Effects of Renal Arterial Infusion of Sodium and Potassium on Renin Secretion in the Dog

By Robert E. Shade, James O. Davis, J. Alan Johnson, and Robert T. Witty

ABSTRACT

The nonfiltering kidney model was used to determine whether sodium or potassium inhibits renin secretion in the absence of a functional macula densa in dogs with thoracic inferior vena caval constriction. The control rate of renin secretion was high, and decreases were readily recognized. After control observations, hypertonic sodium chloride or hypertonic potassium chloride was infused into the renal artery for 1 hour, and renin secretion was measured at 15-minute intervals. An increase in renal venous plasma sodium concentration from 141 to 154–158 mEq/liter caused no change in renin secretion for the first 45 minutes of infusion in dogs with a nonfiltering kidney. In contrast, dogs with thoracic caval constriction but with a filtering kidney showed a striking decrease in renin secretion during intrarenal sodium infusion (3,097 to 1,061 ng angiotensin/min, \( P < 0.02 \)). An increase in renal venous plasma potassium concentration from 3.9 to 6.1 mEq/liter in one group of dogs and from 4.9 to 8.3 mEq/liter in a second group also caused no change in renin secretion in the nonfiltering kidney of dogs with thoracic caval constriction. However, in dogs with thoracic caval constriction and a filtering kidney, potassium infusion decreased renin secretion (1,952 to 984 ng angiotensin/min, \( P < 0.05 \)). In all experiments, infusion of sodium chloride or potassium chloride failed to produce a significant change in renal blood flow, arterial blood pressure, or inferior vena caval pressure. Therefore, no evidence was obtained for a vascular action or a direct effect of sodium or potassium on the juxtaglomerular cells, and the data are consistent with an action mediated by the renal tubular system.

KEY WORDS control of renin release plasma sodium concentration plasma potassium concentration renal baroreceptor macula densa juxtaglomerular cells renal blood flow nonfiltering kidney model thoracic inferior vena caval constriction

Changes in sodium (1) and potassium balance (2–7) influence plasma renin activity. Also, intrarenal arterial infusion of sodium chloride (8, 9) or potassium chloride (10, 11) in the anesthetized dog decreases the rate of renin release, but the exact mechanism by which either electrolyte suppresses renin release is not known. Conceivably, the inhibition could result from an influence on either of two intrarenal receptor mechanisms—the renal vascular receptor (12, 13) or the macula densa (1)—or from a direct effect on the juxtaglomerular cells.

Experiments with the nonfiltering kidney model provide information about renin release in the absence of a functional macula densa (13). Therefore, to obtain evidence about the mechanism by which sodium and potassium decrease renin secretion, sodium or potassium was infused intra-arterially into both filtering and nonfiltering kidneys in dogs with thoracic inferior vena caval constriction. A response to either sodium or potassium only in the
A nonfiltering kidney model would indicate a mechanism that does not involve the macula densa. Alternatively, a response to the ions only in dogs with a filtering kidney would indicate that an intact renal tubular system is necessary for the decrease in renin release. Dogs with caval constriction were used to provide a control rate of renin secretion high enough (14) to demonstrate readily a decrease in secretion during the experimental period, if such a decline occurred.

Methods

Under sterile conditions, the thoracic inferior vena cava was constricted in 25 female dogs, weighing 17–22 kg, by placing a silk ligature around the vein approximately halfway between the diaphragm and the right atrium. Following surgery, the dogs were placed in metabolic cages to determine their daily rate of sodium excretion. Evidence for a successful caval constriction consisted of sodium retention for 4 days or longer with the concomitant formation of ascites. These dogs were used in one of the following experimental groups.

Intrarenal Sodium and Potassium Infusions in Dogs (n = 9) with a Filtering Kidney.—On the day before the acute experiment, the right kidney was excised, and all food was withheld from the dog. The following morning, the dog was anesthetized with sodium pentobarbital (30 mg/kg, iv), polyvinyl catheters were inserted in the femoral artery and vein and in the left renal vein via the ovarian vein, and an electromagnetic flow probe (Carolina Electronic Instruments) was placed around the left renal artery. A 22-gauge needle was inserted in the left renal artery for intrarenal infusions, and another catheter was placed in the ureter for determination of creatinine clearance and electrolyte excretion. Arterial blood pressure was measured with a Sanborn model P23Db pressure transducer. Both arterial blood pressure and renal blood flow were recorded on a Sanborn model 7700 recorder.

Following surgical preparation, a priming solution of creatinine was administered, and a maintenance infusion of creatinine in normal saline was initiated (36 mg/ml at 0.59 ml/min). In addition, normal saline was infused into the renal artery at 0.59 ml/min. Sixty minutes later, two 15-minute control renal clearance studies were performed. Blood samples for determination of the plasma levels of creatinine, sodium, and potassium were drawn at the midpoint of each clearance period. Arterial and renal venous blood samples were collected at the end of each 15-minute period for determination of plasma renin activity. Following the second control renal clearance study, renal arterial infusion of either hypertonic sodium chloride or hypertonic potassium chloride was initiated at 0.59 ml/min at a concentration calculated to increase renal venous plasma concentration 20 mEq/liter for sodium or 2 mEq/liter for potassium. Four successive 15-minute experimental renal clearance studies were performed with concomitant measurements of renal blood flow, arterial blood pressure, and renin secretion at the end of each 15-minute period. After this hour of experimental studies, isotonic saline infusion into the renal artery was reinstituted, and the dog was allowed to recover for 60 minutes. Two 15-minute recovery clearance studies were performed, and then a second 60-minute infusion of either sodium chloride or potassium chloride was given. This 60-minute experimental period was followed by two more recovery clearance studies. In this series of nine dogs, six dogs received sodium first and potassium second, and the remaining three dogs were given potassium first and sodium second. All blood removed for sampling was replaced with fresh donor blood from a normal dog.

Intrarenal Sodium and Potassium Infusions in Dogs (n = 10) with a Nonfiltering Kidney.—A nonfiltering kidney was produced on the left side in each dog by the method described by Blaine et al. (13). This procedure consisted of ligating the left ureter and placing a serrefine clamp on the renal artery for 2 hours. Then 2–3 days later, the right kidney was removed, and the experiment was performed on the nonfiltering kidney the following day.

The surgical preparation and the experimental procedures were identical to those used in the previous experimental series with the exception that the ureter was not cannulated. Following placement of the catheters and flow probe, isotonic sodium chloride was infused into the renal artery for 60 minutes. Two control arterial and renal venous blood samples were collected for determination of renin secretion before infusing either hypertonic sodium chloride or hypertonic potassium chloride as described in the previous experiment. In this series, the order of infusion of sodium and potassium was varied with five dogs receiving the sodium infusion first and the potassium infusion second, and three dogs receiving the potassium first and sodium second. In addition, one dog received only one 60-minute infusion of sodium chloride, and another dog received only the potassium infusion.

Intrarenal Potassium Infusion in Dogs (n = 6) with a Nonfiltering Kidney and Normal Control Plasma Potassium Levels.—Since the control plasma potassium concentrations were high in dogs with a nonfiltering kidney (5.0 mEq/liter),
another group of dogs was studied during potassium infusion into a nonfiltering kidney. Six dogs were prepared with thoracic caval constriction and a nonfiltering kidney as described above except that the filtering kidney was removed at the beginning of the acute experiment rather than the day before the experiment. This change in procedure resulted in normal control plasma potassium levels. After collecting samples for control studies of renin secretion, potassium chloride was infused into the renal artery as described for the preceding two experiments.

**Analytical Procedures.**—Arterial and renal venous blood samples for determination of plasma renin activity were collected in chilled tubes containing 0.1 ml of 10% ethylenediaminetetraacetic acid (EDTA) for each 10 ml of blood. The samples were immediately cooled in an ice bath and centrifuged in the cold to separate the plasma. Plasma samples were then frozen until they were prepared for assay by the method of Schneider et al. (15). This procedure consisted of dialyzing 2 ml of plasma against phosphate buffer (pH 5.3), adding sodium chloride and diisopropylfluorophosphate (DFP), and incubating at 37°C for 3 hours. Following incubation, the samples were placed in a boiling water bath for 10 minutes and then chilled in an ice bath. Each sample was diluted to 4 ml with phosphate buffer, stirred, and centrifuged, and the supernatant fluid was frozen until it was assayed. Samples were assayed by a pressor response in the pentobarbital-anesthetized, pentolinium-blocked rat with angiotensin II (Hypertensin, Ciba) as the standard. Plasma renin concentrations were expressed in nanograms of angiotensin formed per milliliter of plasma. Renin secretion was calculated by subtracting arterial plasma renin activity from the renal venous plasma renin activity and multiplying the difference by renal plasma flow. Renin secretion rates were expressed as nanograms of angiotensin per minute. Plasma and urine concentrations of creatinine were measured by standard methods. Sodium and potassium concentrations in plasma and urine were determined by flame photometry. Hematocrit values were determined in duplicate by a microhematocrit method.

At the end of each experiment with the nonfiltering kidney, a solution of lissamine green dye was injected into the aorta above the kidney to verify the lack of glomerular filtration (13). Examination of the superficial renal tubules with a dissecting microscope revealed that dye failed to appear in the renal tubules in any of the dogs used in this study. Mean differences between control and experimental values were analyzed for significance by Student’s t-test for paired observations.

### Results

**Effects of Intrarenal Sodium Infusion in Dogs with a Filtering Kidney.**—Infusion of hypertonic sodium chloride (2.0–3.4 mEq/ml) increased renal venous plasma sodium concentration from 141 ± 1 (SE) mEq/liter to 154 ± 2 mEq/liter (*P* < 0.05) within 15 minutes and to a maximum of 158 ± 2 mEq/liter (*P* < 0.02) at 60 minutes. These results are presented in Figure 1. The values for renin secretion during the two control periods were 3,609 ± 1,783 (SE) ng angiotensin/min and 2,082 ± 821 ng angiotensin/min; the difference was not significant (*P* > 0.05). Comparison of either control value or of the average control value with the average of 1,061 ± 361 ng angiotensin/min for the 60-minute experimental period showed a significant decrease with all *P* values less than 0.05. Also, comparison of the first and of the second control value with the first 15-minute experimental value revealed a significant reduction in both instances with *P* values less than 0.05. Following 1 hour of recovery, renal venous plasma sodium concentration had returned to

![Figure 1](image-url)
149 ± 2 mEq/liter, and renin secretion was 1,949 ± 575 ng/min (P > 0.05). Infusion of hypertonic sodium chloride produced no consistent or significant changes in renal blood flow and mean arterial blood pressure. After 1 hour of recovery, blood pressure remained unchanged, but renal blood flow had increased significantly from an average of 158 ± 10 ml/min during sodium infusion to 186 ± 10 ml/min (P < 0.02).

The effects of sodium infusion on creatinine clearance and electrolyte excretion are shown in Figure 2. Sodium infusion produced a significant increase in sodium excretion from 6.4 ± 2.4 μEq/min to an average of 95.3 ± 30.8 μEq/min (P < 0.02) for the 60-minute infusion period. Following a recovery period of 1 hour, sodium excretion had significantly decreased to 59.1 ± 28.6 μEq/min (P < 0.05). Intrarenal sodium infusion produced no significant or consistent changes in creatinine clearance and potassium excretion.

Effects of Intrarenal Sodium Infusion in Dogs with a Nonfiltering Kidney.—Intrarenal sodium infusion (1.1-4.1 mEq/ml) into a nonfiltering kidney of dogs with caval constriction increased renal venous plasma sodium concentration from 139 ± 3 mEq/liter to a range of 155 to 159 ± 4 mEq/liter for the 60-minute experimental period (Fig. 3). Renin secretion averaged 540 ± 102 ng angiotensin/min during control observations, 434 ± 99 ng angiotensin/min during the infusion of sodium, and 529 ± 82 ng angiotensin/min after a 60-minute recovery period. The differences between the average control and experimental rates of renin secretion and between the average experimental and recovery rates of renin secretion were not significant (P > 0.05). However, renin secretion determined after 60 minutes of sodium infusion (205 ± 79 ng angiotensin/min) was significantly lower (P < 0.05) than the average control and recovery rates of renin secretion. Renal venous plasma sodium concentration returned to 144–145 mEq/liter during the recovery period. There were no significant changes in renal blood flow and mean arterial blood pressure during the experiment. For comparison, the average rate of renin secretion for five normal dogs with a single nonfiltering kidney is presented at the right side of Figure 3. The control rate of renin secretion in the group of dogs with caval constriction was significantly greater than the rate of renin secretion in normal dogs with a single nonfiltering kidney (P < 0.01).
Effects of Intrarenal Potassium Infusion in Dogs with a Filtering Kidney.—During intrarenal infusion of potassium (0.254-0.427 mEq/ml), renal venous plasma potassium concentration increased from 3.6 mEq/liter to a range of 5.1 to 5.4 mEq/liter (Fig. 4). Associated with the increase in the renal venous plasma potassium concentration was a striking decrease in renin secretion from 1,952 ± 563 ng angiotensin/min to 423 ± 166 ng angiotensin/min (P<0.02); the average decrease for the 60-minute infusion was to 984 ± 270 ng angiotensin/min, and this value was also significantly decreased in comparison to control observations (P<0.05). The initial depression was followed by an "escape" as renin secretion returned toward the control level. Therefore, renin secretion during the recovery period did not differ appreciably from the last experimental value. Renal venous plasma potassium concentration returned to 3.7 mEq/liter (P<0.02). There were no significant changes in renal blood flow or mean arterial blood pressure.

Intrarenal potassium infusion produced no significant changes in creatinine clearance (Fig. 5). Potassium excretion significantly increased from 34.8 ± 5.0 μEq/min to an average of 108.0 ± 14.4 μEq/min (P<0.01) during the infusion and decreased to 67.0 ± 7.2 μEq/min (P<0.01) during recovery. Sodium excretion increased from 50.1 ± 26.2 μEq/min to 105 ± 49 μEq/min (P<0.05) during potassium infusion and decreased to 36 ± 21 μEq/min (P<0.05) during recovery.

Effects of Intrarenal Potassium Infusion in Dogs with a Nonfiltering Kidney.—Infusion of potassium chloride (0.083-0.327 mEq/ml) into dogs with a nonfiltering kidney increased renal venous plasma potassium concentration from 5.0 mEq/liter to a range of 6.4 to 8.3 mEq/liter (Fig. 6); the plasma potassium concentration returned to 5.9 mEq/liter during recovery. There were no significant changes in renin secretion during the experiment. Renin secretion averaged 596 ± 85, 475 ± 90, and 665 ± 170 ng angiotensin/min for control, experimental, and recovery periods, respectively. The values for the last two experimental periods appeared to be lower than the recovery values, but the difference was not significant (P>0.05).
Effects of intrarenal arterial infusion of hypertonic potassium chloride in dogs with caval constriction and a nonfiltering kidney on arterial blood pressure (BP) in mm Hg, renal blood flow (RBF) in ml/min, renal venous plasma potassium concentration (RV plasma K), and renin secretion. Values are means ± SE.

Also, there were no significant changes in mean arterial blood pressure and renal blood flow. Again, the average rate of renin secretion for five normal dogs was significantly lower than the average rate of renin secretion during control observations for this group of dogs with a caval constriction and a single nonfiltering kidney ($P < 0.01$).

**Effects of Intrarenal Potassium Infusion in Dogs with a Nonfiltering Kidney and Normal Control Plasma Potassium Levels.—**This experiment was performed because the control plasma potassium concentration in the preceding experiment was elevated to an average value of 5.0 mEq/liter. Six dogs were studied in a manner identical to that used in the preceding experiment except that the dogs were not anephric for 18-24 hours. The data for these six dogs and for two dogs in the previous series with normal plasma potassium values were averaged. These results are presented in Table 1. Renal venous plasma potassium concentration increased from 3.9 to 5.5-6.1 mEq/liter, but renin secretion was unchanged throughout the experiment. Also, arterial blood pressure and renal blood flow were unaltered.

![Figure 6](image_url)

**TABLE 1**

<table>
<thead>
<tr>
<th>Period of Intrarenal Potassium Infusion</th>
<th>Control period</th>
<th>Recovery period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin secretion (ng angiotensin/min)</td>
<td>100 ± 90</td>
<td>104 ± 5</td>
</tr>
<tr>
<td>Renal venous plasma potassium (mEq/l)</td>
<td>3.9 ± 0.1</td>
<td>105 ± 5</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg)</td>
<td>108 ± 6</td>
<td>109 ± 6</td>
</tr>
</tbody>
</table>

Data are averages ± SE for eight dogs.

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Discussion

Two intrarenal mechanisms have been proposed for the control of renin secretion. The vascular receptor (12, 13) in the renal afferent arterioles appears to respond to changes in wall tension, and the macula densa of the distal tubule appears to sense changes in sodium load (1) or concentration (16). Further details concerning the factors that influence each of these mechanisms are discussed in reviews by Vander (1) and Davis (17).

With the nonfiltering kidney model, renin-release mechanisms have been studied in the absence of a functional macula densa (13). Blaine, et al. (13) found increased renin release in response to hemorrhage in adrenalectomized dogs with denervated nonfiltering kidneys. Their results indicated that some mechanism other than the macula densa, the renal nerves, or the level of plasma catecholamines is capable of controlling renin release; and the study suggested that a vascular receptor is located in the afferent arterioles at the level of the juxtaglomerular cells (13). In the present experiments, the nonfiltering kidney preparation provided information about the effects of sodium or potassium on renin release in the absence of a functional macula densa and in the presence of a severely damaged renal tubular system.

An inverse relationship between sodium balance and plasma renin activity has been well established in man (18-21) and dogs (22, 23). Indirect estimates of renin release provided similar results for rats (24, 25). Acute experiments in anesthetized dogs showed that the increased renin release caused by hypotensive volume expansion (8), suprarenal aortic constriction (8), or ureteral occlusion (9) could be partially blocked by intrarenal infusion of hypertonic sodium chloride. Since infusion of hypertonic sodium chloride inhibited renin release without any observed changes in renal hemodynamics, Nash and associates (8, 9) suggested that sodium controls renin release by a tubular macula densa mechanism. Similar results were obtained with intrarenal arterial sodium chloride infusion in the present experiments in dogs with a filtering kidney. As the renal venous plasma sodium concentration increased, there was a significant decrease in renin secretion after 15 minutes of infusion, but there were no significant changes in renin secretion and creatinine clearance. Although no changes in hemodynamics were observed in the experiments reported by Nash and associates (8, 9) their results did not eliminate the possibility that sodium could inhibit renin release by direct effects on the juxtaglomerular cells or by local regional changes in renal blood flow or hemodynamics. Intrarenal sodium infusion into nonfiltering kidneys produced a significant increase in renal venous plasma sodium concentration but had no significant effect on the average rate of renin secretion for the first 45 minutes of infusion. When compared with the immediate decrease in renin release observed during sodium infusion into filtering kidneys, these data strongly suggest that decreased renin release is related to a renal tubular mechanism. The decrease in renin release observed in nonfiltering kidneys after 60 minutes of hypertonic sodium infusion probably represents a secondary mechanism: the explanation for this finding is not clear, but the finding is important in that it shows that a clear-cut decrease is demonstrable. Also, failure to demonstrate a decrease in renin secretion in the nonfiltering kidney during the first 45 minutes of sodium infusion was not due to renin secretion being too low, since the control level of renin secretion in the experimental group of nine dogs with caval constriction was significantly higher than the rate of renin secretion in a group of five normal dogs with a single nonfiltering kidney.

Recently, potassium balance has also been shown to have a significant influence on plasma renin activity. Veyrat and co-workers (2, 3) reported that potassium loading decreased plasma renin activity in addition to stimulating aldosterone secretion. High potassium intake decreased plasma renin activity in normal (4, 5) and hypertensive subjects (5),
and, conversely, potassium deprivation increased plasma renin activity in normal and hypertensive subjects (5). These effects of chronic changes in potassium balance have also been demonstrated in the rat (6) and the dog (7).

Direct intrarenal arterial infusion of potassium chloride in normal or acutely sodium-depleted anesthetized dogs decreased renal venous renin activity (11). Since there were no changes in renal blood flow as calculated from para-aminobipurate excretion and extraction, it was concluded that the potassium infusion actually produced the decrease in renin release. In the present experiments, direct measurements of renin secretion in filtering kidneys demonstrated a significant decrease in renin release as renal venous plasma potassium concentration increased 1.5—1.8 mEq/liter, and there were no observed changes in renal hemodynamics. In this experiment, as in the previous studies of Vander (11), potassium could have inhibited renin secretion by various mechanisms, e.g., by a tubular effect, by an influence on the intravascular receptor, or by a direct effect on the juxtaglomerular cells. However, since intrarenal infusion of potassium chloride into nonfiltering kidneys had no effect on renin secretion, potassium appears to have decreased renin secretion by a tubular mechanism. Because the control plasma potassium values were elevated in the first experiment with the nonfiltering kidney (Fig. 6), a second study was performed in which the contralateral normal kidney was removed immediately, rather than 18—24 hours, before the acute experiment. This second study with potassium was done to examine the possibility that the failure of renin secretion to fall during potassium infusion into the nonfiltering kidney was due to the high control level of plasma potassium. Again, there was no suggestion that hyperkalemia decreased renin secretion in the nonfiltering kidney. Also, the control rates of renin secretion in the present study were significantly higher than the rate of renin secretion in five normal dogs with a single nonfiltering kidney, and these data show that

failure to observe a decrease in renin secretion with potassium infusion is not the result of a low initial rate of renin secretion. Thus, the present experiments suggest that acute increases in plasma potassium concentration do not inhibit renin release by an effect on the vascular receptor or the juxtaglomerular cells but rather by a mechanism dependent on an intact renal tubular system. The transient decrease in renin secretion in dogs with filtering kidneys along with the return toward the control level during the 60-minute experimental period might reflect the potent mechanism for maintenance of hypersecretion of renin in dogs with caval constriction. No such escape in renin secretion during hyperkalemia in otherwise normal dogs has been reported previously.

Although the experiments with potassium infusion into filtering and nonfiltering kidneys indicate that a tubular mechanism is involved in the inhibition of renin secretion, these results do not reveal the nature of this mechanism. Vander (11) has suggested that the inhibitory effect of potassium on renin secretion is secondary to depression of proximal sodium reabsorption, which has been reported for potassium (26, 27). The increase in sodium excretion observed with potassium infusion in the present study might support this suggestion if the effect on sodium reabsorption is proximal to the macula densa. However, a recent micropuncture study by Schneider and associates (28) in the anesthetized dog revealed that acute renal arterial infusion of potassium chloride in amounts sufficient to suppress renin release does not increase the delivery of sodium from the proximal tubule.

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References


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