Glomerular and Renal Hemodynamics During Converting Enzyme Inhibition (SQ20,881) in the Dog

L. Gabriel Navar, Ph.D., R. A. Lagrange, Ph.D., P. D. Bell, B.S., C. E. Thomas, B.S., and D. W. Ploth, M.D.

SUMMARY It has been suggested that intrarenal levels of angiotensin II may preferentially control efferent arteriolar resistance or may influence the glomerular filtration coefficient ($K_f$). To examine these possibilities, micropuncture and clearance experiments were performed on nine anesthetized dogs evaluating renal and glomerular hemodynamics before and during the administration of an angiotensin converting enzyme inhibitor (SQ20,881). During the micropuncture measurements, renal arterial pressure was reduced to a range of 85 to 90 mm Hg in order to maximize renin secretion and intrarenal formation of angiotensin II. Also, this procedure minimizes potential errors in the determination of single nephron glomerular filtration rate (SNGFR) and of glomerular pressure when estimated by techniques that require complete blockade of proximal tubule fluid flow. During the administration of SQ20,881, a converting enzyme inhibitor (CEI), renal blood flow increased significantly by 13%, but GFR was not altered. There were no significant alterations in SNGFR, proximal tubule pressure, peritubular capillary pressure or estimated glomerular pressure. By using the micropressure measurements in combination with the whole kidney hemodynamic data, it was estimated that afferent resistance was reduced 23%. Although significant decreases in efferent resistance could not be documented, there was a tendency for this variable to decrease also. Neither $K_f$ nor effective filtration pressure were altered significantly by CEI. These results do not support the contention that intrarenal effects of angiotensin II are exerted predominantly on the efferent arteriolar resistance segments; rather, they suggest that angiotensin may exert a modest tonic effect on both pre- and postglomerular resistance elements in the anesthetized hydropenic dog. (Hypertension 1: 371-377, 1979)

KEY WORDS
- micropuncture
- renin-angiotensin
- glomerular dynamics
- glomerular filtration coefficient
- renal blood flow
- renal vascular resistance

The unique anatomical arrangement of the juxtaglomerular apparatus, the element generally accepted as being responsible for synthesis and release of renin, has provided the basis for suggestions by various investigators that the renin-angiotensin system might serve as a local hormone system regulating some aspect of renal function. According to this general concept, the secretion of renin, either into the blood stream or the surrounding interstitial areas could catalyze the generation of angiotensin I from its circulating precursor. To the extent that adequate converting enzyme is present in the vicinity of the glomerular structures, angiotensin II could be formed locally and perhaps exert a direct effect on one or more aspects of glomerular function. Some investigators have suggested that angiotensin exerts its hemodynamic effects on preglomerular vascular resistance either directly or by an influence on the distal tubular feedback mechanism. In contrast, results based on experiments utilizing overall renal hemodynamic responses to angiotensin or angiotensin antagonists have sometimes been interpreted as being consistent with the concept that the effects of angiotensin occur predominantly at postglomerular or efferent vascular sites. In particular, recent studies in dogs have led to the suggestion that the increased renin release that occurs at reduced levels of renal arterial pressure may have a regulatory influence on efferent arteriolar resistance. However, the experimental approaches that have been utilized previously have not allowed more direct localization of these intrarenal effects.

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For the present study, micropuncture procedures were used in order to attempt a more direct evaluation of the influence of the renin-angiotensin system on glomerular hemodynamics and on the glomerular filtration coefficient, \((K_f)\). Although previous investigators have considered the effects of exogenous angiotensin on glomerular dynamics, these studies probably reflect renal responses to circulating concentrations and are of questionable value in providing insight regarding possible local effects of angiotensin II formed at intrarenal sites. As is now recognized, the assessment of the potential role of the renin-angiotensin system can best be done by using inhibitors or competitive antagonists which presumably block the local formation of angiotensin II or block the effect of angiotensin II. In the present study the nonapeptide converting enzyme inhibitor (SQ20,881) was used. It should be recognized, however, that even with this approach, it is not possible to exclude with certainty the contribution of decreased circulating angiotensin II concentrations to the observed responses to angiotensin inhibition. Experiments were performed in dogs to allow direct comparison with previous studies germane to this concept. In addition, all measurements were performed at reduced levels of renal arterial pressure, a condition shown to increase the renal secretion rate and tissue renin levels. We have previously presented evidence that at reduced renal arterial pressure, micropuncture procedures can be used to obtain representative estimates of single nephron glomerular pressure and filtration rate even when these involve proximal tubule blockade and interference with distal volume delivery. Consequently, this approach was utilized to assess the possible influence of converting enzyme inhibition on single nephron hemodynamics in the normal dog.

Methods

Experiments were performed on nine mongrel dogs, anesthetized with sodium pentobarbital and prepared for simultaneous micropuncture and whole kidney clearance studies as described previously. A tracheotomy was performed to maintain a patent airway, and a Harvard respirator (Harvard Apparatus, Inc., Millis, MA) was used when necessary to provide adequate ventilation. The respirator was used when the normal respiratory pattern was erratic and led to movement of the kidney that precluded micropuncture procedures or, less frequently, when respiratory rate was lower than 8 to 10 breaths per minute. The left jugular vein was catheterized to allow the administration of an inulin solution (5 g/dl) at a rate sufficient to establish a plasma inulin concentration of approximately 0.8 mg/ml. This requires a priming dose of 3 ml/kg of body weight and a sustaining infusion of 0.05 ml/min/kg. The left foreleg vein was catheterized for the administration of anesthetic as required. A catheter was inserted in the left femoral artery to measure systemic arterial pressure using a Statham pressure transducer (Statham Laboratories, Inc., Hato Rey, Puerto Rico) and a Grass polygraph recorder (Grass Instrument Co., Quincy, MA). Blood samples were also collected from this femoral arterial catheter.

The kidney was exposed through a left flank incision and the renal artery, vein and ureter were freed of surrounding tissue. An electromagnetic flow transducer (Carolina Medical Electronics, Inc., King, NC) was placed around the base of the renal artery for continuous measurement of renal blood flow (RBF). When the renal artery was sufficiently long, a small 22-gauge curved needle was inserted into the artery and kept patent by constant infusion of heparinized saline at 0.2 ml/min. This allowed continuous measurement of renal arterial pressure (RAP) with a second pressure transducer. An adjustable plastic clamp was placed around the renal artery between the flow probe and the needle. In three dogs, this was not possible and an aortic clamp was used. The left ureter was catheterized to allow collection of timed urine volumes. The kidney was placed on a lucite holder and approximately 2 sq cm of the renal capsule was removed. The kidney was wrapped in warmed, saline-soaked gauze and stabilized as described previously. The exposed area of the cortex was bathed with a warmed heparinized saline solution and dripped through a quartz glass rod that was also used to illuminate the kidney surface.

For each experiment, a minimum of 40 minutes was allowed after the initiation of the inulin infusion. The clearance measurements and the micropuncture procedures were conducted simultaneously during each period with systemic arterial pressure, renal arterial pressure and renal blood flow being monitored continuously. By adjusting the renal artery clamp, renal perfusion pressure was slowly lowered to the lower limits of the autoregulatory range. After stabilization, control clearance and micropuncture measurements were taken at the reduced arterial pressure. Measurements of proximal tubule pressure, peritubule capillary pressure, and stop-flow pressure were determined using a micropressure servo-null system (Instrumentation for Physiology and Medicine, San Diego, CA). Stop-flow pressure was measured in tubules blocked with stained castor oil. Glomerular pressure was estimated using the sum of the stop-flow pressure and the arterial plasma colloid osmotic pressure. Timed proximal tubule fluid samples were collected to determine single nephron glomerular filtration rate (SNGFR). At least two clearance periods were taken during control measurements. Converting enzyme inhibitor (CEI) was then administered directly into the renal artery. Two to 5 mg were given in a single injection followed by a continuous infusion at 5 mg/hr. In pilot studies, it was demonstrated that this dose effectively blocked the pressor and vasoconstrictor responses to test doses of angiotensin I. Thirty minutes after initiating the CEI infusion, clearance and micropuncture measurements were repeated as described above. After all measurements were complete, the electromagnetic flow probe was calibrated in situ by catheterizing the
renal artery and collecting timed blood samples into a graduated cylinder. The kidney was removed, stripped of all surrounding tissue, blotted dry and weighed.

To determine tubular fluid volumes, samples were placed in a calibrated constant bore capillary and measured with a slide comparator (Gaertner Scientific Corp., Chicago, IL). Inulin concentration in tubular fluid samples was determined using a microfluorometric method, and SNGFR was calculated from the product of tubular flow rate and the tubule fluid to plasma inulin concentration ratio. Hematocrit measurements were performed on all femoral arterial blood samples. An anthrone technique was used to determine inulin concentration in plasma samples and in urine samples. Glomerular filtration rate (GFR) was calculated by the standard clearance formula. Whole kidney filtration fraction was determined from the calculated values for GFR and from the measured values for RBF and arterial hematocrit. Measurements of sodium and potassium concentrations (Instrumentation Laboratory, Inc., Lexington, MA) were performed on all urine and plasma samples. Plasma colloid osmotic pressure was measured directly, using a membrane osmometer mounted on a Statham pressure transducer. Calibration procedures and the quantitative relationship between plasma protein concentration and colloid osmotic pressure for the dog have been described in detail. Protein concentration (Cₚ) was measured with the biuret technique.

In the present series of experiments, the data derived from the micropressure measurements were used not only for the evaluation of superficial nephron function but also to provide representative estimates of glomerular pressure and peritubular capillary pressure. These values, when coupled with whole kidney measurements of RBF and GFR, allowed the assessment of changes in segmental renal vascular resistance in response to administration of CEI. The micropuncture measurements were also used to assess the influence of CEI on single nephron filtration dynamics and on the glomerular filtration coefficient (K₁) using a derived equation that has been described in detail previously. Briefly, K₁ was calculated from the equation:

\[ K₁ = \frac{\text{SNGFR}}{\Delta p} \left( 1 - \frac{A \cdot Cₚ}{FF \cdot \Delta p} \right) \left( 1 - \frac{\text{FF} \cdot \Delta p \cdot \piₚ}{A \cdot Cₚ \cdot (\Delta p - \piₚ)} \right) \]

where \( \Delta p \) is the transglomerular hydrostatic pressure, Cₚ is the plasma protein concentration, FF is the filtration fraction, \( \piₚ \) is the plasma colloid osmotic pressure, and A is a constant that relates \( \piₚ \) to Cₚ. For dog samples, it has been found to be 2.08.

The use of whole kidney filtration fraction as an estimate of single nephron filtration fraction is justified on the basis of previous data indicating close agreement between whole kidney filtration fraction and superficial nephron filtration calculated on the basis of efferent arteriolar blood hematocrits. The values for average effective filtration pressure (EFP) were then calculated from: \( EFP = \frac{\text{SNGFR}}{K₁} \). Preglomerular (afferent) resistance (RA) was calculated by the equation:

\[ RA = \frac{\text{RAP} - \text{PG}}{\text{RBF} - \text{GFR}} \]

and efferent arteriolar resistance was calculated according to

\[ RE = \frac{\text{PG} - \text{PC}}{\text{RBF} - \text{GFR}} \]

where PG is glomerular pressure, PC is peritubular capillary pressure and the resistance units are expressed as

\[ \text{mm Hg} \cdot \text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \]

Plasma renin activity (PRA) was not measured directly in this group of dogs. However, in an earlier series of experiments (R.A. LaGrange, unpublished observations), six dogs were subjected to renal arterial constriction and PRA was measured in arterial and renal venous blood (Squibb Kit). Renin secretion rates were calculated from the product of renal plasma flow and the renal venous-arterial renin concentration difference. During control arterial pressure, renin secretion rate was 507 ± 330 ng Al per min and increased significantly to 2512 ± 1015 ng Al per min when the renal arterial pressure was reduced to 88 ± 1 mm Hg, a level comparable to that used in the present study.

**Results**

All measurements were made at reduced arterial pressure since previous studies have indicated that the most pronounced hemodynamic effects of angiotensin antagonists are observed at the arterial pressures just above the lower limit of the autoregulatory range. Table 1 presents the average whole kidney hemodynamic, clearance and urine excretion measurements obtained before and during the administration of CEI. Although systemic arterial pressure decreased significantly following administration of CEI, renal perfusion pressure was maintained relatively constant by adjustment of the renal arterial clamp. On the average, however, there was a significant decrease of 3 mm Hg in perfusion pressure. Renal blood flow increased consistently by an average 13%. The GFR was not altered significantly and the filtration fraction was decreased slightly. Presumably, the reduced arterial pressure minimized the urinary responses to CEI; however, the increases in sodium excretion rate and potassium excretion rate were statistically significant. These excretory responses, although small, are consistent with results from other laboratories indicating that angiotensin II blockade leads to increases in sodium excretion, while infusion of small amounts of angiotensin II stimulates sodium reabsorption.
The micropuncture results obtained from these same dogs are shown in table 2. Although there were slight changes in some of the variables measured, the average values obtained before and during the administration of CEI were not altered to a significant extent. Corresponding afferent and efferent arteriolar resistance values for all experiments were calculated from data obtained before and during administration of CEI and the results are shown in figure 1. Control preglomerular resistance averaged 9.6 ± 1.1 resistance units and was significantly reduced to 7.3 ± 1.1 units during CEI infusion. There was also an indication of a reduction in average efferent arteriolar resistance from 13.2 ± 1.8 to 11.2 ± 0.9 units; however, the changes in efferent resistance were less consistent and did not achieve statistical significance. Nevertheless, the observed decreases in renal vascular resistance could be accounted for on the basis of approximately equivalent decreases in both preglomerular (−2.3 units) and postglomerular (−1.9 units) resistances.

The effects of CEI on the glomerular filtration coefficient (K_f) and effective filtration pressure were assessed in eight of the nine dogs. In accord with previous studies, we consistently observed positive efferent effective filtration pressure values; thus it was possible to calculate unique values for K_f during both control and experimental conditions. The values for K_f and average EFP obtained before and during CEI are depicted in figure 2. Control K_f in this group of dogs averaged 5.04 ± 0.5 nl/min • mm Hg and was not significantly altered (4.61 ± 0.67 nl/min • mm Hg) during the administration of CEI. Average effective filtration pressure was not altered being 13.4 ± 1.03 mm Hg during control and 13.8 ± 1.9 mm Hg during CEI administration.

## Discussion

The present experiments were conducted to test the hypothesis that the renin-angiotensin system exerts a preferential regulatory influence on efferent arteriolar resistance and to evaluate other possible effects of CEI on glomerular filtration dynamics. In agreement with previous studies, we observed a modest increase in RBF in response to the administration of CEI. To the extent that effective inhibition of intrarenal converting enzyme activity was achieved, these results may be used as an index of the role of the renin-angiotensin system in the baseline control of renal hemodynamics in the anesthetized dog. However, it is recognized that CEI depresses the rate of degradation of bradykinin and other kinin species. Thus, it is possible that the observed renal vasodilation was also due to kinin accumulation rather than depressed levels of angiotensin II. However, previous studies using blockers of the renin-angiotensin system such as 1-sarcosine-8-alanine angiotensin II have also yielded similar degrees of renal vasodilation. This agreement would support the premise that the major effects of CEI are probably due predominantly to the reduced levels of

### Table 1. Renal Responses to Converting Enzyme Inhibition (CEI) in Nine Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (mean ± SE)</th>
<th>CEI (mean ± SE)</th>
<th>Difference (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP (mm Hg)</td>
<td>116 ± 6</td>
<td>101 ± 6</td>
<td>−14.2 ± 3.6*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>88 ± 2.4</td>
<td>85 ± 2.6</td>
<td>−3 ± 0.87*</td>
</tr>
<tr>
<td>RBF (ml/min g)</td>
<td>4.1 ± 0.4</td>
<td>4.6 ± 0.2</td>
<td>0.52 ± 0.16*</td>
</tr>
<tr>
<td>GFR (ml/min g)</td>
<td>0.65 ± 0.02</td>
<td>0.67 ± 0.03</td>
<td>0.02 ± 0.03</td>
</tr>
<tr>
<td>Plasma colloid osmotic pressure (mm Hg)</td>
<td>14.7 ± 0.9</td>
<td>13.4 ± 0.8</td>
<td>−1.2 ± 1.02</td>
</tr>
<tr>
<td>Plasma protein concentration (g/dl)</td>
<td>5.3 ± 0.3</td>
<td>5.0 ± 0.2</td>
<td>−0.35 ± 0.11*</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.29 ± 0.02</td>
<td>0.26 ± 0.02</td>
<td>−0.03 ± 0.01*</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.42 ± 0.02</td>
<td>0.43 ± 0.03</td>
<td>0.01 ± 0.01</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>0.20 ± 0.02</td>
<td>0.29 ± 0.08</td>
<td>0.09 ± 0.06</td>
</tr>
<tr>
<td>Sodium excretion (μEq/min)</td>
<td>14 ± 3.5</td>
<td>19 ± 4.6</td>
<td>4.9 ± 1.19*</td>
</tr>
<tr>
<td>Potassium excretion (μEq/min)</td>
<td>23 ± 3.5</td>
<td>32 ± 3.5</td>
<td>9.5 ± 2.9*</td>
</tr>
</tbody>
</table>

*Values are significantly different at 5% level based on paired analysis. The other four values are not statistically significant.

Abbreviations: SAP = systemic arterial pressure; RAP = renal arterial pressure; RBF = renal blood flow; GFR = glomerular filtration rate.

### Table 2. Micropuncture Measurements Before and During Converting Enzyme Inhibition (CEI) Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (mean ± SE)</th>
<th>CEI (mean ± SE)</th>
<th>Difference (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule pressure (mm Hg)</td>
<td>18.8 ± 0.9</td>
<td>20.3 ± 0.9</td>
<td>1.6 ± 1.0</td>
</tr>
<tr>
<td>Peritubular capillary pressure (mm Hg)</td>
<td>11.6 ± 0.9</td>
<td>10.6 ± 0.7</td>
<td>−1 ± 0.8</td>
</tr>
<tr>
<td>Stop-flow pressure (mm Hg)</td>
<td>37.8 ± 1.7</td>
<td>39.9 ± 2.3</td>
<td>2 ± 1.9</td>
</tr>
<tr>
<td>Glomerular pressure (estimated) (mm Hg)</td>
<td>52 ± 1.9</td>
<td>53.2 ± 2.7</td>
<td>1.2 ± 2.0</td>
</tr>
<tr>
<td>Δ Hydrostatic pressure (mm Hg)</td>
<td>33.1 ± 1.9</td>
<td>31.6 ± 2.6</td>
<td>−1.6 ± 1.6</td>
</tr>
<tr>
<td>SNGFR (ml/min) (n = 8)</td>
<td>65.1 ± 5.4</td>
<td>57.6 ± 5.8</td>
<td>−7.5 ± 4.6</td>
</tr>
</tbody>
</table>

*The values for all measurements are not statistically significant.

Abbreviation: SNGFR = single nephron glomerular filtration rate.
 angiotensin II.\textsuperscript{90} Whether the vasodilation is due to an inhibition of the intrarenal formation of angiotensin II or to reduced circulating concentrations of angiotensin II cannot be determined with certainty. If intrarenally generated angiotensin II were exerting a substantial influence on any specific element within the kidney, it might be expected that this effect would be negated by the CEI, assuming that the agent achieved access to the converting enzyme. Since much of the converting enzyme has been localized to the vascular endothelium,\textsuperscript{8}, \textsuperscript{91} it seems reasonable to assume that a substantial component of the local formation of angiotensin II can be inhibited with CEI. Nevertheless, the reduction in systemic arterial pressure suggests that there were also decreases in circulating angiotensin II concentrations which could have contributed to the observed vasodilation. Thus, we can only assess the maximal possible influence that could be due to reduced intrarenal angiotensin II formation.

By using the estimates of glomerular pressure and peritubular capillary pressure, obtained from the micropressure measurements, in conjunction with the whole kidney data for renal blood flow and GFR, it was possible to obtain estimates of the afferent and efferent resistance changes that occurred in response to CEI. It should be emphasized that afferent resistance under the experimental conditions of this study was already at reduced levels as a consequence of autoregulatory adjustments in response to reduced arterial pressure\textsuperscript{22, 92} and should, therefore, be considered a physiologically minimal value. In spite of this, it seemed that CEI reduced preglomerular resistance even more. Although the results suggest that efferent arteriolar resistance was also reduced by CEI, the significant finding of this study is that reduc-
tion in the resistances of both pre- and postglomerular vascular elements occurred and no evidence was obtained to support the contention that blockade of the renin-angiotensin system results in a preferential reduction of efferent arteriolar resistance.

In spite of the increased RBF, GFR was not altered. In accord with the GFR of the total nephron population, SNGFR was also maintained relatively constant during the administration of CEI. Since the measured values for the various forces that are used to calculate the effective filtration pressure and \( K_f \) were also not altered, it is not surprising that \( K_f \) was not influenced significantly by CEI. However, these results should not be construed to indicate that angiotensin does not have an effect on glomerular and renal hemodynamics.15, 19, 23, 34 Recent micropuncture studies18 have demonstrated that the exogenous administration of pharmacological doses of angiotensin II may lead to a reduction in \( K_f \). Presumably, those levels existing in the normal dog preparation are not sufficiently high to exert an influence on \( K_f \), and thus an inhibition of the formation of angiotensin II does not lead to alteration in \( K_f \). Alternatively, the elevated levels of renin and angiotensin I known to occur during CEI12, 14, 18, 52 might be responsible for the maintenance of \( K_f \); however, there is no evidence at the present time to evaluate this possibility further.

Although it is difficult to obtain true direct measurements of afferent and efferent arteriolar resistance for the total nephron population, the present technique offers an alternative to less direct means that require additional assumptions regarding the changes in proximal tubule pressure, peritubular capillary pressure and glomerular pressure. In the present study these variables were measured, and, since there was close agreement between the GFR responses at whole kidney and single nephron levels, it is reasonable to assume that superficial nephron function reflected that of the total nephron population. In particular, it should be recognized that GFR remained unaltered during CEI and that the decrease in filtration fraction was due to the elevations in RBF. In some previous whole kidney studies, such changes have been interpreted to signify a preferential decrease in efferent arteriolar resistance. The reasons for the differences in interpretation of the results are not completely apparent. The indirect techniques4, 13 utilize the same basic hemodynamic equations as in the present study. However, glomerular pressure and peritubular capillary pressure are generally estimated indirectly or simply assumed on the basis of other studies. Average peritubular capillary pressure can be approached from intrarenal venous pressure measurements22, 36 when this variable is measured. Glomerular pressure is often estimated from whole kidney GFR measurements, assumed \( K_f \) and proximal tubule pressure values, and estimated average glomerular colloid osmotic pressures.9 This approach, even applied to the present data, would lead to the impression that CEI exerted a predominant effect on postglomerular rather than preglomerular resistance. Thus, it would seem that the less direct methods for calculating glomerular pressure should be applied with caution and the conclusions based on such calculations should be reserved.

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