Bilateral Renal Function Responses to Converting Enzyme Inhibitor (SQ 20,881) in Two-Kidney, One Clip Goldblatt Hypertensive Rats

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SUMMARY The influence of the renin-angiotensin system on individual kidney function of two-kidney, one clip Goldblatt hypertensive (GH) rats was evaluated by determining renal functional responses during intravenous infusion of converting enzyme inhibitor (CEI) (SQ 20,881, 0.3 mg/100 g-hr) for 3.5 hours. Rats were made hypertensive by placing a 0.25 mm silver clip on the right renal artery 3-4 weeks prior to study. Normal rats and GH rats were prepared to allow urine collections from each kidney. Mean arterial pressure of GH rats fell significantly from preinfusion levels of 153 ± 7 to 126 ± 4 mm Hg during CEI infusion. Despite this decrease in arterial pressure, the nondipped kidneys with reduced renal renin activity (14 ± 5 vs 293 ± 40 ng Al/mg-hr in the clipped kidney) exhibited dramatic increases in glomerular filtration rate (GFR) (from 1.45 ± 0.06 to 2.56 ± 0.35 ml/min), urine flow (4.82 ± 0.71 to 9.11 ± 1.19 µl/min), sodium excretion (0.10 ± 0.02 to 1.15 ± 0.39 µEq/min), fractional sodium excretion (0.05% ± 0.02% to 0.43% ± 0.18%), and potassium excretion (0.94 ± 0.08 to 2.50 ± 0.55 µEq/min). Significant arterial-pressure-associated decreases in GFR, urine flow, and salt excretion were observed in the clipped kidney. In normal rats, CEI infusion produced reductions in arterial pressure and increases in GFR, urine flow, and sodium excretion that were of smaller magnitude than those observed in the nonclipped kidneys of GH rats. Plasma renin activity was significantly higher in GH rats than in normal rats (24.0 ± 2.7 vs 12.8 ± 3.4 ng Al/mM/hr). The augmented renal responses to CEI by the nonclipped kidney suggest that elevated circulating angiotensin levels exert a substantial influence on hemodynamic and excretory function of these kidneys even though intrarenal renin activity is markedly reduced. This influence may lead to fluid and electrolyte retention and may partially explain the apparent failure of the nonclipped kidney to prevent the development of hypertension.

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KEY WORDS • renal hypertension • glomerular filtration rate • sodium excretion • renin-angiotensin • urine flow

THE two-kidney, one clip Goldblatt hypertensive model has been studied extensively, especially in the rat. It has often been presumed that the nonclipped contralateral kidney must be influenced, either directly or indirectly, by the clipped kidney such that it is rendered incapable of responding appropriately to the progressive elevation of arterial pressure. Indeed, several previous studies have demonstrated differences in hemodynamics and tubular function between the clipped kidney, which is not exposed to the elevated arterial pressure, and the contralateral untouched kidney, which is exposed to the elevated arterial pressure. For example, it has been reported that the clipped kidney exhibits a decreased or unchanged renal blood flow; decreased or normal water and sodium excretion, and increased renal renin activity. In contrast, the contralateral kidney generally has demonstrated an overall increased renal function and depressed kidney renin activity. In both clamped and contralateral kidneys. It has been suggested that increased activity of the renin-angiotensin system resulting from clipping of one renal artery would be expected to influence the
This has received support from studies demonstrating that administration of angio-
tensin antagonists reduce the elevated renal vascular resistance in the contralateral kidney.3110 If
however, there is little information regarding the individual GFR and excretory responses of the clipped and non-
clipped kidneys to blockade of the renin-angiotensin system. Of interest is the unique circumstance oc-
curring in this hypertensive model of a renin-depleted kidney existing in an environment of elevated plasma
renin levels. Thus, it was anticipated that further evaluation of individual kidney function might provide
some insight regarding the relative responses of the clipped and nonclipped kidneys to inhibition of con-
verting enzyme. The converting enzyme inhibitor (CEI) SQ 20,881 was selected to avoid the possible agonist
effect of receptor blockers of the renin-
angiotensin system.14 With CEI administration, a
reduction in circulating and tissue angiotensin II levels would be expected,15,16 thereby unmasking any pre-
xisting influences of preformed or locally generated angiotensin on renal hemodynamics and fluid and salt excretion. Thus, the present study was designed to characterize renal functional responses of both the clipped and the nonclipped kidneys to converting en-
zyme inhibition and to compare the responses of the contralateral kidneys of hypertensive rats with those
occurring in the corresponding kidneys of normal rats.

Methods

A total of 18 normal and 25 two-kidney, one clip Goldblatt hypertensive (GH) Sprague-Dawley rats
weighing 220 to 420 g were used in this study. The hypertensive rats were prepared by placing a silver clip
with an internal diameter of 0.25 mm on the right renal artery 3 to 4 weeks prior to the experiment. All
rats were maintained on regular rat chow (Wayne Lab Blox, Chicago, Illinois) and water ad libitum.

The hypertensive and normal rats were anesthetized with intraperitoneal pentobarbital (5.0 mg/100 g body
weight). Rats were prepared for clearance studies on a
heated table, and body temperature was maintained at 37°C by a thermostatic system that monitored the
rectal temperature. Surgical preparation included in-
sertion of a tracheal cannula, cannulation of the right
external jugular vein with three PE-10 tubes for infu-
sion of inulin, drugs, and supplemental anesthetic, and
catheterization of the femoral artery to collect blood
samples and measure blood pressure. Arterial blood
pressure was continuously monitored using a Statham
P23 DC transducer (Gould-Statham Instruments Inc.,
Hato Rey, Puerto Rico) and a P7 Grass polygraph
(Grass Instrument Co., Quincy, Massachusetts). The
left kidney was isolated through a flank incision and
placed in a lucite micropuncture cup to expose the left
ureter, which was catheterized with a short poly-
ethylene catheter having an internal diameter of 0.45
to 0.5 mm. The urinary bladder was also cannulated
with a polyethylene tube (PE 160) through an ab-
dominal incision for collecting urine emerging from
the right kidney. This approach allowed collection of
sequential urine samples from both kidneys simultaneously.

At the beginning of surgery, an intravenous infusion
of isotonic saline solution was initiated at 0.02
ml/min. After completion of the surgery, 0.4 ml of
15% polyfructosan-normal saline solution (Inutest,
Lazavosan-Gesellschaft, Linz, Austria) was ad-
ministered as a prime dose and followed by a sustain-
ing infusion of 0.01 ml/min; to maintain total volume
infusion rate constant, the saline infusion was reduced to
0.01 ml/min. Thirty minutes were allowed to reach a
steady state before initiating control urine collec-
tions. Urine samples were collected under oil in
preweighed plastic containers for two 30-minute
clearance periods; blood samples were also taken at the
midpoint of each period.

Following the control periods, 2 mg/ml of SQ
20,881 (E.R. Squibb & Sons, Princeton, New Jersey)
was administered at an initial dose of 1 mg and then
followed by a constant infusion of 0.3 mg/100 g/hr for
3.5 hours without changing the total volume infusion
rate. The effectiveness of this dose of CEI was tested as previously described17 by determining the vasopressor responses to i.v. doses of 50 and 100 ng of
angiotensin I before and during CEI administration.

Before CEI administration, 100 ng of angiotensin I
caused an increase in arterial pressure of 25 ± 2.3 mm
Hg (n = 5) in clipped GH; during CEI infusion, the
responses to 50 ng were not perceptible, and the re-
ponses to 100 ng of angiotensin I were markedly re-
duced to 3.6 ± 0.5 mm Hg. Thirty minutes after termi-
nation of CEI infusion, three additional clearance
periods were made. Upon completing the experiment, both kidneys were removed, drained, and weighed.

Inulin concentrations in plasma and urine were mea-
ured with a semimicroanthrone colorimetric tech-
nique. Plasma and urine sodium and potassium con-
centrations were determined with flame photometer
(Model 443, Instrumentation Lab, Lexington,
Massachusetts).

Thirteen GH rats and 12 normal rats were used in
one series of experiments involving standard clearance
measurements. Glomerular filtration rate (GFR),
urine flow, and sodium and potassium excretions were
evaluated before, during CEI infusion and following
cessation of CEI.

CEI infusion caused a marked decrease in the
arterial pressure of GH rats. To assess the direct
effects of reduced arterial pressure in the absence of
CEI, an adjustable constrictor clamp was placed
around the aorta above the origin of the renal arteries
in five GH rats. By constriction of the clamp, arterial
pressure was reduced to levels comparable to those
observed during CEI infusion, and clearance deter-
minations were made.

Plasma renin activity and tissue (kidney) renin con-
centrations were determined in seven GH rats and six
normal rats. After administering pentobarbital, an ab-
dominal incision was made, the renal pedicles ligated,
and the kidneys removed immediately. A blood sam-
ple was then taken through a carotid artery catheter.
All of the kidneys and blood samples were taken at the same time of day with identical techniques to minimize the possible changes due to circadian rhythm and sampling techniques. The kidneys were frozen immediately in acetone and dry ice, weighed, and stored at −20°C until extracted. Blood samples were collected in chilled tubes containing EDTA (1 mM/mL). The blood was chilled, centrifuged at 4°C, and the plasma was separated, frozen, and stored at −20°C until analysis.

Tissue renin content was determined by radioimmunoassay after extraction of homogenized rat kidney as described by Serban et al. This involves the incubation of an aliquot of the tissue homogenate with a fixed amount of renin substrate; the subsequent angiotensin I generated was assayed and tissue renin concentration reported as nanograms of angiotensin I per milligram of wet kidney weight per hour of incubation. The renin substrate pool was plasma from rats nephrectomized for 24–48 hours. The pooled plasma was subjected to transitory acidification to reduce the activity of angiotensinases. Recovery of added angiotensin I after incubation at 37°C for 24 hours was 92.5%, and linear angiotensin I generation was documented. Plasma renin activities were determined by radioimmunoassay as described by Menard and Catt.

The results are expressed as mean ± SEM. Differences between pre- and postinfusion of CEI in each period were evaluated by paired analysis.

Results

Before CEI infusion, the mean arterial pressure and clearance observations were made sequentially for up to 1½ hours in some rats of both GH and normal groups. No significant time-related variations were observed in these control observations. CEI infusion during a 3½-hour period caused greater reduction of arterial blood pressure in GH rats than in normal rats. As shown in figure 1, mean arterial pressure (MAP) in GH rats fell from the preinfusion level of 153 ± 6.9 to 137 ± 7.3 mm Hg after 30 minutes of CEI infusion; blood pressure continued to decrease during CEI infusion, and a maximum decrease of 27 ± 4 mm Hg was achieved by the end of the infusion period. After cessation of CEI infusion, there was a tendency for blood pressure to return to previous levels, although it did not reach control preinfusion levels during the ensuing 1-hour period. Normal rats exhibited a control BP of 119 ± 3 mm Hg and CEI infusion produced a slight hypotensive effect by the first 30 minutes. Continuous infusion of CEI resulted in a progressive decrease in arterial pressure. The maximum decrease averaged 8.4 ± 3.4 mm Hg, a value significantly less than that achieved in GH rats.

The body weights of GH and normal rats were 289 ± 11 g and 340 ± 17 g, respectively. In GH rats, the weight of the nonclipped contralateral kidney was significantly greater than that of the clipped kidney (1.29 ± 0.03 vs 1.08 ± 0.05 g). In control rats, kidney weights were similar (1.31 ± 0.06 g for left kidney and 1.34 ± 0.06 g for right kidney); and also similar to the weights of nonclipped kidneys in GH rats. The control GFR before CEI infusion was 1451 ± 64 µl/min for the left nonclipped kidney of GH rats and 1525 ± 127 µl/min for the left corresponding kidney of normal rats. The GFR of the clipped kidneys of GH rats averaged 1177 ± 145 µl/min, which was significantly less (p < 0.05) than that for the contralateral kidney. When factored by kidney weight, GFR was comparable in nonclipped kidneys of GH rats and corresponding kidneys of normal rats (1150 ± 43 vs 1143 ± 62 µl/min-g). Also, GFR in the clipped kidneys of GH rats (1043 ± 114 µl/min-g) was not significantly different from that of the contralateral kidney when the differences in kidney weight were considered. As shown in figure 2, GFR increased significantly in the nonclipped contralateral kidneys of GH rats following 30 minutes of CEI infusion and continued to increase during CEI infusion. The GFR was still elevated 1 hour after cessation of CEI infusion and then decreased toward preinfusion levels during the next hour. Increases in GFR were also seen in the corresponding left kidneys of normal rats; however, these increases in GFR were significantly less than those observed in GH rats. In contrast, slight but consistent decreases in GFR were observed in the clipped kidneys of normal rats.
Figure 2. Responses of the glomerular filtration rate (GFR, \(\mu \text{L/min}\)) of the clipped and nonclipped kidneys of Goldblatt hypertensive (GH) rats during infusion of CEI. The responses of the left kidneys of normal animals, which correspond to the nonclipped kidney of GH rats, are shown for comparison. The mean maximum increase of GFR of the nonclipped kidney was 73% compared to an increase of 22% for normal kidneys of control rats (p < 0.01). Statistical notation is identical to that shown on figure 1.

Figure 3. Urine flow (\(\mu \text{L/min}\)) responses during infusion of CEI for clipped kidneys, nonclipped (left) kidneys and corresponding left kidneys of control rats. The mean maximum increase in urine flow for nonclipped kidneys was 104% compared to 45% for kidneys of control rats (p < 0.05). See figure 1 for asterisk notation.
BILATERAL RENAL FUNCTION IN GOLDBLATT HYPERTENSIVE RATS/Huang et al.

Figure 4. Responses of urinary sodium excretion (µEq/min) during CEI infusion for clipped kidneys, nonclipped kidneys, and left kidneys of control rats. The mean maximum increase of nonclipped kidneys was 1045% compared to 731% for kidneys of control rats (p < 0.05). See figure 1 for explanation of asterisks.

Figure 5. Effect of CEI infusion on the fraction of the filtered load of sodium excreted (FE Na, %) from clipped and nonclipped kidneys of GH rats and from the left kidneys of control rats. The mean maximum increase in fraction of sodium excreted of nonclipped kidneys was 653% compared to 49% for kidneys of control rats (p < 0.01).

Figure 6. Responses of potassium excretion (µEq/min) during CEI infusion for clipped kidneys (open circles), nonclipped kidneys (solid circles) and left kidneys of control rats (triangles). The mean maximum increase of nonclipped kidneys was 179% compared to 72% for kidneys of control rats (p < 0.01).

associated reduction of arterial pressure during CEI infusion. Renal function was evaluated in both kidneys following reduction in arterial pressure by aortic clamping to values seen during CEI infusion. The effects of this reduction in arterial pressure are shown in figures 7 and 8. In clipped kidneys (fig. 7), parallel decreases of urine flow, sodium excretion, and GFR were noted when arterial pressure was reduced by CEI infusion or by aortic clamping. In nonclipped contralateral kidneys (fig. 8), aortic clamping produced decreases in GFR, sodium excretion, and urine flow while CEI infusion resulted in increased GFR, diuresis, and natriuresis despite the concomitant reduction of arterial pressure. The effects of aortic clamping were reversible. During the control period, the arterial pressure was 161 ± 5 mm Hg. The clipped kidney's GFR was 1129 ± 196 µl/min, urine flow was 3.7 ± 0.5 µl/min, and sodium excretion was 0.123 ± 0.034 µEq/min. The corresponding values for the contralateral kidney were 1802 ± 135 µl/min, 6.6 ± 1.3 µl/min, and 0.232 ± 0.092 µEq/min. After the aortic clamp was released, the arterial pressure was 152 ± 3.3 mm Hg. The GFR, urine flow, and sodium excretion values for the clipped kidneys were 1213 ± 127 µl/min, 3.5 ± 0.3 µl/min, and 0.090 ± 0.016 µEq/min. The corresponding values for the contralateral kidneys were 1801 ± 96 µl/min, 6.7 ± 1.1 µl/min, and 0.252 ± 0.090 µEq/min, respectively. There were no significant differences between the values obtained at the end of the experimental period and the control values.
The results of the plasma renin activity and kidney renin measurements are shown in table 1. There were no significant differences in body weight between these two groups of rats; however, the nonclipped kidneys were significantly larger and the clipped kidneys were significantly smaller than control kidneys from normal rats. The plasma renin activity of GH rats was significantly higher than that of normal rats. Renal tissue renin level was found to be markedly decreased in the nonclipped kidneys of GH rats. Renal renin content of the clipped kidneys was slightly but not significantly higher than that measured in normal rat kidneys.

![Graphs showing arterial pressure, GFR, urine flow, and sodium excretion](image)

**FIGURE 7.** Clipped kidneys of Goldblatt hypertensive rats. Effects of reduction of arterial pressure during infusion of CEI (solid circles) and by aortic clamping (open circles) on GFR (μl/min), urine flow (μl/min), and sodium excretion (μEq/min).

**FIGURE 8.** Contralateral kidneys of Goldblatt hypertensive rats. Effects of reduction of arterial pressure during infusion of CEI (solid circles) and by aortic clamping (open circles) on GFR (μl/min), urine flow (μl/min), and sodium excretion (μEq/min).

### Table 1. Comparison of Blood Pressure, Kidney Weight, Plasma Renin Activity, and Kidney Renin Activity of Normal and Goldblatt Hypertensive Rats (Mean ± SEM)

<table>
<thead>
<tr>
<th>Rat</th>
<th>BP (mm Hg)</th>
<th>BW (g)</th>
<th>Kidney wt. (g)</th>
<th>PRA (ng/ml/hr)</th>
<th>Kidney renin (ng/mg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left (L)</td>
<td>Right (R)</td>
<td>Left</td>
</tr>
<tr>
<td>Normal (N)</td>
<td>119 ± 3</td>
<td>293</td>
<td>1.47 ± 0.06</td>
<td>1.43 ± 0.06</td>
<td>12.8 ± 3.4</td>
</tr>
<tr>
<td>(6)</td>
<td>± 14</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Goldblatt (GH)</td>
<td>164 ± 6</td>
<td>308</td>
<td>1.69 ± 0.05</td>
<td>1.28 ± 0.02</td>
<td>24.0 ± 2.7</td>
</tr>
<tr>
<td>(7)</td>
<td>± 11</td>
<td></td>
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<tr>
<td>N vs GH (p)</td>
<td>&lt; 0.001</td>
<td>ns</td>
<td>&lt; 0.05</td>
<td>&lt; 0.05</td>
<td>&lt; 0.001</td>
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<tr>
<td>L vs R of GH (p)</td>
<td>&lt; 0.001</td>
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Discusssion

The two-kidney, one clip Goldblatt hypertensive rat is an intriguing model because it allows evaluation of the function of one kidney as it responds and adapts to the direct and indirect consequences of clipping the renal artery of the other kidney. Previous studies using a variety of blockers or inhibitors have emphasized the major role played by the renin-angiotensin system in the initiation and, to some extent, in the maintenance of elevated blood pressure in this model of experimental hypertension. Although it is recognized that several effects could result from elevations in circulating angiotensin II, one possible mechanism relates to the influence that angiotensin II might have on the tubular function and hemodynamics in the kidney contralateral to the stenotic kidney. As mentioned, earlier studies have suggested the existence of altered tubular function and hemodynamics in the kidney contralateral to the stenotic kidney.

The present studies demonstrate that renal function in the nonclipped kidneys increased dramatically and to a greater extent than in the corresponding kidneys of normal rats in response to administration of converting enzyme inhibitor. Interestingly, the changes occurred in spite of the greater reduction of arterial pressure in the GH rats. These responses to acute inhibition of angiotensin formation support the hypothesis that renal hemodynamics and sodium excretion in the nonclipped, contralateral kidneys of GH rats are under a substantial influence of the renin-angiotensin system and that at least some of the derangements in GFR and urinary fluid and electrolyte excretion occurring in the nonclipped kidney of GH rats may be reversed by the administration of CEI.

In contrast, the clipped kidney exhibited slight reductions of renal excretory function during the CEI infusion. These decreases in renal clearance and excretory function in clipped kidneys of GH rats were associated with the reductions in systemic blood pressure. As shown in figures 7 and 8, when arterial pressure was reduced by aortic clamping to comparable levels as those induced by CEI infusion, decreases in GFR, urine flow, and sodium excretion were parallel to those observed during CEI infusion in clipped kidneys; these results seem to suggest that the influence of CEI on the clipped kidney was different from that on the contralateral kidney. The data shown in figure 7 permit us to interpret that a profound fall in pressure perfusing the clipped kidney can account for the depressed renal function observed in the clipped kidney. Before CEI infusion, the renal perfusion pressure was presumably slightly below normal arterial pressure. Following administration of CEI, perfusion pressure to the kidney probably decreased at least as much as the decreases in systemic arterial pressure, and thus reached hypotensive levels. If there was an exaggerated vasodilation in this kidney, these decreases might be even greater due to the fixed resistance characteristics of the clip. These depressor effects induced by CEI infusion could have masked or prevented demonstration of direct effects resulting from angiotensin blockade on the clipped kidney.

As shown in table 1, this two-kidney hypertensive model is characterized by an elevated plasma renin activity, a high tissue renin activity in the clipped kidney, and a low intrarenal renin activity in the nonclipped kidney. Although it has been suggested that actual intrarenal angiotensin II levels in the contralateral kidney may not be depressed to the same extent as renin activity, administration of CEI has been shown to suppress both circulating and intrarenal angiotensin II levels. Thus, it can be concluded that the contralateral renal responses observed were the consequence, at least in part, of the reduced circulating and perhaps local levels of angiotensin II.

In addition to blocking the conversion of angiotensin I to angiotensin II, CEI has been reported to potentiate bradykinin effects and possibly to stimulate prostaglandin synthesis. Therefore, it is possible that the observed changes in renal function during infusion of CEI were also due to CEI-mediated influences other than blockade of angiotensin II formation. At present, there are no specific data to allow precise evaluation of these possibilities. However, in other studies, similar effects on renal hemodynamics and salt and water excretion have been reported when either CEI or competitive angiotensin II antagonists were used in normal or sodium-restricted animals. These findings suggest that most of the responses observed during CEI infusion are due to inhibition of angiotensin II formation.

It should be noted that, even though one renal artery was clipped, the control GFR values prior to CEI infusion were similar in both kidneys (1.04 ml/min·g for the clipped kidneys and 1.15 ml/min·g for the contralateral kidneys). These values are comparable with those reported by Lowitz et al. in which the clipped kidneys were clamped with a smaller (0.2 mm) clip. In preliminary experiments, we found that while it was possible to conduct control clearance measurements from kidneys clipped with a 0.2 mm clip, anuria often developed following initiation of CEI infusion. To obtain renal clearance measurements not only during control conditions but also during the CEI period, a 0.25 mm clip was chosen for the present experiments. With this size clip, hypertension developed in rats with a level of renal function in the clipped kidneys adequate to allow evaluation even after the marked decrease in arterial pressure during CEI infusion.

Previous reports have indicated that the intrarenal renin levels in clipped kidneys may be either higher or lower than in normal kidneys of control rats. In the present study, we failed to observe a significant difference in kidney tissue renin levels between the clipped kidneys of GH rats and kidneys of control rats. The failure to demonstrate any significant increase in renin content of the clipped kidney may be due to the size of the clip used for the present study. Since the renal renin concentration has been shown to be inversely related to the size of the ischemic kidney.
in GH rats, the relative maintenance of size by the clipped kidney is consistent with a lesser increase in tissue renin content. Perhaps arterial pressure perfusing the clipped kidney was near normotensive levels when the steady state hypertensive stages were reached. On the other hand, the findings of reduced tissue renin content of contralateral kidneys compared to either clipped kidneys or normal kidneys of control tissue renin content. Perhaps arterial pressure perfusing the clipped kidney is consistent with a lesser increase in tissue renin content. However, Schmid et al. indicated that, at comparable low plasma antirenin levels, normal dogs have a greater amount of renal renin than the two-kidney Goldblatt hypertensive dogs. If we consider the two-pool hypothesis of renin secretion, we see that the greater total renal renin content existing in the control rats may not necessarily mean an increased plasma renin activity. Also, it is possible that changes in renal hemodynamics or other factors may alter the turnover rate or metabolic degradation of renin in GH rats. Without a comprehensive study of renin kinetics occurring under these conditions, it is not possible to determine how the dissociation between renal renin content and plasma renin activity occurs in GH rats.

The observations that GFR and salt and water excretion rates were increased in contralateral kidneys of GH rats and in kidneys of normal rats during intravenous CEI infusion are consistent with those obtained in acute whole kidney studies of sodium-depleted and normal rats. Furthermore, they provide support for the contention advanced by Bengis and Coleman that changes in excretory function of the contralateral kidney induced by CEI contributed to the restoration of arterial pressure in this experimental model. The mechanism for this striking increase in sodium excretion cannot be determined from the present studies. The concomitant increase in potassium excretion during CEI infusion as well as the very rapid effects observed would seem to exclude the possibility that this early natriuresis resulted from the suppression of aldosterone secretion. Several studies have suggested that angiotensin II can stimulate tubular sodium and water reabsorption. Our studies support this view since CEI infusion led to marked increases in both total sodium excretion and the fraction of the filtered load of sodium that was excreted. However, it is also possible that these increased excretory responses occurred as a consequence of the marked increases in GFR that occurred during CEI administration. Whether the natriuresis and diuresis following CEI infusion are due to an increased filtered load secondary to augmented GFR or to depressed tubular reabsorption, or perhaps to both mechanisms working synergistically, remains an issue for further investigation.

In summary, these experiments demonstrate that marked increases in GFR and salt and water excretion occur in response to intravenous infusion of CEI in renin-depleted, nonclipped, contralateral kidneys of two-kidney, one clip hypertensive rats. In contrast, decreases in these same indices of renal function occur in clipped kidneys during infusion of CEI. The decreases in renal function of clipped kidneys may be the result of CEI-induced reductions in blood pressure. The observed changes in the renal function of nonclipped, contralateral kidneys are probably a reflection of renin-angiotensin system influences exerted on these kidneys during this phase of the hypertensive state.

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