immediate effect (24 hours) of aortic constriction.

tP2 = level of significance compared to the data 7 to 14 days following aortic constriction.

§Dogs showing a typical escape response (n = 3).
†Dogs which failed to show escape response (n = 4).

Mean femoral artery pressure was decreased from 109 to 82 mm Hg (P < 0.01) and LVEDP increased from 26 to 33 mm Hg (P < 0.02).

Four of these 12 dogs died within a week in pulmonary edema with left ventricular end diastolic pressures over 35 mm Hg, elevated plasma renin activity, and sodium retention (see Fig. 1). These animals showed no change in right ventricular diastolic pressure which indicates that the pulmonary edema was due to isolated failure of the left ventricle.
Eight dogs recovered from the acute effects of aortic constriction (Table 1). Following aortic constriction, these animals showed a 4-day period of positive sodium balances which averaged for the group 45, 34, 18, and 15 mEq of sodium per day for days 1 to 4, respectively. However, by day 5 the animals had returned to sodium balance (Figs. 4 and 6). Seven to 14 days following the aortic constriction, these dogs showed an average plasma renin activity of 5.5 ± 0.57 and a range of LVEDP from 15 to 38 mm Hg. These animals subsequently died in pulmonary edema either spontaneously or as a result of the administration of DOCA.

**Spontaneous Pulmonary Edema After Recovery from the Acute Effects of Aortic Constriction.**—(n = 5) Five dogs died in pulmonary edema at least 7 days following aortic constriction (Table 1, Figs. 4-6). The development of fulminating pulmonary edema was associated with a marked rise in plasma renin activity to 47.8 ± 16.1 ng angiotensin/ml plasma. The course of the experimental syndrome in these animals shows two distinct patterns in the changes in sodium balance. First, data presented in Figures 4 and 5 show a long terminal period of moderate sodium retention associated with LVEDPs over 35 mm Hg and a high plasma renin activity.
Effects of DOCA on sodium excretion, plasma renin activity, and left ventricular end-diastolic pressure after constriction of the aorta in a dog with aortic-left atrial shunt.

Second, the dog in Figure 6 represents a typical example of an animal which was in sodium balance, with normal plasma renin activity until the sudden precipitation of fulminating pulmonary edema. This terminal event was associated with marked sodium retention, a sudden fall in femoral arterial pressure and a rise in plasma renin activity over a period of 2 or 3 days. For the group of five dogs, LVEDP averaged 38 mm Hg before pulmonary edema developed. Animals, in which it was possible to obtain measurements during pulmonary edema, had lower LVEDP than on the immediately preceding days. Right ventricular systolic pressure declined to 68 mm Hg (P < 0.05) before the onset of pulmonary edema. The range of right ventricular diastolic pressure was from 4 to 10 mm Hg and the two dogs with the highest pressures (Figs. 5 and 6) also had approximately 1.5 liters of ascitic fluid at autopsy.

Effects of Deoxycorticosterone Acetate (DOCA).—(n = 6). On the basis of the different responses to DOCA administration (15 mg/day), the six dogs have been subdivided into two groups (Table 1 and Figs. 2, 3 and 6). One dog (Fig. 2) belonged to both groups since the first response to DOCA was normal and, later, with further aortic constriction, sodium retention was almost complete during DOCA administration.

Group 1 (n = 3).—These animals showed the normal escape response to excessive DOCA administration. The dogs retained sodium for 1 to 3 days but returned to sodium balance despite the continuation of DOCA for up to 14 days (see Fig. 5). The average peak LVEDP during DOCA administration was 23 mm Hg (range 16 to 31 mm Hg) and the average femoral arterial pressure was 94 mm Hg (Table 1). Although these values were not
Effects of DOCA on sodium excretion, plasma renin activity, and left ventricular end-diastolic pressure in a dog with aortic-left atrial shunt without constriction of the aorta.

significantly different from those obtained before DOCA administration, one of these animals showed an initial fall of 42 mm Hg in arterial pressure immediately after aortic constriction while LVEDP remained unchanged. In all animals the plasma renin activity was significantly below normal (1.6 ng angiotensin/ml plasma) (Table 1).

Group 2 (n = 4)—These dogs did not show escape response from the sodium-retaining effect of DOCA but showed almost complete sodium retention for the entire period of DOCA administration. As in group 1, plasma renin activity was significantly decreased to 1.4 ng angiotensin/ml plasma (Table 1). The hemodynamic changes associated with these findings included (1) an average peak LVEDP of 43 mm Hg (range from 37 to 52 mm Hg), (2) right ventricular systolic pressure of 80 mm Hg, (3) right ventricular diastolic pressure of 3 mm Hg, and (4) an average femoral arterial pressure of 94 mm Hg. The increases in LVEDP and right ventricular systolic pressure were significant statistically in comparison with the values obtained 7 to 14 days after aortic constriction.

The effects of DOCA were studied on two separate occasions in two dogs (Figs. 3 and 6) and both series of injections resulted in the same pattern of almost complete sodium retention. In both animals the highest LVEDP reached during each course of DOCA was associated with clinical signs of pulmonary edema (dyspnea and rales) which subsided after the steroid was stopped. Dog in Figure 2 is of particular interest in that this animal received three series of injections of DOCA. During the chronic course of the study, the aorta was constricted three times. Following the first two constrictions, left ventricular end-diastolic pressure did not rise above 34 mm Hg during DOCA administration and the animal showed a typical normal escape pattern (Fig. 2). However, following the third
aortic constriction, the dog failed to show the escape response from the sodium-retaining effects of the mineralocorticoid and died in pulmonary edema after 5 days of DOCA administration with a LVEDP of 37 mm Hg. Of the four dogs in this group which failed to show the escape response, two are of interest in that DOCA resulted in almost complete retention of sodium without prior constriction of the aorta. Indeed, one of these two animals died in pulmonary edema after 8 days of DOCA with a LVEDP of 45 mm Hg.

Discussion
Numerous studies (2) have been conducted to define the role of the renin-angiotensin system in right-sided congestive heart failure but little is known about this system in left heart failure. In the present study, plasma renin activity was measured to evaluate the status of the renin-angiotensin system (1) in dogs with an aortic-left atrial shunt but without evidence of heart failure, and (2) in dogs with aortic constriction superimposed upon an aortic-left atrial shunt with and without a failing left ventricular myocardium.

In the 16 animals with an aortic-left atrial shunt alone without evidence of heart failure, plasma renin activity was within normal limits. The average LVEDP for the group was 26 mm Hg but some of the dogs had pressures as high as 38 mm Hg without signs of pulmonary edema. Metabolic balance studies revealed that these dogs were in sodium balance. The data show, therefore, that marked distension of the left atrium failed to
Changes in left ventricular filling pressure, plasma renin activity, and renal sodium excretion during the slow progressive development of left heart failure which terminated in pulmonary edema.

produce a change in renal sodium excretion. This observation makes it unlikely that stretch receptors, important in the regulation of sodium excretion, are localized in the left atrium. These results agree with the findings of Gilmore and Daggett (4) that cardiac denervation including section of the nerves to the left atrium failed to alter the natriuresis of saline loading.

In the dogs with aortic constriction superimposed on an aorto-left atrial shunt, pulmonary edema developed within a week in seven dogs. In three of these dogs, death occurred within the first 24 hours and no physiological studies were done. In the other four animals, observations revealed an elevation in plasma renin activity and sodium retention was marked. In another four animals, an acute transient rise in plasma renin activity and sodium retention occurred and lasted for 1 to 4 days following the superimposed aortic constriction. Such transient increases in plasma renin activity and sodium retention have been observed during aortic constriction alone (5, 6) and several mechanisms including a decreased rate of glomerular filtration and transient activation of the renin-angiotensin-aldosterone system have been implicated to explain the changes. Thus, in the four dogs that died in pulmonary edema within a week after aortic constriction, it is not possible to relate the changes in plasma renin activity and sodium retention to a failing left ventricular myocardium and to exclude the effects of aortic constriction per se on these functions.

In contrast, in animals in which the development of pulmonary edema was separated from the acute effects of aortic constriction, the importance of increased plasma renin activity in relation to sodium retention can be evaluated in the pathogenesis of left ventricular failure. Five dogs ran a chronic course following aortic constriction and, thus, are in this category; all five animals died in fulminating pulmonary edema. The development of pulmonary edema was associated with marked sodium retention for 1 to 2 days or it was
preceded by a more chronic phase of moderate sodium retention. This increase in plasma renin activity was uniformly associated with a high LVEDP. There is a paucity of such data on plasma renin activity in patients with left heart failure, and associated data on alterations in cardiovascular function are also lacking.

It is suggested that the mechanism responsible for the increased plasma renin activity involves a decrease in the perfusion of the renal afferent arteriole. It seems likely that a decreased output resulted from the overloaded left ventricle and this combined with decreased arterial pressure activated a stretch receptor mechanism in the renal afferent arteriole (2). Another possibility involves a shift in "effective" blood volume from the systemic to the pulmonary circulation with a similar effect on this stretch receptor mechanism in the renal afferent arterioles. Both autopsy data of the lung weight/body weight ratios (1) and the markedly elevated right ventricular systolic pressure observed in dogs preterminally indicate marked pulmonary congestion. Thus, it is possible that the kidney, in some yet unknown manner, perceives changes in volume or pressure and through intrarenal stretch receptors controls the secretion of renin.

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The second major portion of this study is concerned with the effects of mineralocorticoid excess on sodium excretion in dogs with chronic left ventricular overload. The data obtained provide information on two important points: namely, (1) the functional role of mineralocorticoid excess in left ventricular failure, and (2) the evidence for an additional factor or factors other than aldosterone in the pathogenesis of sodium retention in left heart failure.

Administration of a large dose of DOCA to four of the dogs with chronic left ventricular overload but not in failure produced almost complete retention of sodium by the kidney. Indeed, two of the animals given DOCA died in pulmonary edema after retaining sodium avidly for several days. These observations demonstrate that the renal tubules in these dogs with chronic left ventricular overload were unusually responsive to a mineralocorticoid hormone and that escape response from the sodium-retaining steroid failed to occur. Indeed, in dogs with chronic left ventricular overload and a LVEDP above 35 mm Hg, all that was required to produce sodium retention and eventually pulmonary edema was mineralocorticoid excess. It is suggested that this unusual responsiveness to a mineralocorticoid hormone occurs first in the natural history of the development of heart failure and that activation of the renin-angiotensin system increases aldosterone secretion and sodium retention ensues. It is evident, therefore, that in left heart failure as well as in various experimental models of right-sided congestive failure (2, 7-9) some factor or factors (referred to here in a descriptive way as the unusual responsiveness of the renal tubules to DOCA) in addition to aldosterone itself leads to marked sodium retention and prevents the normal escape pattern.

It should be emphasized that the unusual responsiveness of the renal tubules to a mineralocorticoid hormone was not related to aortic constriction. In the dogs that received DOCA, the transient effects of aortic constriction had subsided. Also, in one dog, aortic constriction resulted in a marked decrease in femoral artery pressure but the normal escape pattern occurred during DOCA administration, and two animals in which the aorta was not constricted failed to show the escape response from DOCA and developed signs of pulmonary edema with marked renal sodium retention. In previous work (5) it was demonstrated that the renal hemodynamic changes following renal artery constriction did not make the renal tubules unusually responsive to DOCA.

In both groups of dogs with left ventricular overload given DOCA in the present study, plasma renin activity was markedly depressed. This response to DOCA has been noted by numerous investigators (see 10). The possible mechanisms proposed to explain this effect include (1) a negative feedback system by way of the expanded intravascular volume and pressure, and (2) a direct action of DOCA on the juxtaglomerular or macula densa cells (10). It should be emphasized that this observation in no way precludes the involvement of a high plasma renin activity in the pathogenesis of heart failure.

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Fishman et al. (11) have reported that the virtual volume of distribution of sodium is larger in the lung than in other tissues. In experimental pulmonary edema secondary to alloxan or epinephrine, Pearce (12) has recently demonstrated a significant loss of Na+ from the pulmonary circulation. Mechanisms which result in sodium retention provide an excess of salt and water for extravasation from the pulmonary vascular bed in the presence of an elevated hydrostatic pressure and other factors. It is concluded that two important precipitating factors in the pathogenesis of pulmonary edema in left heart failure are (1) the unusual responsiveness of the renal tubules to aldosterone, and (2) the activation of the renin-angiotensin-aldosterone system with subsequent sodium retention and fluid accumulation in the pulmonary tissues and alveoli.
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References


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