Influence of Converting Enzyme Inhibition on Renal Hemodynamics and Glomerular Dynamics in Sodium-Restricted Dogs

L. Gabriel Navar, Ph.D., Dusit Jirakulsomchok, Ph.D., D.V.M., P. Darwin Bell, Ph.D., Charles E. Thomas, B.S., and Wann-Chu Huang, M.S.

SUMMARY  Clearance and micropuncture experiments were performed to evaluate the influence of converting enzyme inhibition (CEI) (SQ 14,225) on renal hemodynamics, glomerular filtration rate (GFR), segmental vascular resistances, and superficial nephron function in anesthetized sodium restricted dogs. In one series (n = 8), renal blood flow (RBF) and GFR exhibited a high degree of autoregulatory efficiency when renal arterial pressure (RAP) was reduced from 126 ± 5 to 86 ± 1 mm Hg. With RAP maintained at the reduced level, CEI elicited increases in RBF (3.9 ± 0.3 to 5.8 ± 0.5 ml/min per g kw) and GFR (0.81 ± 0.03 to 0.94 ± 0.04 ml/min per g kw). With return of RAP to spontaneous levels during continued CEI, RBF and GFR autoregulatory efficiency was maintained, and was similar to that observed in control dogs subjected to the same procedures (n = 5). In the micropuncture experiments (n = 12), RAP was maintained at the reduced level (87.5 ± 0.9 mm Hg), and measurements were made before and during CEI. Proximal tubule pressure, peritubular capillary pressure, stop flow pressure, and single nephron GFR (SNGFR) increased significantly. Regression analysis suggested that the increases in SNGFR were associated with small increases in the filtration coefficient. CEI reduced preglomerular resistance by 29% to 35% and efferent arteriolar resistance by 24% to 32%. These results indicate that the increased activity of the renin-angiotensin system that occurs during salt restriction exerts approximately equivalent vasoconstrictor influences on both preglomerular and postglomerular vascular resistance elements. (Hypertension 4: 58-68, 1982)

KEY WORDS  • renal autoregulation • renal vasodilation • glomerular filtration rate • renin-angiotensin system • glomerular pressure • glomerular filtration coefficient • renal vascular resistance • micropuncture • single nephron filtration rate • tubule pressures

THE role exerted by the renin-angiotensin system in the control of renal hemodynamics and sodium excretion during various physiologic or pathophysiologic states remains a topic of interest and controversy. It has been suggested that angiotensin I (AI) is formed directly within the kidney as a consequence of changes in renin secretion rate, and that, under the influence of converting enzyme present on the endothelial structures of the renal vasculature, angiotensin II (AII) is formed and exerts an intrarenal action. However, the large quantities of converting enzyme present in other vascular beds, particularly the lung, allow substantial extrarenal conversion of AI resulting in effects of circulating AII. As a means of evaluating the preexisting influence exerted by angiotensin, investigators have utilized pharmacological inhibitors or antagonists that block the formation or action of AII. Some of the results have indicated that angiotensin exerts a substantial influence on the preglomerular resistance vessels while other studies have suggested a preferential effect on the postglomerular resistance vessels. Recent micropuncture studies in rats have also indicated that angiotensin can alter the filtration characteristics of the glomerular capillaries.
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Methods

Experiments were performed on 25 mongrel dogs of both sexes ranging in weight from 15 to 22 kg. Dogs in Groups 1 (n = 5) were fed with standard dog food (Purina Dog Chow) and were used for control whole kidney clearance experiments. Dogs in Group 2 (n = 8) and Group 3 (n = 12) were maintained on a low sodium diet (Hill’s Division, Riviana Foods; 3.3 mEq sodium per day) for a period of 7 to 14 days. Group 2 animals were used for whole kidney studies only whereas micropuncture measurements were also made on Group 3 dogs. The dogs were anesthetized with pentobarbital sodium (30 mg/kg body weight), and additional anesthetic was given as necessary throughout the duration of the experiment. After placement of a tracheal cannula, the left jugular vein was catheterized for the infusion of inulin (2.5% solution for Group 1 and 2 and 5% solution for Group 3) at a rate sufficient to establish a plasma inulin concentration of about 0.2 mg/ml for Groups 1 and 2 and 0.8 mg/ml for Group 3 dogs. A catheter was inserted into a foreleg vein for the administration of a saline solution (approximately 0.5 ml/min) to replace fluid losses, and for the administration of drugs. A catheter was placed into a femoral artery to collect blood samples and to measure systemic arterial pressure.

A retroperitoneal left flank incision was made to expose the left kidney, and the ureter was cannulated for urine collections. An electromagnetic blood flow probe (Carolina Medical Electronics, Inc., King, North Carolina) was placed around the renal artery close to the aorta. A 22-gauge curved needle was inserted in the artery to measure renal arterial pressure (RAP) and was kept patent by continuous infusion of heparinized saline solution at the rate of 0.2 ml/min. To adjust RAP, a plastic clamp was placed around the renal artery between the needle and the flow probe. In three of the dogs having renal arteries with early bifurcations, an aortic clamp was used. At least 45 minutes of equilibration time was allowed after commencing the inulin infusion before the initiation of clearance studies.

In Groups 1 and 2, the protocol consisted of four experimental phases during which renal function and urinary excretion rates were assessed. During each phase, two or three clearance periods of 20 to 30 minutes each were undertaken, and blood samples were drawn at the mid-point of each clearance period. During the first phase, the kidney was perfused at the spontaneous blood pressure. The renal arterial clamp was then constricted to decrease RAP to 85-90 mm Hg. After a 15-minute stabilization period, urine collection periods were repeated. With RAP maintained at the reduced value, SQ 14,225 (Captopril, E.R. Squibb and Sons) was administered systemically (i.v.) at a dosage of 1 mg/kg followed by a continuous infusion at a rate of 1 mg/kg per hour. After a minimal stabilization period of 30 minutes, two to three clearance measurements were taken. Although systemic arterial pressure decreased to a variable extent, RAP was maintained constant by adjustment of
the renal arterial clamp. Finally, the clamp was released while the infusion of SQ 14,225 was maintained, and subsequent collection periods ensued.

The dose of SQ 14,225 used was evaluated in 15 dogs. Test doses of AI (1-5 µg) were given i.v. before and during the infusion of SQ 14,225 to test the effectiveness of the converting enzyme inhibitor. Pressor and renal vasoconstrictor effects were reduced by 100% and 80%, respectively.

In Group 3 dogs, the tissue and fascia surrounding the kidney were removed, and the renal artery, vein, and ureter were dissected free. The kidney was placed on a lucite holder, and approximately 2 cm² of renal capsule were removed. The kidney was wrapped and the exposed surface bathed with warm saline solution dripped through a quartz glass rod also used to illuminate the surface of the kidney. After preparation of the kidney for micropuncture, RAP was reduced to 85-90 mm Hg and maintained at this level for the duration of the experiment. Because of the time constraints inherent in dog micropuncture experiments, Group 3 dogs were subjected to only two experimental phases. After the control measurements, SQ 14,225 was administered as described earlier. The micropressure measurements and tubular fluid collections were performed simultaneously with the clearance measurements. Proximal tubular pressure (PTP), stop flow pressure (SFP), and peritubular capillary pressure (PCP) were measured with a micropressure servo-null system (Instrumentation for Physiology and Medicine, San Diego, California). Stop flow pressure was measured in tubules blocked with stained castor oil, and glomerular pressure (GP) was estimated from the sum of SFP and the plasma colloid osmotic pressure (σo). Three to five measurements of each of the pressures were obtained during each maneuver. Also, three to five exactly timed, 1- to 1½-minute samples of fluid were collected from proximal convoluted tubules to assess the responses of single nephron glomerular filtration rate (SNGFR). When possible, efferent arteriolar blood samples were collected using heparinized micropipettes with tip diameters of 12 to 15 µ. The microsample of efferent arteriolar blood was centrifuged and the efferent hematocrit (He) measured with a slide comparator (Gaertner Scientific Corporation, Chicago, Illinois).

To determine tubular fluid volumes, samples were transferred to a calibrated constant pore capillary and measured with a slide comparator. Inulin concentration in tubular fluid samples was determined using a microfluorometric method. SNGFR was calculated from the product of tubular flow rate and the tubule fluid to plasma inulin concentration ratio. Hematocrit (He) measurements were performed on all femoral arterial blood samples. An anthrone technique was used to determine inulin concentration in plasma samples and urine samples. Glomerular filtration rate (GFR) was calculated by the standard clearance formula. Whole kidney filtration fraction (FF) was determined from the calculated values for GFR and renal plasma flow derived from the measured values for RBF and arterial hematocrit.

Measurements of sodium and potassium concentrations (Instrumentation Laboratory Inc., Lexington, Massachusetts) were performed on all urine and plasma samples. Plasma colloid osmotic pressure was measured directly with a membrane osmometer. Calibration procedures and the quantitative relationship between plasma protein concentration and colloid osmotic pressure for the dog have been described in detail.

Plasma renin activity (PRA) was determined on blood samples collected into separate chilled tubes containing EDTA by radioimmunoassay procedure.

The micropressure measurements were used for the evaluation of superficial nephron function and also to provide estimates of glomerular pressure and peritubular capillary pressure for the total nephron population.

These values, when coupled with whole kidney measurements of RBF and GFR, allowed the overall assessment of changes in segmental renal vascular resistance in response to CEI.

An estimate of overall preglomerular (afferent) resistance (AR) was calculated by the expression:

\[
AR = \frac{R_{AP} - GP}{RBF}
\]

and postglomerular (efferent) resistance (ER) was estimated using the formula:

\[
ER = \frac{GP - PCP}{RBF - GFR}.
\]

The resistance units are expressed as mm Hg • ml⁻¹•min⁻¹

To assess the influence of CEI on single nephron filtration dynamics, the glomerular filtration coefficient (Kf) was calculated using an equation previously described:

\[
K_f = \frac{SNGFR}{\Delta P} \cdot \frac{R \cdot \sigma_o}{\frac{FF \cdot \Delta P \cdot (R + \sigma_o)}{R \cdot (\Delta P - \sigma) + \frac{FF \cdot \sigma}{R \cdot (\Delta P - \sigma)}})
\]

where \(\Delta P\) is the transglomerular hydrostatic pressure, and \(R\) is a constant that relates \(\sigma\) and FF to the efferent colloid osmotic pressure. This approach is particularly useful in the dog studies because \(R\) (43.3) is affected only slightly by variations in albumin-to-globulin ratios, which are substantial in this species.

The average effective filtration pressure (ETF) was calculated from:

\[
ETF = \frac{SNGFR}{K_f}.
\]

To evaluate superficial nephron responses, superficial nephron filtration fraction (SFF) was calculated on the basis of efferent arteriolar hematocrits in seven of the micropuncture experiments in which efferent collections were obtained using the following equations previously described:

\[
SFF = \frac{SNGFR}{K_f}
\]
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\[ SFF = \frac{1 - H_e}{1 - H_a} \]

where \( H_a \) = arterial blood hematocrit, and \( H_e \) = efferent arteriole hematocrit. Glomerular plasma flow (GPF) was then determined by

\[ GPF = \frac{SNGFR}{SFF} \]

and glomerular blood flow (GBF) was calculated as:

\[ GBF = \frac{GPF}{(1 - H_e)} \]

With these indices of superficial hemodynamics, single nephron preglomerular (afferent) resistance (AR<sub>SN</sub>) and single nephron postglomerular (efferent) resistance (ER<sub>SN</sub>) were also determined as described for the whole kidney resistance calculations except that the resistance units are expressed as mm Hg·nl<sup>-1</sup>·min<sup>-1</sup> per glomerulus. This analysis was also conducted using whole kidney filtration fractions as estimates of superficial filtration fractions for all dogs.

Statistical evaluation of differences was conducted using Student's t test for paired and grouped data as appropriate. Statistical differences were accepted when p values were 0.05 or less. Linear regression analysis was used to evaluate the degree of association between the SNGFR and K<sub>r</sub> responses.

Results

Hemodynamic and Clearance Experiments

The initial studies focused on whole kidney responses in dogs maintained on normal diet and dogs fed a low sodium diet for 7-14 days prior to the experiment. Table 1 provides the control data obtained in these two groups. The sodium-restricted dogs exhibited significantly greater PRA values and significantly lower values of absolute and fractional sodium excretion.

<table>
<thead>
<tr>
<th></th>
<th>Normal diet (n = 5)</th>
<th>Low Na diet (n = 8)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>127 ± 3</td>
<td>126 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>RBF (ml/min·g)</td>
<td>3.78 ± 0.53</td>
<td>3.68 ± 0.42</td>
<td>NS</td>
</tr>
<tr>
<td>GFR (ml/min·g)</td>
<td>0.75 ± 0.07</td>
<td>0.79 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.37 ± 0.03</td>
<td>0.40 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>43.4 ± 1.5</td>
<td>43.8 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng/ml·hr)</td>
<td>3.7 ± 1.3</td>
<td>121.1 ± 2.8</td>
<td>*</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>0.24 ± 0.06</td>
<td>0.16 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Na excretion (μEq/min)</td>
<td>47 ± 9</td>
<td>21 ± 7</td>
<td>*</td>
</tr>
<tr>
<td>Fractional Na excretion (%)</td>
<td>1.04 ± 0.32</td>
<td>0.49 ± 0.15</td>
<td>*</td>
</tr>
<tr>
<td>K excretion (μEq/min)</td>
<td>33 ± 4</td>
<td>35 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Fractional K excretion (%)</td>
<td>27 ± 3</td>
<td>32 ± 3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE. n designates number of dogs. MAP = mean systemic arterial pressure; RBF = renal blood flow; GFR = glomerular filtration rate; PRA = plasma renin activity.

*Values are significantly different at 5% level based on unpaired t test; NS designates not significant.

The hemodynamic responses observed in the sodium-restricted dogs are shown in figure 2. RBF, GFR, and FF were not altered significantly during reduction in RAP from 126 to 86 mm Hg. In response to CEI, RBF increased from 3.9 ± 0.3 to 5.8 ± 0.5 ml/min·g kw and GFR increased from 0.81 ± 0.03 to 0.94 ± 0.04 ml/min·g. Since GFR increased by an average of 16% while RFB increased by 47%, there was a significant decrease in FF from 0.38 to 0.30. PRA increased markedly following CEI but was not altered further with return of RAP to spontaneous levels. Likewise, RBF (5.8 ± 0.5 ml/min·g) and GFR (.99 ± 0.05 ml/min·g) were not altered significantly following release of the renal arterial clamp and return of RAP. Thus, autoregulation of RBF and GFR were observed during both control periods and during the CEI period. FF was not altered significantly (0.30 ± 0.02 vs 0.31 ± 0.02) following release of the renal arterial clamp.

The effects of CEI on urine flow, sodium and potassium excretion rates, and fractional excretion of sodium and potassium at control and reduced RAP are shown in table 2. The average data for sodium excretion and fractional sodium excretion obtained in both the control and sodium-restricted dogs are plotted as a function of RAP in figure 3. In the control dogs, sodium excretion and fractional sodium excretion were not altered significantly during CEI at either control or reduced pressure. In the sodium-restricted dogs, sodium excretion and fractional sodium excretion increased significantly following release of the renal arterial clamp.
Normal Diet (n = 5)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>†RAP</th>
<th>‡RAP+CEI</th>
<th>CEI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAP</strong> (mmHg)</td>
<td>127 ± 3</td>
<td>82 ± 1</td>
<td>86 ± 1</td>
<td>119 ± 7</td>
</tr>
<tr>
<td><strong>PRA</strong> (ng/ml-hr)</td>
<td>37 ± 13</td>
<td>81 ± 27</td>
<td>155 ± 73</td>
<td>185 ± 85</td>
</tr>
</tbody>
</table>

RBF (ml/min) = renal blood flow; GFR (ml/min) = glomerular filtration rate; FF = filtration fraction; PRA = plasma renin activity.

**FIGURE 1.** Average values (± standard error) for renal blood flow (RBF), glomerular filtration rate (GFR), filtration fraction (FF), and plasma renin activity (PRA) obtained in five dogs on normal diet in sequential clearance periods during the four phases of the experimental protocol: spontaneous arterial pressure, reduced renal arterial pressure, reduced renal arterial pressure plus CEI, and continued CEI infusion after release of renal arterial constriction. Asterisks indicate that the values in that panel are significantly different from those in the preceding panel.

**TABLE 2.** Effects of CEI on Urine Flow and Electrolyte Excretion at Spontaneous and Reduced Arterial Pressure in Control Dogs (C) and Sodium-Restricted Dogs (R). Values are presented as mean ± SE. **U₅V** = urinary Na excretion; **U₆V** = urinary K excretion; **FE₅** = fractional Na excretion; **FE₆** = fractional K excretion.

<table>
<thead>
<tr>
<th></th>
<th>C (ml/min)</th>
<th>R (ml/min)</th>
<th>C (μEq/min)</th>
<th>R (μEq/min)</th>
<th>C (%)</th>
<th>R (%)</th>
<th>C (μEq/min)</th>
<th>R (μEq/min)</th>
<th>C (%)</th>
<th>R (%)</th>
<th>C (μEq/min)</th>
<th>R (μEq/min)</th>
<th>C (%)</th>
<th>R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous RAP</td>
<td>0.24 ± 0.06</td>
<td>0.16 ± 0.04</td>
<td>47 ± 9</td>
<td>21 ± 7</td>
<td>1.04 ± 0.32</td>
<td>0.49 ± 0.15</td>
<td>33 ± 4</td>
<td>35 ± 3</td>
<td>27 ± 4</td>
<td>32 ± 4</td>
<td>0.94 ± 0.28</td>
<td>0.93 ± 0.23</td>
<td>45 ± 9</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>Reduced RAP</td>
<td>0.15 ± 0.03</td>
<td>0.15 ± 0.04</td>
<td>19 ± 5</td>
<td>10 ± 5</td>
<td>0.41 ± 0.11</td>
<td>0.26 ± 0.11</td>
<td>27 ± 4</td>
<td>32 ± 4</td>
<td>22 ± 4</td>
<td>28 ± 4</td>
<td>0.45 ± 0.16</td>
<td>0.47 ± 0.13</td>
<td>35 ± 8</td>
<td>38 ± 8</td>
</tr>
<tr>
<td>Reduced RAP + CEI</td>
<td>0.17 ± 0.06</td>
<td>0.20 ± 0.03</td>
<td>23 ± 7</td>
<td>24 ± 7</td>
<td>0.45 ± 0.16</td>
<td>0.47 ± 0.13</td>
<td>35 ± 8</td>
<td>38 ± 8</td>
<td>22 ± 4</td>
<td>30 ± 4</td>
<td>0.94 ± 0.28</td>
<td>0.93 ± 0.23</td>
<td>45 ± 9</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>Spontaneous RAP + CEI</td>
<td>0.30 ± 0.09</td>
<td>0.32 ± 0.06</td>
<td>50 ± 14</td>
<td>53 ± 15</td>
<td>0.94 ± 0.28</td>
<td>0.93 ± 0.23</td>
<td>45 ± 9</td>
<td>46 ± 9</td>
<td>32 ± 4</td>
<td>35 ± 4</td>
<td>0.94 ± 0.28</td>
<td>0.93 ± 0.23</td>
<td>45 ± 9</td>
<td>46 ± 9</td>
</tr>
</tbody>
</table>

*Indicates that values were significantly altered from previous value based on paired t test.
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<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>↓ RAP</th>
<th>↓ RAP + CEI</th>
<th>CEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>126 ± 5</td>
<td>85 ± 1</td>
<td>85 ± 1</td>
<td>103 ± 6</td>
</tr>
<tr>
<td>PRA (ng/ml-hr)</td>
<td>12 ± 2 ± 8</td>
<td>19 ± 3 ± 7</td>
<td>817 ± 18 ± 90</td>
<td>60 ± 2 ± 23 ± 7</td>
</tr>
<tr>
<td>RBF (ml/min-g)</td>
<td>70 - 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min-g)</td>
<td>110 - 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>40 - 35</td>
<td></td>
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</table>

**Figure 2.** Average values for renal blood flow (RBF), glomerular filtration rate (GFR), filtration fraction (FF), and plasma renin activity (PRA) obtained in eight dogs maintained on a Na-restricted diet in sequential clearance periods during four phases of experiments: spontaneous arterial pressure, reduced renal arterial pressure, reduced renal arterial pressure plus CEI, and continued CEI infusion after release of renal arterial constriction.

dogs, the changes in absolute or fractional sodium excretion in response to reductions in RAP were not statistically significant. However, during CEI, the increases in urine flow, sodium excretion, and fractional sodium excretion were significant, and absolute and fractional sodium excretion values achieved levels similar to those obtained in the control dogs even though systemic arterial pressure averaged only 103 mm Hg in the salt-restricted dogs. In contrast, potassium excretion rates were not affected significantly by CEI at either spontaneous or reduced pressures.

**Sodium-Restricted Dogs Subjected To Micropuncture Procedures**

In Group 3 dogs, RAP was reduced to the range of 85 to 90 mm Hg prior to the initiation of control clearance and micropuncture procedures. Table 3 presents the average hemodynamic and whole kidney function data obtained before and during CEI in this group of dogs. As in Group 2 dogs, CEI elicited significant increases in RBF and GFR and significant decreases in filtration fraction. Figure 4 presents the average micropressure measurements observed in these dogs. PCP increased from 12.1 ± 0.8 to 14.5 ± 1.2 mm Hg; PTP increased from 19.2 ± 0.5 to 22.4 ± 1.0 mm Hg, and SFP increased from 40.8 ± 0.7 to 43.3 ± 0.7 mm Hg. The increase in GP from 56.0 ± 0.9 to 57.6 ± 1.2 mm Hg was not statistically significant.

Figure 5 shows the estimated changes in segmental vascular resistance using the GP and PCP data in conjunction with the whole kidney hemodynamic data. Significant decreases in both preglomerular and efferent resistance occurred. Preglomerular resistance decreased by an average of 29% ± 2% while efferent arteriolar resistance decreased by 24% ± 3%.

SNGFR, measured during control and CEI periods in 11 dogs, increased significantly from 48.8 ± 3.7 to 60.7 ± 5.3 nl/min. Superficial nephron filtration dynamics were assessed utilizing whole kidney filtration fractions in all 11 dogs. In seven of these 11 dogs, filtration dynamics were assessed using the superficial filtration fractions calculated from efferent arteriolar...
hematocrits. The SNGFR and glomerular plasma flow values are shown in figure 6 left. These data demonstrate that significant increases in glomerular plasma flow accompanied the increases in SNGFR. However, as shown in figure 6 right, there were no significant changes in the transglomerular hydrostatic pressure difference, AP (37 vs 36 mm Hg); average effective filtration pressure, EFP (15 vs 17 mm Hg); or filtration coefficient, K_f (3.5 vs 3.9 nl/min·mm Hg). Similar to previous results in the dog, a positive effective filtration pressure existed throughout the glomerular capillary during both control and CEI flow.

Table 3. Hemodynamic Responses to Converting Enzyme Inhibition in Group 3 Dogs Subjected to Micropuncture Procedures (n = 12)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CEI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arterial pressure (mm Hg)</td>
<td>119 ± 5</td>
<td>102 ± 6</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Renal arterial pressure (mm Hg)</td>
<td>87.5 ± 0.9</td>
<td>85.7 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Renal blood flow (ml/min·g)</td>
<td>3.56 ± 0.21</td>
<td>4.46 ± 0.25</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>GFR (ml/min·g)</td>
<td>0.66 ± 0.04</td>
<td>0.70 ± 0.04</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.35 ± 0.02</td>
<td>0.29 ± 0.02</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Plasma colloid osmotic pressure (mm Hg)</td>
<td>15.2 ± 0.5</td>
<td>14.6 ± 0.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Arterial hematocrit</td>
<td>45.9 ± 1.4</td>
<td>45.0 ± 1.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SE; analysis of differences was based on paired t test.
periods. Efferent effective filtration pressure was significantly greater than zero under both conditions averaging 5.1 ± 1.9 mm Hg during control conditions and 8.2 ± 2.0 mm Hg during CEI.

To evaluate if the relatively small increases in $K_r$ or $EFP$ were associated with the increases in SNGFR, regression analysis was conducted between the SNGFR changes and the $EFP$ or $K_r$ changes. The relationship between $\Delta K_r$ and $\Delta SNGFR$ yielded a statistically significant correlation coefficient of 0.75, suggesting that the increase in SNGFR during CEI was attributable, in part, to associated increases in $K_r$.

Figure 7 depicts the preglomerular resistance and efferent arteriolar resistance values calculated for the superficial nephrons using both WKFF and SFF. Similar values are obtained using either method, and these results agree closely with the estimates of segmental vascular resistances for the whole kidney. Preglomerular resistance decreased by an average of 32% ± 7.5% when whole kidney filtration fraction was used and by 35% ± 8.5% when the analysis was based on only the seven dogs having superficial filtration fractions. Likewise, efferent arteriolar resistance decreased by 32% ± 5% in the 11 dogs and 31% ± 9.6% in the seven dogs. In both cases, there were significant and approximately equivalent relative decreases in both preglomerular and efferent arteriolar resistances.

**Discussion**

Although studies utilizing pharmacological antagonists of the renin-angiotensin system allow an assessment of the physiologic actions of AII, there are several uncertainties associated with the use of these agents. In the case of converting enzyme inhibitors, it is known that the rate of degradation of bradykinin and other kinin species is depressed. Therefore, it is recognized that the effects occurring in response to SQ14,225 infusions may not be due entirely to diminished activity of AII. Furthermore, the observed responses are probably due to a combination of inhibi-
filtration fractions (n = 11) and superficial nephron filtration fractions (n = 7).

**Figure 7.** Comparison of the segmental resistance decreases in response to CEI in sodium-restricted dogs. AR and ER resistance were calculated using both whole kidney filtration fractions (n = 11) and superficial nephron filtration fractions (n = 7).

The results obtained in the first two groups of dogs demonstrated that the hemodynamic responses of sodium-restricted animals to CEI were qualitatively similar but quantitatively greater than those observed in the control experiments. Because of the desired measurements, these experiments had to be conducted in anesthetized animals. Thus, it is possible that the changes observed in the control animals reflect, in part, the effects of anesthesia. Prior studies have indicated that conscious animals on a normal sodium diet respond to a lesser extent to converting enzyme inhibition.

In the present study, both RBF and GFR exhibited a high degree of autoregulatory efficiency in response to RAP reductions. During CEI, both RBF and GFR increased significantly, and the decrease in filtration fraction was the consequence of proportionately greater increases in plasma flow than in GFR. Furthermore, when RAP was allowed to return to spontaneous arterial pressure levels during CEI, GFR as well as RBF, was autoregulated effectively such that no significant increase in GFR occurred as a consequence of the increased arterial pressure. Thus, these results fail to support previous suggestions that GFR autoregulation is dissociated from RBF autoregulation when angiotensin blockade is imposed on sodium restricted dogs. They are in general agreement with the reports of Murray and Malvin and Gagnon et al. that have indicated that the renin-angiotensin system does not exert a major influence on RBF or GFR autoregulation capability.

While there is general agreement that angiotensin blockade increases RBF in sodium restricted animals, the GFR responses have been more variable with some reports indicating an associated increase in GFR, while other studies have reported that GFR was unaltered following angiotensin blockade. In the present study, CEI resulted in increases in GFR, especially in the sodium restricted dogs. However, the increases in GFR were of lesser magnitude than the changes in RBF resulting in decreases in filtration fraction. It should be emphasized, however, that decreases in filtration fraction alone do not necessarily imply that the vasodilation was localized to efferent arteriolar segments. Furthermore, GFR increased even when the renal arterial pressure was maintained at reduced levels. In this regard, the present results are at variance with previous suggestions that angiotensin blockade may actually decrease GFR when RAP is near the lower limit of the autoregulatory range. The reasons for these differences are not apparent; however, in the present study several clearance periods were taken at each arterial pressure level to ensure that adequate steady state values had been achieved.

The difference between the PRA values observed in the sodium-restricted dogs and those maintained on a normal diet is similar to that previously reported. As expected, renal arterial constriction resulted in increases in PRA in both groups of dogs. CEI led to further increases in PRA and also apparently dissociated the influence of renal perfusion pressure on PRA. In both groups, PRA remained approximately at the same levels as it had reached under the combined influence of reduced renal arterial pressure and CEI. Of interest is the finding that the sodium-restricted dogs exhibited a very dramatic increase in PRA following administration of SQ 14,225. Presumably, this increase in PRA was due to the withdrawal of the negative feedback influence of All on renin release.

Estimates of overall changes in afferent and efferent arteriolar resistances were obtained by using the glomerular pressure and peritubular capillary pressure data in conjunction with the whole kidney GFR and RBF values. It should be recognized that the control values for pregglomerular resistance were already reduced due to the autoregulatory responses to decreases in RAP. Even under these circumstances, CEI elicited further reductions in afferent resistance as well as reductions in efferent resistance. The changes in superficial nephron hemodynamics during CEI calculated using both whole kidney filtration fractions and superficial nephron filtration fractions are compatible with this conclusion. Also, no significant differences were observed between the superficial nephron responses and the whole kidney responses indicating that there was consistency between the changes in superficial nephron hemodynamics and those occurring in the total nephron population. Therefore, these studies support the concept that the
elevated levels of intrarenal and circulating AII existing in the salt-restricted dogs exerted approximately equivalent vasoconstrictor influences on the preglomerular and postglomerular vessels. Our findings extend those previously obtained in normal and sodium-restricted animals, although the rats in a previous study were markedly NaCl depleted and not just subjected to NaCl restriction as in the present study. Steiner et al. observed that saralasin decreased afferent arteriolar resistance; however, part of the decrease in afferent resistance could have been caused by an autoregulatory response secondary to the saralasin-induced decrease in arterial pressure. The contribution of the autoregulatory mechanism was minimized in the present study by maintaining RAP at an arterial pressure close to the lower levels of the autoregulatory range and unchanged during CEI. Under these conditions CEI elicited significant decreases in preglomerular resistance that were not attributable to autoregulatory adjustments.

As mentioned, CEI did not significantly alter Kf when a paired t test was used. However, regression analysis of the SNGFR responses and the changes in Kf revealed a significant association indicating that the magnitude of the increase in SNGFR was determined, in part, by the Kf responsiveness. Thus, these results suggest that there may be a slight influence of angiotensin to influence one or more determinants of the filtration coefficient in the dog. However, this effect could be indirect and is of much lesser magnitude than has been observed in rats. In addition, the influence of increases in plasma flow under conditions where filtration pressure equilibrium is not attained, as has been shown to be the case for the dog, 20, 21 would not be very great so that SNGFR would not increase proportionately and filtration fraction would fall. In essence then, it would seem that the increases in SNGFR were effected by the combination of subtle increases in Kf, EFP, and glomerular plasma flow.

The results of these experiments are also of interest with regard to the influence of CEI on the relationship between renal arterial pressure and sodium excretion. The dogs on normal diet exhibited typical conditions where filtration pressure equilibrium is not attained, as has been shown to be the case for the dog. However, this sensitivity was enhanced, and the slope of the relation to changes in RAP prior to CEI. During CEI, however, this sensitivity was enhanced, and the slope of the relationship between arterial pressure and sodium excretion was increased. These results support the suggestion that, during high angiotensin states, the mechanism responsible for arterial-pressure-induced changes in sodium excretion is suppressed. The mechanism for these adaptations remains incompletely understood. However, since RBF and GFR exhibited autoregulatory behavior both before and during CEI, the sodium excretion responses are consistent with the notion that AII can directly enhance tubular sodium transport. The authors thank Carolyn McLean, Grace Davis, and Phil Youngblood for their technical assistance; Becky Smith and Cathy Dastmalchi for secretarial assistance; Ellen Bernstein for illustrations and photography; Dr. Jack Work and Sunanda Ram for the analysis of plasma renin activity; Dr. Kenneth L. Duchin, Assistant Clinical Pharmacologist Director of the Squibb Institute for Medical Research, for advice and some unpublished data; and S. J. Lucania of E. R. Squibb and Sons for providing the converting enzyme inhibitor (SQ 14,225, Batch RRO54ND); and Dr Fred Sias, Department of Electrical Engineering, Clemson University, South Carolina, for assistance in the computational techniques.

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21. Steiner RW, Blantz RC. Acute reversal by saralasin of multiple...
Influence of converting enzyme inhibition on renal hemodynamics and glomerular dynamics in sodium-restricted dogs.
L G Navar, D Jirakulsomchok, P D Bell, C E Thomas and W C Huang

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