Renin Release after Hemorrhage and after Suprarenal Aortic Constriction in Dogs without Sodium Delivery to the Macula Densa

By Edward H. Blaine, Ph.D., James O. Davis, Ph.D., M.D., and Robert T. Witty, Ph.D.

ABSTRACT
To study the possible factors that control renin secretion by the kidney, a model has been developed to prevent glomerular filtration in the dog. Ureteral ligation was combined with a 2-hour period of total renal ischemia to induce tubular degeneration and cessation of glomerular filtration. After the surgical procedures, the dogs were maintained for 4 days by peritoneal dialysis. The absence of lissamine green dye in the renal tubules after an intra-aortic injection provided evidence that filtration had ceased. Plasma renin activity was significantly increased in six conscious dogs at 30, 60, and 90 minutes after hemorrhage of 20 ml/kg body weight. In another group of five conscious animals, suprarenal aortic constriction produced increases in plasma renin activity at 30, 60, and 90 minutes that were 3 to 4 times the control values before aortic constriction. Plasma renin substrate concentration did not change significantly after hemorrhage or after aortic constriction. In a third group of five dogs, only the left kidney was subjected to ureteral ligation and renal ischemia. These dogs were anesthetized and renal blood flow was measured with an electromagnetic flowmeter. After hemorrhage (20 ml/kg), renin secretion increased significantly above control levels at 30, 45, and 60 minutes. It is concluded that sodium delivery to the macula densa is not essential for renin secretion.

ADDITIONAL KEY WORDS baroreceptor hypothesis renal ischemia ureteral ligation plasma renin activity nonfiltering kidney plasma renin substrate lissamine green dye

Currently there are two popular hypotheses concerning the intrarenal receptor which receives the signal leading to renin release (1). Some workers support the idea that the sensor is in the juxtaglomerular granular cells of the renal afferent arteriole and responds to decreased stretch (2-4). Others have suggested that the macula densa responds to changes in the sodium load or concentration (5, 6). Both the granular cells and the macula densa could conceivably act as receptors and cytological (7) as well as histochemical evidence (8) indicates that both structures respond to stimuli which lead to increased renin secretion. The difficulty that has arisen in assessing the role of these two possible receptors is that stimuli that affect one almost invariably affect the other.

In the present study, the macula densa mechanism has been rendered nonfunctional by extensive renal tubular damage, cast formation, and by prevention of glomerular filtration in the dog. Hemorrhage or suprarenal aortic constriction has been used to stimulate renin release in this model. By this
experimental design, the juxtaglomerular cells of the renal afferent arteriole remain intact as a possible intrarenal receptor.

Materials and Methods

Design for Study of Plasma Renin Activity after Hemorrhage in Conscious Dogs with Nonfiltering Kidneys.—Seven female mongrel dogs weighing 15 to 20 kg were used in this portion of the study. Under sterile conditions and with pentobarbital anesthesia (30 mg/kg), the ureters were ligated and sectioned via retroperitoneal flank incisions. A suture clamp was applied to each renal artery near its origin from the aorta and allowed to remain for 2 hours. After this period of renal ischemia, the clamps were removed and the incisions closed. Following recovery from the operation, the oral intake of food and water was discontinued. Daily peritoneal dialysis of the conscious dog was begun on the day following surgery. The dialysis fluid used daily was 1500 to 2000 ml of 4.5% dextrose in commercially available dialysis solution (McGaw Laboratories, Inc.). The total amount of dialysis fluid was always recovered. The dogs were given 200 ml of 20% dextrose in distilled water daily by an indwelling saphenous vein catheter. This was done to replace insensible water loss and to maintain to some extent the dogs’ caloric intake. Daily measurements were made of arterial pressure by direct femoral arterial puncture, plasma sodium, and potassium concentrations, hematocrit and body weight. On the fourth day after surgery, two control blood samples were obtained through the saphenous vein catheter for determination of plasma renin activity and renin substrate concentration. The conscious dogs were rapidly bled 20 ml/kg of body weight and the arterial pressure was again measured. Subsequently, the dogs were allowed to lie on the floor undisturbed and blood samples were taken at 30, 60, and 90 minutes. Plasma renin substrate concentration was also measured at the 90-minute period to ascertain if hemorrhage affected it. After the last sampling period, the blood was reinfused and the dogs were anesthetized with pentobarbital. A long midline incision was made and both kidneys were observed for glomerular filtration as previously described.

Design for Study of Renin Secretion after Suprarenal Aortic Constriction in Conscious Dogs with Nonfiltering Kidneys.—The seven mongrel dogs of this experiment weighed 14 to 20 kg. The surgical preparation of the model was the same as previously described except that a loop of polyethylene tubing was placed loosely around the aorta immediately above the origin of the right renal artery. The ends of the tubing were passed through another length of large bore polyethylene tubing and sutured beneath the skin a few centimeters from the incision. In this experimental series, peritoneal dialysis was begun on the second day after surgery and two cycles of dialysis were performed; the same quantity of 4.5% dextrose solution was used for each dialysis. On the third day after the operation, dialysis was done but only one cycle was completed. On the fourth day, a catheter was introduced into the femoral artery and the tip positioned immediately below the aortic ligation. The free end of the catheter was also exposed at this time. Both of these minor surgical procedures were performed under local anesthesia and a 30-minute recovery period was allowed before beginning the experiment.

The acute experiment was done in conscious dogs resting quietly on the floor. Blood pressure was measured continuously with a Statham pressure transducer and Sanborn recording system. Two control blood samples were obtained through the saphenous vein catheter for determination of plasma renin activity and plasma renin substrate concentration. The aorta was constricted to decrease renal arterial perfusion pressure to a level of 40 to 80 mm Hg. Blood samples were subsequently collected at 30, 60, and 90 minutes after aortic constriction. After the last blood collection, the constriction was released and the dogs anesthetized with pentobarbital. A long midline incision was made and both kidneys were observed for glomerular filtration as previously described.

Design for Study of Renin Secretion after Hemorrhage in Anesthetized Dogs with Nonfiltering Kidneys.—The five mongrel dogs of this experiment weighed 14 to 20 kg. Under pentobarbital anesthesia, the left kidney was subjected to ureteral ligation and renal ischemia as previously described. After recovery from the operation, the animals were allowed food and water ad libitum. On the third day after the operation, a right nephrectomy was performed. Food was removed at this time but 200 ml of water were allowed after recovery from the anesthetic. The following morning the dogs were again anesthetized and a catheter was introduced into the femoral artery and the tip positioned immediately above the origin of the renal arteries. With the exception of dogs 1 and 3, which had a flow transducer and ovarian vein catheter chronically implanted at the time of surgery.
### TABLE 1

Data from Individual Conscious Dogs with Nonfiltering Kidneys on the Day of Acute Hemorrhage

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>Plasma renin activity* (ng/mL)</th>
<th>Mean AP (mm Hg)</th>
<th>Change in AP after hemorrhage (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.5</td>
<td>6.5</td>
<td>15.0</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>10.0</td>
<td>12.0</td>
<td>18.0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>2.8</td>
<td>2.5</td>
<td>4.0</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>6.2</td>
<td>5.0</td>
<td>12.8</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>6.1</td>
<td>3.9</td>
<td>14.2</td>
<td>3.5</td>
</tr>
<tr>
<td>6</td>
<td>49.6</td>
<td>57.0</td>
<td>72.0</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>2.9</td>
<td>2.0</td>
<td>3.8</td>
<td>5.5</td>
</tr>
<tr>
<td>Mean</td>
<td>11.9</td>
<td>13.4</td>
<td>18.0</td>
<td>25.4</td>
</tr>
</tbody>
</table>

*Plasma renin activity is the amount of angiotensin per milliliter of plasma; data obtained before hemorrhage.

### TABLE 2

Data from Individual Conscious Dogs with Nonfiltering Kidneys on the Day of Acute Suprarenal Aortic Constriction

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>Plasma renin activity* (ng/mL)</th>
<th>Mean AP (mm Hg)</th>
<th>Change in AP after hemorrhage (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.6</td>
<td>8.2</td>
<td>20.0</td>
<td>10.0</td>
</tr>
<tr>
<td>2</td>
<td>7.4</td>
<td>7.4</td>
<td>19.0</td>
<td>20.0</td>
</tr>
<tr>
<td>3</td>
<td>17.0</td>
<td>14.0</td>
<td>63.0</td>
<td>24.0</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>5.2</td>
<td>24.0</td>
<td>24.0</td>
</tr>
<tr>
<td>5</td>
<td>10.5</td>
<td>12.0</td>
<td>34.7</td>
<td>34.7</td>
</tr>
<tr>
<td>Mean</td>
<td>9.4</td>
<td>9.4</td>
<td>27.3</td>
<td>37.0</td>
</tr>
</tbody>
</table>

*Plasma renin activity is the amount of angiotensin per milliliter of plasma; data obtained before hemorrhage. AP = arterial pressure.
Data from Individual, Anesthetized Dogs with a Single Nonfiltering Kidney on the Day of Acute Hemorrhage

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>Renin secretion (ng angio./min)</th>
<th>After acute hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15 min</td>
<td>30 min</td>
</tr>
<tr>
<td>1</td>
<td>160</td>
<td>437</td>
<td>381</td>
</tr>
<tr>
<td>2</td>
<td>306</td>
<td>88</td>
<td>488</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>287</td>
<td>476</td>
</tr>
<tr>
<td>4</td>
<td>129</td>
<td>365</td>
<td>532</td>
</tr>
<tr>
<td>5</td>
<td>86</td>
<td>207</td>
<td>319</td>
</tr>
</tbody>
</table>

Mean | 170 | 275 | 439 | 479 | 475

*p* >0.4 <0.01 <0.05 <0.05

*Data obtained before hemorrhage. Abbreviations: Angio. = angiotensin; AP = arterial pressure; Max. = maximum; BF = blood flow.

renal ischemia and ureteral ligation, the left kidney was exposed through a flank incision and a noncannulating flow transducer placed around the renal artery near its origin from the aorta. A square wave electromagnetic flowmeter (Carolina Electronic Instruments) was used to measure renal blood flow. A catheter was introduced into the left ovarian vein to obtain renal venous blood samples. The animals were allowed to recover for at least 1 hour after all surgical procedures were completed. Two control blood samples for determination of renin secretion were obtained by simultaneous withdrawal of blood from the renal vein and aorta. The animals were rapidly bled 20 ml/kg of body weight from the aortic catheter. Simultaneous blood samples from the aorta and renal vein were obtained 15, 30, 45, and 60 minutes after hemorrhage. After the 60-minute sample was obtained, the blood was reinfused and the kidney viewed for glomerular filtration as previously described. At this time in the experimental protocol, the renal artery flow transducer was calibrated directly by cannulating the artery distal to the transducer and collecting timed blood volumes.

**Analytical Methods.**—Ten milliliter blood samples were collected in cold tubes containing 0.1 ml of 10% ethylenediaminetetraacetate (EDTA). The blood was centrifuged and the plasma was separated and frozen. For determination of plasma renin activity, the thawed plasma was dialyzed against 0.01M EDTA for 6 hours and then against a phosphate buffer (pH 5.3) for 12 hours. The dialyate was incubated at 37°C for four hours with added EDTA and diisopropylphosphoryl fluoride (DFP) to inhibit angiotensinase activity according to the method of Schneider et al. (9). The reaction was stopped by placing the tubes in boiling water. For the measurement of renin substrate concentration, a 1:10 dilution of dog plasma was made with phosphate buffer at pH 5.3. To 2 ml of this solution, 0.1 ml of a 1:10 dog renin solution (approximately 1 Goldblatt unit/ml) was added along with 0.05 ml of 1:100 DFP, 0.05 ml saturated sodium chloride, and 0.1 ml of a 10% solution of EDTA. This mixture was incubated at 37°C for 3 hours. The tubes were placed in boiling water for 10 minutes and then cooled in ice. The volume was adjusted with phosphate buffer (pH 5.3) to 4 ml and the solution was mixed and centrifuged; the supernatant fluid was retained for assay. The angiotensin generated by these procedures was assayed in the vagotomized, pentolinium blocked rat with val5-angiotensin II amide (Hypertensin, Ciba, Ltd.) as the standard. Renin activity and substrate concentration are expressed as nanograms of angiotensin per milliliter of plasma. Renin secretion is expressed as nanograms of angiotensin per minute. Plasma electrolytes were determined by flame photometry and hematocrit by the capillary tube method.

**Results**

Effects of Hemorrhage on Plasma Renin Activity in Dogs with Nonfiltering Kidneys.—Data from individual dogs on the day of hemorrhage are presented in Table 1. Plasma sodium and potassium concentrations and hematocrit were obtained before the hemorrhage. Although dialysis was not performed on this day, uremic changes were not excessive and the dogs showed only slight elevation in plasma potassium concentration. Arterial press...
sure decreased 6 to 60 mm Hg in response to hemorrhage; the largest changes were observed in the two dogs with the highest control blood pressures. Dog 6 was excluded from the statistical analysis by Chauvenet’s criterion (10), since its resting blood pressure was very high (190 mm Hg) and its control renin levels were excessively elevated. It should be noted, however, that this dog responded in the same manner as the other animals.

Excluding data from dog 6, the average plasma renin activity during the two control periods was 5.8 ng angiotensin/ml of plasma. This increased to 9.6 at 30 minutes, to 10.8 ng at 60 minutes and to 13.0 ng angiotensin/ml of plasma at 90 minutes. All three changes were statistically significant. Renin substrate concentration did not change significantly with hemorrhage.

Upon injection of lissamine green dye into the suprarenal aorta, a green flush was observed as the dye was carried to the surface of the kidney in the blood but dye did not appear in the renal tubules of any of these dogs.

### Effects of Suprarenal Aortic Constriction on Plasma Renin Activity in Dogs with Nonfiltering Kidneys

Seven dogs were used in this experiment but two were excluded because a few of their renal tubules contained dye during the observations after lissamine green dye injection. No dye was observed in the tubules of the kidneys of the other five dogs of this series but there was always a green flush to the kidneys as the dye was carried to the surface in the blood.

The individual data from the five dogs of this experiment are presented in Table 2. Dialysis was not carried out on this day and plasma potassium concentration was slightly elevated. The plasma sodium concentration of these dogs was slightly but significantly below normal (P<0.05). For the five dogs with nonfiltering kidneys, the mean control value for plasma renin activity was 9.4 ng angiotensin/ml of plasma. This increased to 27.3 at 30 minutes, 33.1 at 60 minutes, and 37.0 at 90 minutes. The increases are statistically significant at the 60- and 90-minute periods. Plasma renin substrate concentration did not change significantly during the experiment.

### Effects of Hemorrhage on Renin Secretion in Dogs with Nonfiltering Kidneys

Individual data from the five dogs of this experiment on the day of the acute hemorrhage are presented in Table 3. Blood pressure decreased between 4 to 52 mm Hg after the 20 ml/kg hemorrhage. The decrease in blood pressure was associated with a decrease in renal blood flow of 32 to 49 ml/min. The mean value for the two control periods for renin secretion was 190 ng angiotensin/min; this increased to 275 at 15 minutes, 439 at 30 minutes, 479 at 45 minutes, and 476 ng angiotensin/min at 60 minutes. The increases in renin secretion were statistically significant at the periods of 30, 45, and 60 minutes. Mean arterial blood pressures

### Table 1: Hemodynamic Data

<table>
<thead>
<tr>
<th>Plasma electrolytes* (mEq/liter)</th>
<th>Hematocrit* (%)</th>
<th>Mean AP before hemorrhage (mm Hg)</th>
<th>Max. change in AP after hemorrhage (mm Hg)</th>
<th>Mean renal BF before hemorrhage (ml/min)</th>
<th>Max. change in renal BF (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na 144</td>
<td>30</td>
<td>132</td>
<td>-36</td>
<td>73</td>
<td>-39</td>
</tr>
<tr>
<td>K 4.7</td>
<td>4.9</td>
<td>102</td>
<td>-34</td>
<td>89</td>
<td>-46</td>
</tr>
<tr>
<td>HCO3 2.6</td>
<td>7.6</td>
<td>162</td>
<td>-10</td>
<td>100</td>
<td>-21</td>
</tr>
<tr>
<td>Hematocrit 35</td>
<td>38</td>
<td>126</td>
<td>-4</td>
<td>124</td>
<td>-52</td>
</tr>
<tr>
<td>Mean AP before hemorrhage</td>
<td>136</td>
<td>128</td>
<td>-32</td>
<td>87</td>
<td>-37</td>
</tr>
<tr>
<td>Max. change in AP after hemorrhage</td>
<td>142</td>
<td>94</td>
<td>-27</td>
<td>8.9</td>
<td>-4.2</td>
</tr>
<tr>
<td>Mean renal BF before hemorrhage</td>
<td>72</td>
<td>6.4</td>
<td>-8.9</td>
<td>8.0</td>
<td>-4.2</td>
</tr>
</tbody>
</table>

*Data from individual dogs.
Photomicrograph of a dog kidney which had been subjected to ureteral ligation and a 2-hour period of renal ischemia 4 days previously (×125).

at 15, 30, 45, and 60 minutes were 123, 119, 121, and 117 mm Hg, respectively; renal blood flows were 68, 74, 77, and 68 ml/min, respectively. Glomerular filtration was not observed in any of the dogs of this experiment.

Gross and Histological Findings in Nonfiltering Dog Kidneys.—The renal tubules of the nonfiltering kidneys were frequently filled with casts which gave a "thready" appearance to the surface of the kidneys when viewed through the dissecting microscope. Areas were encountered that did not contain casts and these were generally associated with capsular vessels. None of these areas showed any glomerular filtration. Histologically, the damage to the renal tubular system ranged from diffuse coagulation necrosis to marked cast formation in the tubular lumens (Fig. 1). The proximal tubules were more affected than the distal tubules and the macula densa remained intact. The renal circulation was maintained.
and the glomerular tufts appeared to be well perfused. Randomly selected kidney sections were stained for juxtaglomerular granules by the Bowie technique. Granules were observed in all of these sections but were abundant in only a few instances.

Discussion

Three mechanisms have been proposed that might control renin release by the kidney: (1) The baroreceptor hypothesis which suggests that an intrarenal pressure variable regulates renin release; (2) the macula densa theory which suggests that an intrarenal sodium variable regulates renin release; (3) the renal sympathetic nerve hypothesis. Skinner et al. (3, 4) demonstrated that renin release occurred following constriction of the aorta above the renal arteries. This response occurred with or without a concomitant decrease in renal blood flow. Other stimuli, such as hemorrhage (11), injection of histamine (12), or administration of sodium nitroprusside (13), which produce systemic hypotension, also resulted in increased plasma renin activity. These results might be interpreted to indicate that decreased stretch of the afferent glomerular arterioles led to renin release. On the other hand, Vander and Miller (5) found that increased renin release secondary to aortic constriction was prevented by simultaneously administering diuretic drugs; they suggested that increased sodium load at the macula densa blocked the release of renin.

In support of an extrarenal mechanism, Vander (15) has shown that direct stimulation of the renal nerves resulted in renin release. However, a number of investigators (16-18) have demonstrated that the renal sympathetic nerves are not essential for renin secretion.

One difficulty in interpreting the influence of various experimental manipulations on renin release arises from attempts to separate the effects on the afferent arteriole from the effects on the macula densa. For example, reduction of renal perfusion pressure decreases the rate of glomerular filtration and, presumably, sodium delivery to the macula densa. Diuretic drugs not only change the sodium load to the macula densa but frequently alter afferent arteriolar tone (19-21) and, therefore, could influence a "sensing" mechanism in the afferent arteriole. Tobian (14) reported a 10% decrease in renal vascular resistance when plasma with a high sodium concentration perfused the kidney. This also could have altered renin release through changes in the afferent arteriole.

In the present study, the macula densa has been eliminated as a receptor for changes in tubular fluid composition by rendering the kidney incapable of glomerular filtration. This was accomplished by a combination of ureteral ligation and ischemic damage to the renal tubular system. Both ureteral ligation and renal ischemia produced tubular damage and loss of renal function. When only the ureters were ligated, the kidneys became hydronephrotic with slow loss of tubular mass secondary to pressure necrosis (22), and glomerular filtration continued after 4 days even with ureteral pressures in excess of 70 mm Hg (personal observations). With only renal ischemia for 2 hours, there was initial loss of renal function that was incomplete and returned toward normal over a period of several weeks (23, 24). In the present study, these techniques have been combined to induce tubular damage. Since glomerular filtration was absent in surface renal tubules, cast formation was extensive in some kidneys, and coagulation necrosis or more severe renal tubular damage was present, it is unlikely that
acute alterations of tubular sodium occurred at the macula densa in the present study. Even if glomerular filtration had occurred in some nephrons, it is difficult to conceive of either hemorrhage or aortic constriction producing the usual changes in renal tubular fluid to provide a signal at the macula densa when tubules were filled with casts and the tubule cells were necrotic. The renal tubules in deep juxtamedullary nephrons were not, of course, visualized for evidence of glomerular filtration. In this connection, however, it should be pointed out that the juxtaglomerular index of granulation was fourfold higher in the outer renal cortex than in the juxtamedullary cortex in dogs (25). In view of this localization of renin in the outer cortex and the consistent and frequently marked increase in plasma renin activity following both hemorrhage and aortic constriction (Tables 1-3), it seems likely that renin release occurred without alterations in sodium delivery to the macula densa.

Peritoneal dialysis was used to maintain the animals during the 4-day period of total anuria and elevated plasma potassium was a routine finding in these animals. Maebashi et al. (26) have reported that high potassium levels suppress renin release. Thus, the presence of an elevated plasma potassium concentration in these studies could have made it more difficult to demonstrate increased renin release than would conceivably have occurred in normokalemic animals.

The use of conscious, undisturbed dogs in portions of this study necessitated measurement of plasma renin activity as an indication of renin secretion. In addition to increased secretion, decreased renin metabolism and increased plasma renin substrate concentration can result in increased plasma renin activity. Plasma renin substrate concentration was measured in this study and did not increase during the experimental periods. Decreases in renin metabolism are of minor significance after hemorrhage (27), unless the degree of hemorrhage is massive (28). More importantly, the present study reveals that renin secretion was increased after a 20 ml/kg hemorrhage in anesthetized dogs with a single nonfiltering kidney. Finally, suprarenal aortic constriction was also used to increase plasma renin activity since it is unlikely that hepatic blood flow and, consequently, renin metabolism would be altered after this stimulus. Altered hepatic blood flow is a primary determinant of renin metabolism (29).

It has been demonstrated in this study that peripheral plasma renin activity was significantly increased after hemorrhage and after suprarenal aortic constriction in conscious, undisturbed dogs with nonfiltering kidneys. In addition, it was also demonstrated that renin secretion was increased after hemorrhage in the anesthetized dog with a single nonfiltering kidney. This model circumvents most of the difficulties inherent in past experiments in which both possible intrarenal receptors were operative, since alterations in tubular fluid composition failed to occur at the macula densa.

Although these experiments do not eliminate a possible role of the renal nerves in renin secretion, it is not possible in this study for the renal nerves to have affected renin secretion by modulation of glomerular filtration rate as suggested by Vander (14). If the renal nerves did influence renin release, they did so by either a direct action on the renin secreting cells or by altering the tone of the renal vessels, since changes in glomerular filtration rate did not occur. The results of this study suggest, therefore, that acute changes in tubular sodium at the macula densa are not essential for renin to be released and that the renin secreting system is sensitive to either alterations in intrarenal vascular pressure or nervous influences.

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References

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