Effects of SQ 20,881 on the Intact Kidney of Dogs With Two-Kidney, One Clip Hypertension

ZENJIRO MASAKI, M.D., CARLOS M. FERRARIO, M.D., AND F. MERLIN BUMPUS, PH.D.

SUMMARY It has been suggested that in two-kidney, one clip hypertension, the unclamped kidney (UK) actively contributes to hypertension by reducing its excretory ability in response to increased levels of circulating angiotensin II. By exteriorizing the ureter to the dog’s flank several weeks beforehand, we measured renal function directly from the UK of six chronic renal hypertensive (> 3 weeks) and six normal dogs (ND). Mean blood pressure (indwelling catheter) and renal function were measured in the trained dogs for two 20-minute periods before and during a 40-minute intravenous infusion of SQ 20,881, at a dose (300 μg/kg + 3 μg/kg/min) that caused no changes in blood pressure (BP). In dogs with chronic renal hypertension [121 mm Hg ± 2 SE] and mild elevation of plasma renin activity (2.0 ± 0.4 vs 0.4 ± 0.1 ng/ml/hr in ND), infusion of SQ 20,881 caused marked increases in sodium excretion (UNaV), glomerular filtration rate, and effective renal plasma flow. Moreover, the changes in UNaV and effective renal plasma flow were highly correlated (r = 0.77, p < 0.001). In normotensive dogs (99 ± 2 mm Hg) SQ 20,881 caused a 30% ± 5% rise in UNaV, a modest increase in glomerular filtration rate (4% ± 2%) and no change in effective renal plasma flow. Infusion of a mild pressor dose of angiotensin II (4 ng/kg/min) produced decreases in sodium excretion, effective renal plasma flow, and glomerular filtration rate in the normotensive dogs. In the hypertensive animals, the same infusion rate of angiotensin II caused significant natriuresis without changes in effective renal plasma flow and glomerular filtration rate. These results suggest that the mild increases in plasma renin activity associated with the chronic phase of two-kidney, one clip hypertension contribute in modifying the renal function of the untouched kidney. (Hypertension 2: 649-656, 1980)

KEY WORDS • renal function • renal artery stenosis • arterial pressure • urinary diversion • sodium excretion • angiotensin II • arterial hypertension

IT HAS BEEN suggested that overactivity of the renin-angiotensin system in the acute phase of two-kidney, one clip hypertension depresses renal function in the unclamped kidney, preventing diuresis and enhancing sodium and water retention. Whether these effects are still present during the chronic phase of renal hypertension continues to await clarification, due in part to technical limitations that have precluded evaluation of the function of the untouched kidney in conscious chronic hypertensive animals before and after blockade of the endogenous formation of angiotensin II (All). Technical difficulties impeding progress in this area of hypertension research were recently resolved in this laboratory, first by the development of a procedure that provides a reliable model of chronic two-kidney one clip hypertension in the dog and, second, by implementation of a modified method of surgical diversion of the ureter that allows for unilateral renal function studies. Because these problems were circumvented, we are now able to report the changes in the function of the untouched kidney of dogs with chronic two-kidney, one clip hypertension both before and after acute blockade of the endogenous formation of angiotensin II with the converting enzyme inhibitor (CEI) SQ-20,881.

METHODS

Before and during the studies, 12 male mongrel dogs weighing 18-25 kg were fed a normal diet (Ken-L-Ration Biskit, The Quaker Oats Co., Chicago, Illinois) containing 60 mEq/day of sodium and 45 mEq/day of potassium; water was given ad libitum.
Urine Collection, Arterial Pressure Determination, and Production of Renal Hypertension

A modified version of the technique of single-side tubeless cutaneous ureterostomy was employed in these studies to obtain urine from the right kidney of conscious, trained dogs. The surgical procedure, as implemented in our laboratory, is described in detail elsewhere. Briefly, 2 weeks after creation of a skin flap in the dog's side, the right ureter was approached transperitoneally and detached from adjacent structures throughout its entire course in the abdominal cavity. The isolated ureter was then divided at the ureterovesical junction, tunneled through the abdominal wall, and housed into the skin flap. A ureteral nipple was constructed by stitching the free end of the ureter to the vertex of the skin process. A commercially available urinary appliance (Marlen Post-operative Urinary Pouch, Model MUPO-9, Marlen Manufacturing and Development Company, Bedford, Ohio) was modified in our laboratory and attached to the stoma for the continuous collection of urine.

Before the abdomen was closed, the right external iliac artery was isolated, and a Tygon catheter (outer diameter, 0.125 in.; inner diameter, 0.0625 in.; Norton, Plastic Division, U.S. Stoneware Inc., Akron, Ohio) was inserted into the vessel with the tip placed in the abdominal aorta below the renal arteries. The free end of the catheter was tunneled through the subcutaneous tissue to the back of the dog's neck.

In six of these 12 dogs, two-kidney, one clip hypertension was produced using the technique described by Masaki et al. The procedure was performed in two steps carried out 14 days apart. During the first surgical step, the left renal artery was constricted with an externally adjustable clamp to about 50% of its original diameter. Two weeks later the previously constricted renal artery was occluded from the outside under light anesthesia (sodium thiamylal, 30 mg/kg i.v., Surital, Parke Davis Company, Detroit, Michigan).

All other surgical procedures were performed with sodium pentobarbital (30 mg/kg, i.v. Diabutal, Diamond Laboratories, Des Moines, Iowa) following premedication with morphine sulfate (1 mg/kg i.m.). The dogs convalesced for at least 1 week in individual pens and were cared for daily by a full-time veterinarian. Nursing included administering antibiotics to prevent infection, cleansing the healing wounds, and recording body temperature, weight variations, and daily food intake. At the time of the renal function studies, the animals were in good health, had fully recovered from surgical procedures, and were gaining weight.

Radiographic evaluation of the urinary tract by intravenous pyelography (i.v.p.) and bacteriological examination of the urine coming from the diverted ureter ruled out the development of either hydronephrosis or infection. Animals classified as having either grade A (normal) or B (slight ureteral dilatation) urographic findings were used. Dogs with hydronephrosis (Grade C X-ray findings) were excluded.

Renal Function Studies

Twenty-minute renal clearance periods were obtained in six normotensive and six renal hypertensive dogs after they were mildly hydrated with a mixture of 40 g of canned meat (LK-ration) dissolved in 300 ml of water 2 hours prior to the studies. Details of the procedures are described elsewhere. During measurements, animals remained relatively motionless as a result of having been trained for several weeks to lie on their sides on a cushioned pad in a laboratory shielded from auditory and visual disturbances. During an initial 1-hour stabilization period and for 1½ hours thereafter, the animals received an intravenous infusion of 0.45% sodium chloride and 2.5% dextrose in water at a rate of 1.0 ml/min to compensate for calculated urinary losses of sodium and water. In addition, ortho-sodium 185 iodohippurate (Hippuran, Mallinkrodt Inc., St. Louis, Missouri) and sodium 125 iothalamate (Glofill, 1st, Abbott Laboratories, North Chicago, Illinois) were diluted in sterile water and infused at a rate of 0.15 ml/min following an i.v. priming dose of 0.5 μCi/kg of each isotope. Dilution of these agents in water was deemed necessary to avoid dissociation of the radioactive label from Hippuran. Normotonicity was restored partially by the concurrent administration of 0.9% sodium chloride (0.15 ml/min) through another port of a three-way valve. The total volume of fluids given to the animals during the 2½ hours of the study averaged 195 ml. Since urinary output ranged between 0.6 and 2.2 ml/min (average 1.3 ± 0.2 ml/min), water balance was maintained.

The initial 60-minute equilibration period was used to achieve constant levels of the indicators in plasma; thereafter, four consecutive 20-minute clearance periods were obtained in each dog. The first two clearance periods were used to determine control values; during the last two periods either CEI-SQ 20,881 (Squibb Company, 3 μg/kg i.v., following a bolus injection of 300 μg/kg) or angiotensin II (Asp1, Ile8, synthesized by Dr. M. C. Khosla of the Cleveland Clinic, 4 ng/kg) were infused intravenously at a rate of 0.18 and 0.15 ml/min respectively. In the experiments in which SQ 20,881 was given to the dogs, effective blockade of the endogenous formation of angiotensin II was assessed by documenting the disappearance of the pressor response to the bolus intravenous administration of 500 ng of (Asp1, Ile8) angiotensin I. Samples of arterial blood were obtained at the midpoint of each clearance period. The validity of these procedures as well as the reproducibility of the values of consecutive clearance periods are documented.

In two normotensive and two renal hypertensive dogs, urinary sodium excretion was monitored during graded changes in mean arterial pressure. For this purpose, animals received an intravenous infusion of either sodium nitroprusside, 200 μg/min (Nipride,
Roche Laboratories, Nutley, New Jersey) or phenylephrine hydrochloride, 30-60 μg/min (Neo-Synephrine, Winthrop Laboratories, New York, New York).

Analytical Methods

Plasma renin activity was determined by radioimmunoassay, and plasma and urinary electrolytes by flame photometry. The concentration of $^{131}$ orthoiodohippurate and $^{125}$ sodium iothalamate from aliquots of plasma and urine were counted in an automatic gamma scintillation counter with a dual-channel pulse-height analysis system for the discrimination of the simultaneous counting of $^{131}$ and $^{125}$.

Statistics

All data were normalized to the average control values, which were taken as the mean of the two consecutive 20-minute clearance periods. Mean percent differences between the first and second control periods were calculated as the percent deviation from the average control value of the particular variable. Statistics involving significance of changes were evaluated by the paired and unpaired Student's t test. Results were considered significant when $p < 0.05$.

Results

Arterial Pressure, Plasma Renin Activity, Unilateral Glomerular Filtration Rate, and Effective Renal Plasma Flow

Average values for mean arterial pressure, plasma renin activity, and unilateral renal clearances in six normal (ND) and six renal hypertensive dogs (RHT) are summarized in table I. Dogs with two-kidney, one clip hypertension were studied 4 weeks after complete occlusion of the renal artery. At this time, their mean arterial pressure was increased significantly and plasma renin activity averaged a fivefold increase compared to normotensive dogs. Average values for effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in the right kidney were essentially the same in normotensive and renal hypertensive dogs. Urinary volume and sodium excretion tended to be greater in renal hypertensive compared to normotensive dogs, but these differences did not attain statistical significance. In the dogs with chronic renal hypertension, urinary potassium excretion averaged 21.75 μEq/ml/min compared to 9.45 μEq/ml/min ($p < 0.05$) in the normotensive group.

Effects of SQ 20,881 on the Excretory Function of the Right Kidney

In dogs with and without renal hypertension, infusion of SQ 20,881 caused marked differences in the response of the kidney to the blockade of the endogenous formation of angiotensin II. The absolute and percent changes in renal clearance in dogs with and without two-kidney, one clip hypertension are shown in table I and figure 1 respectively. During the first renal clearance period following administration of SQ 20,881, dogs with renal hypertension excreted a greater proportion of urinary sodium (UNaV) than normotensive dogs. The increase in UNaV averaged 94% ± 8% above control values in renal hypertensive dogs compared to a 30% ± 5% increase in the group of normal dogs ($p < 0.001$). In hypertensive dogs, the increases in urinary sodium excretion were associated with a 13% ± 3% rise in effective renal plasma flow and an 11% ± 3% rise in glomerular filtration rate. These changes were significantly greater than those obtained in the group of normal dogs (0.3% ± 2% and 4% ± 1% for ERPF and GFR respectively). Estimated fractional sodium excretion (UNaV/GFR) rose from 2.39 to 4.13 μEq in hypertensive dogs during the first 20 minutes of SQ 20,881 administration. In

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Percent changes in urinary sodium excretion (UNaV), effective renal plasma flow (ERPF), glomerular filtration rate (GFR), and mean arterial pressure (BP) before (C1, C2) and during (I1, I2) infusion of CEI in six normotensive (clear bars) and six renal hypertensive (hatched bars) dogs. Values are means ± 1 ss of two experiments carried out on different days in each dog. Repeatability of two consecutive renal function clearances are illustrated as the average percent deviation of values from the mean control value (solid line). Asterisk indicates $p < 0.05$ relative to the response in normotensive dogs. Absolute values as in table I.
TABLE 1. Average Values of Renal Clearance in Six Normotensive and Six Dogs with Two-Kidney One Clip Hypertension

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normotensive dogs</th>
<th>Hypertensive dogs</th>
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<tbody>
<tr>
<td></td>
<td>Control 1st period</td>
<td>CEI 1st period</td>
</tr>
<tr>
<td></td>
<td>2nd period</td>
<td>2nd period</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>99 ± 2</td>
<td>97 ± 3</td>
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<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>0.4 ± 0.1</td>
<td>0.6 ± 0.2</td>
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<tr>
<td></td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Effective renal plasma flow (ml/min)</td>
<td>112 ± 6</td>
<td>109 ± 5</td>
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<td></td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>39 ± 2</td>
<td>40 ± 2</td>
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<td>ns</td>
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<tr>
<td>Urinary volume (ml/min)</td>
<td>0.83 ± 0.15</td>
<td>1.09 ± 0.18*</td>
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<td></td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Urinary sodium excretion (µEq/ml/min)</td>
<td>70 ± 9</td>
<td>87 ± 9*</td>
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<tr>
<td></td>
<td>ns</td>
<td>ns</td>
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<tr>
<td>Urinary potassium excretion (µEq/ml/min)</td>
<td>10.5 ± 3.0</td>
<td>8.4 ± 2.0</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

*p values denote statistical differences in the baseline levels (1st and 2nd control periods) of renal function between normotensive and renal hypertensive dogs as assessed by the Student t test for unpaired data. Statistical differences between the experimental periods (1st and 2nd CEI) and their corresponding controls as denoted by asterisk (*) = p < 0.05 as assessed by the Student t test for paired data.

Normotensive dogs, fractional sodium excretion averaged 1.77 before, and 2.18 µEq after. In both groups of dogs, filtration fraction estimated as the ratio GFR/ERPF did not change.

Although natriuresis in RHT was accompanied by increases in both ERPF and GFR, the amounts of sodium excreted by the intact kidney of RHT dogs correlated only with the change in ERPF (fig. 2) but not GFR. The correlation coefficient averaged 0.77 (p < 0.001). In the normotensive dogs, the percent change in urinary sodium excretion did not correlate with the changes in effective renal plasma flow (r = 0.02, p > 0.05).

During the second 20-minute clearance period, the increases in UNaV, ERPF, and GFR found in dogs with two-kidney, one clip hypertension were attenuated compared to the changes observed during the first period of SQ 20,881 infusion (fig. 1). Urinary sodium excretion averaged 47% ± 12% above control values compared to 32% ± 9% in the normotensive group (p > 0.05). The ERPF decreased toward control values, and GFR remained elevated. These values, however, were not significantly different from those obtained in the normal group of dogs. Blunting of the natriuretic effect observed during the second clearance period in renal hypertensive dogs may be due to the effects of angiotensin II overcoming the blocking

**FIGURE 2.** Correlation between changes in urinary sodium excretion (UNaV) and effective renal plasma flow (ERPF) in normotensive (clear circles) and renal hypertensive (solid circles) dogs. In dogs with two-kidney, one clip hypertension, changes in UNaV correlated with ∆% ERPF (r = 0.77, p < 0.001; UNaV = 40.36 UNaV + 3.29 ERPF). In the normotensive group, natriuresis during CEI did not correlate with ∆% ERPF (r = 0.02, p > 0.05).
capacity of the inhibitor. This view is supported by the very large rises in plasma renin activity present in the RHT dogs (table 1) during the second clearance period. In normotensive animals, plasma renin activity did not increase during SQ 20,881 infusion, and there was no blunting of the hemodynamic response to this infusion.

Changes in renal function were independent of alterations in mean arterial pressure. In the dogs with renal hypertension, the infusion of SQ 20,881 at the dose given had no direct effect on the elevated arterial blood pressure; hypertension persisted during both the first and second clearance periods. The same lack of effect of SQ 20,881 on arterial pressure was observed in normal animals. In both groups of dogs, however, the vasoconstrictor effects of a bolus injection of angiotensin I were prevented during CEI administration.

Changes in UNaV. Sodium excretion rose to between 130% and 170% above control levels as mean arterial pressure was increased. Urinary sodium excretion fell as much as 80% as mean arterial pressure was reduced by about 15 mm Hg from the previous hypertensive level of 120 mm Hg.

Discussion

Measurements of renal function from the intact kidney of conscious trained dogs during the chronic phase of renal hypertension give credence to the possibility that the stenotic kidney influences the sodium excretory capacity of the opposite intact one. This effect appears to be related to an action of angiotensin II on the renal arterioles of the intact kidney. However, an additional effect of the hormone changes in UNaV. Sodium excretion rose to between 130% and 170% above control levels as mean arterial pressure was increased. Urinary sodium excretion fell as much as 80% as mean arterial pressure was reduced by about 15 mm Hg from the previous hypertensive level of 120 mm Hg.

Effect of Intravenous Angiotensin II on Renal Clearance

The renal hemodynamic response to an intravenous infusion of angiotensin II was assessed in four normotensive and four renal hypertensive dogs. These studies were carried out on days other than those on which CEI was given. The findings are summarized in figure 3. Average values for arterial pressure and renal function prior to the infusion of the octapeptide were comparable to those obtained in the experiments in which CEI was given.

In normal dogs, the infusion of a small dose of All (4 ng/kg/min) caused a 24 mm Hg rise in arterial pressure and a significant fall in UNaV, ERPF, and GFR. The hemodynamic changes found in the untouched kidney of renal hypertensive dogs, however, did not mimic the pattern observed in the kidney of normotensive controls (fig. 3). The hypertensive response (16 mm Hg) to the infusion of angiotensin II was accompanied by natriuresis sustained during both the first and second clearance periods. During the first clearance period, ERPF and GFR remained unchanged, but on the second clearance period, ERPF was reduced to values close to those recorded in the normal group while GFR remained essentially unchanged.

Dependence of Sodium Excretion on Blood Pressure

To determine whether natriuresis in hypertensive dogs during the infusion of angiotensin II was in part mediated by differences in baseline mean arterial blood pressure, the relationship between UNaV and BP was investigated in two of the six animals from each group. Urinary sodium excretion was determined both before and during the intravenous infusion of either sodium nitroprusside or phenylephrine hydrochloride. The findings are summarized in figure 4. In normotensive dogs, UNaV remained essentially unchanged as arterial BP was varied between 90 and 130 mm Hg. At pressures below 90 mm Hg, there was a decrease in UNaV. In contrast, increasing mean arterial pressure from 120 to 180 mm Hg in the two hypertensive dogs caused approximately linear changes in UNaV. Sodium excretion rose to between 130% and 170% above control levels as mean arterial pressure was increased. Urinary sodium excretion fell as much as 80% as mean arterial pressure was reduced by about 15 mm Hg from the previous hypertensive level of 120 mm Hg.

![Figure 3. Percent changes in urinary sodium excretion (UNaV), effective renal plasma flow (ERPF), and glomerular filtration rate (GFR) during the intravenous infusion of a moderate dose of angiotensin II (4 ng/kg/min). For this experiment, baseline values for normotensive dogs are: 73.50 ± 9.86 μEq/liter for UNaV; 111.92 ± 3.32 ml/min for ERPF; and 36.65 ± 1.25 ml/min for GFR. Other labels as in figure 1.](http://hyper.ahajournals.org/)
on the renal tubules7 cannot be excluded. During the first clearance period that followed infusion of SQ 20,881, the contralateral kidney of dogs with chronic renal hypertension consistently excreted far greater quantities of sodium and water than the normal kidney of a control group of dogs infused with CEI in the same manner. Natriuresis was associated with a significant increase in effective renal plasma flow that correlated with sodium excretion; such a correlation was not present in the normal dogs. Compared to the normotensive group of dogs, GFR increased proportionally more in the renal hypertensive animals. From these observations, we are able to infer that blockade of the intrarenal action of angiotensin II by CEI causes a decrease in renal vascular resistance in the intact kidney of dogs with chronic renal hypertension, exposing the glomeruli and peritubular capillaries to the direct effects of the elevated BP. Alternatively, the observed renal vasodilation may be due to kinin accumulation, since CEI depresses the rate of bradykinin degradation.8 Concurrent changes in peritubular oncotic pressure appear not to have substantially contributed to the increase in sodium excretion since in these experiments filtration fraction did not change.

The present experiments were conducted in unanesthetized trained dogs to avoid the influence of anesthesia on arterial pressure, plasma renin activity, and renal function.9,10 A technique was developed to produce a dog model of two-kidney, one clip hypertension in which the elevation in arterial pressure is sustained for months.4 This was achieved by occlusion of a left renal artery in two steps. During an initial 14-day period, the constriction applied to the renal artery stimulated growth of collateral vessels and prepared the kidney to be deprived of its renal artery blood supply without undergoing atrophy.2 The characteristics of this experimental model of renovascular hypertension in terms of the time course of the changes in arterial pressure, plasma renin activity, and the dependence of the hypertension on increased activity of the renin-angiotensin system were detailed by Masaki et al.4 In brief, lasting hypertension develops which is amenable to the administration of (Sar1, Thr9) angiotensin II during the early (< 1 wk) but not the chronic phase of the disease. However, removal of the ischemic kidney even as long as 7 weeks after onset of hypertension normalized the elevated arterial pressure and plasma renin activity.

A new method was used for the repeated collection of urine from a single kidney without inserting an indwelling catheter into a ureter. The procedure entailed the surgical diversion of a ureter to the dog's flank employing a technique described by us previously.2 Urine was obtained from the stoma with a commercially available urinary appliance modified in the laboratory both to ease the collection of urine and improve the reliability of renal clearance studies in conscious trained dogs. This technique was shown to circumvent the possibility of either upper urinary tract infection or hydronephrotic complications that frequently arise with other procedures. In addition, unilateral renal function studies were obtained with ease in unrestrained animals, and this was reflected by the small intra- and inter-day variability of renal function values and arterial pressure in the animals (table 1).

In the present experiments, stability of the arterial BP during renal function studies was considered to be an important prerequisite, since urinary sodium excretion is influenced by arterial pressure and sympathetic nerve activity. It is recognized, however, that in the present experiments comparisons are made between two groups of dogs rather than on the same animals before and after development of renal hypertension. The latter alternative, albeit a desirable one, would have prolonged the overall time of observation in each dog to a point at which technical problems might have arisen, such as keeping catheters patent and animals in good health. Thus, the former alternative was chosen. Precautions were taken, however, to ensure that the baseline values obtained in the group of normotensive and hypertensive animals agreed well with results published previously in terms of arterial pressure levels, plasma renin activity, and renal function.2,4,10 Comparison of unilateral renal function values in conscious dogs with and without renal hypertension revealed subtle but not significant differences in UNaV and GFR. These are probably related to the presence of compensatory hypertrophy in the right kidney of hypertensive animals.2 DeForrest et al.10 have performed separate renal function studies in conscious dogs with two-kidney, one clip hypertension. In their experiments, GFR and ERPF in the contralateral kidney remained unchanged or even tended

![Figure 4. Comparison of percent changes in urinary sodium excretion (UNaV) as a function of mean arterial pressure (BP).](image-url)
to increase within 2 to 28 days after onset of hypertension. Sodium and potassium excretion as well as urinary output increased significantly. In our experiments, urinary output and sodium and potassium excretion tended also to be higher in hypertensive animals, a finding that is also consistent with results obtained in man.19

The increased excretion of Na and water by the intact kidney of dogs with chronic RHT may represent a compensatory mechanism that attempts only in part to normalize excessive sodium and water retention by the clipped kidney.8, 10 Since in our experiments the intact kidney of RHT dogs was perfused at pressures about 22 mm Hg above normal, we would have expected, as described by Coleman et al.,8 a greater than twofold increase in urinary volume. They showed that the sensitivity of urine flow to changes in arterial pressure is such that a 30 to 50 mm Hg increase in arterial pressure should cause a two- to fivefold increase in urinary output. Thompson and Pitts14 have reached similar conclusions. It is therefore possible to conclude that, despite the elevation in arterial pressure and the development of compensatory hypertrophy, the intact kidney of RHT dogs manifested a relative degree of antidiuresis and antinatriuresis. These changes may in part be caused by increased levels of circulating angiotensin II resulting from the extrinsic activity of renin in the non-clipped kidney. This is in accord with the mild but significant increases in baseline levels of plasma renin activity and the profound diuresis and natriuresis that developed during the infusion of CEI at a dose that did not reduce the elevated BP.

The exaggerated natriuresis and diuresis following CEI administration in RHT dogs may be accounted for by the effects of one or more of the following factors: 1) direct removal of the intrarenal action of angiotensin II;14, 16 2) blockade of the effect of angiotensin on adrenal steroid secretion; and 3) increased activity of the renal kallikrein-kinin system. Although in the present studies the contribution of each of these factors could not be differentiated, some can be excluded. While angiotensin is known to have an immediate effect on the secretion of aldosterone,16 the activation of this mineralocorticoid does not affect renal function for more than 30 minutes.17 Furthermore, McCaa et al.8 showed in dogs that the increase in UNaV in response to SQ 14,225 administration was independent of changes in plasma aldosterone concentration. Thus, the natriuresis observed during the initial 20-minute period of CEI infusion may represent predominantly either the direct effects of angiotensin blockade or kinin potentiation. Micropuncture measurements during CEI administration in anesthetized dogs suggest that the predominant effect is related to blockade of the intrarenal function of angiotensin II on both pre- and postglomerular resistance elements.18 Yet, in another study on hypertensive subjects the systemic depressor response to SQ 20,881 correlated better with urine kinins and plasma prostaglandin E than with changes in plasma levels of angiotensin II.18

In RHT animals, renal vasodilation was not sustained during the second 20-minute clearance study following administration of CEI. Attenuation of the hemodynamic response was accompanied by a marked increase in plasma renin activity. Therefore, it is likely that excessive generation of AI led to an increase in renal vascular resistance as a result of overflow from the blocking capacity of CEI. Since arterial BP did not change and exogenous administration of a previously vasoconstrictive dose of AI was without effect, it appears that the renal vascular bed may be more sensitive to the vasoconstrictive action of AI than systemic vascular smooth muscle. Hollenberg et al.20 and Keim et al.21 provided some support for this possibility.

Both infusion of angiotensin II and blockade of the endogenous action of AI led to different hemodynamic effects in normal versus RHT dogs. In NDs, AI infusion produced antinatriuresis due to decreases in GFR and ERPF; conversely, blockade of the AI action caused mild natriuresis without significant changes in GFR and ERPF. Therefore, dissociation between sodium excretion and GFR under circumstances of increased and decreased AI levels might suggest the involvement of an additional factor, possibly activation of the kalilkrein-kinin system.29 In RHT dogs, both AI and CEI caused significant natriuresis apparently resulting from different effects on the renal circulation. While in hypertensive animals a decrease in pre- and postglomerular resistance appears to be the most likely cause for the sodium diuresis produced by CEI, an increase in postglomerular capillary pressure may account for the results obtained with infusion of angiotensin II. In this respect, a decrease in the distensibility of renal vessels in the contralateral kidney of dogs with RHT may alter the relationship between arterial pressure, urinary volume, and sodium output.28, 29 This possibility was further established by examining the relationship between arterial pressure and sodium excretion in normal and renal hypertensive dogs. The linear dependence of sodium output to BP in RHT contrasted markedly with the lack of a similar effect in normotensive dogs.

In summary, this experiment indicates that angiotensin II may play a role in the maintenance of two-kidney, one clip hypertension by affecting the excretory capacity of the intact kidney.

Acknowledgment

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