Renal and Systemic Effects of Enalapril in Chronic One-Kidney Hypertension

ROBYN L. WOODS, WARWICK P. ANDERSON, AND PAUL I. KORNER

SUMMARY We have investigated the role of angiotensin II in the development of high blood pressure and in the maintenance of renal function during 2 weeks of one-kidney renal artery stenosis in conscious dogs. Responses to a fixed degree of inflation of a balloon cuff around the renal artery were compared in dogs with or without continuous enalapril (MK 421) treatment. In six untreated dogs, mean aortic pressure was increased by 17.1 ± 2.0 mm Hg, due primarily to increases in total peripheral resistance with little change in cardiac output, while glomerular filtration rate, renal blood flow, renal artery pressure, and plasma renin activity were back to prestenosis levels. In seven enalapril-treated dogs mean aortic pressure was increased by 23.0 ± 2.7 mm Hg and was not significantly different from that occurring in untreated dogs. This rise was due to increases in total peripheral resistance (10%) and cardiac output (12%). In the absence of angiotensin II, glomerular filtration rate remained low, at only 56 ± 6% of prestenosis levels. Renal blood flow returned to normal, but the renal artery pressure remained 25% lower than control values. Thus, the main role of angiotensin II in chronic one-kidney Goldblatt hypertension does not appear to be through its pressor properties but rather through its actions in the kidney to preserve glomerular filtration. This effect on renal function persisted throughout the course of the hypertension, even when the plasma renin levels returned to normal. (Hypertension 8: 109–116, 1986)

KEY WORDS renal blood flow • glomerular filtration rate • renin • vasopressin

ONE-KIDNEY Goldblatt hypertension is said to be renin-dependent initially and renin-independent in the chronic phase.1,2 This concept has arisen from measurements of plasma renin and angiotensin II (ANG II) levels in plasma and from observations of the acute depressor responses to ANG II blockade. Recent studies from our laboratory during the initial “renin-dependent” phase have shown that the rise in blood pressure in dogs is only partially renin-dependent.3,4 In these studies, arterial pressure rose after renal artery stenosis even when ANG II formation was blocked, but the rise in pressure was only half as great as in dogs without blockade and was due to increased cardiac output rather than to increased peripheral resistance. The glomerular filtration rate, however, was markedly renin-dependent: it was only about 15% of normal during the first two days of stenosis in ANG II-blocked dogs, compared with 50% in untreated dogs subjected to the same degree of renal artery stenosis.4

The present study was undertaken to determine whether this dependency of glomerular filtration extends into the chronic phase, when circulating ANG II levels have returned to normal. We also investigated whether blood pressure continues to rise into this phase in ANG II–blocked dogs and whether it is due to increased cardiac output or to increased peripheral resistance. Thus, we assessed whether ANG II is essential for the development of high arterial pressure and for the maintenance of renal function following renal artery stenosis.

Materials and Methods

The experiments were performed on trained, conscious male mongrel dogs (age, 1–3 years; weight, 20–30 kg) that had a fixed dietary intake resulting in average daily urinary excretions of 65 mmol of sodium and 70 mmol of potassium.

Surgical Preparation

Details of the surgical preparations of the dogs have been published previously.3,5 With the dogs under halothane and nitrous oxide anesthesia, a Doppler ultra-

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sonic flow transducer and an inflatable, saline-filled Silastic cuff (Hazen Everett, NJ, USA) were placed around the left renal artery. A catheter was inserted through the renal artery wall with its tip distal to the cuff. Catheters also were placed in the aorta, vena cava, and right atrium, and a thermistor was placed in the aorta. The right kidney was removed. All flow-meter wires and catheters were exteriorized on the dog's back and protected by a canvas jacket. Pethidine (50 mg i.m.) was given postoperatively for 1 day, and cefoxitin (250 mg, twice daily, p.o.) was given for 5 days postoperatively. At least 2 weeks was allowed between the preparative operation and the first experimental measurements.

Protocol
During each measurement period the dog lay recumbent in a quiet laboratory for 2 to 3 hours while hemodynamic measurements were made and blood samples taken. For 2 days prior to this, the dogs were housed in metabolic cages for the collection of urine. Water was allowed ad libitum, and the volume was measured daily.

The experiments consisted of 2 days of control observations (C1 and C2, performed 2–3 days apart) followed by 2 weeks of renal artery stenosis. During renal artery stenosis, hemodynamic and other measurements were made on Days 7 and 14 while metabolic studies were performed between Days 5 through 7 and 12 through 14. Renal artery stenosis was induced by inflating the balloon cuff around the renal artery at the end of the second day of control observations. The balloon was rapidly inflated with saline to totally occlude the vessel, the volume was measured, and the balloon was then deflated to 80% of total occlusion volume. Six hours later, a further 7% of initial total occlusion volume was added and the exteriorized catheter attached to the cuff was clamped to maintain this 87% occlusion for the next 2 weeks. At the end of the 14-day study, the cuff was deflated and measurement of the recovered volume of saline verified that there had been no significant losses during stenosis.

A total of 17 dogs were studied according to this protocol. In 8 of these dogs enalapril (2–3 mg/kg/day p.o.) was administered continuously from 3 days before the first control period until release of the balloon. The effectiveness of the blockade of ANG II formation by enalapril in these dogs was checked by measuring the pressor responses to exogenous angiotensin I before and 3 days after starting the enalapril treatment. A 10-fold shift in the dose-response curve to angiotensin I after enalapril administration was considered effective blockade.

Cardiovascular Measurements
Phasic and mean aortic and renal artery pressures (Statham P23Dc transducer, Oxnard, CA, USA) and phasic and mean blood flows were recorded on a Devices (Welwyn Garden City, England) recorder. Renal blood flow was measured by the continuous Doppler ultrasonic method. \(^3\)–\(^5\), \(^7\)–\(^8\) The Doppler shift (kHz) and volume flow (ml/min) are linearly related over a wide range of pressures and flows \(^4\) and have a conversion factor to absolute flow of 84 (±4) ml/min per kHz of Doppler shift. \(^4\) Cardiac output was measured by thermodilution. \(^9\)

Renal Measurements
Glomerular filtration rate (GFR) was derived from the total endogenous creatinine clearance for each 48-hour urine collection period, with plasma for creatinine determinations collected at the end of this period. Creatinine clearance has been shown to be identical with inulin clearance under a variety of conditions in the dog. \(^10\) Water intake, urine output, and excretion rates of Na\(^+\) and K\(^+\) were calculated.

Biochemical Measurements
Blood was collected into 2,3 dimercaptopropanol-ethylenediaminetetraacetic acid (1:10 vol/vol) for determination of plasma renin activity by radioimmunoassay measurement of enzymatically generated angiotensin I. \(^11\) Plasma vasopressin was measured by radioimmunoassay \(^12\) on duplicate 1-ml plasma samples after acetone-petroleum ether extraction. Plasma creatinine was measured using a modification of the method of Brod and Sirotta. \(^13\) Urinary and plasma Na\(^+\) and K\(^+\) concentrations were measured using a Corning 430 flame photometer (Corning, NY, USA). Evans' blue (5 mg i.v.) was used to measure plasma volume.

Calculations and Statistical Analysis
Resistance to blood flow was calculated as pressure/flow; total peripheral resistance = (mean aortic pressure – central venous pressure)/cardiac output; total renal resistance = (mean aortic pressure – central venous pressure/renal blood flow); renal vascular resistance = distal renal artery pressure/renal blood flow.

The statistical significance of the responses to renal artery stenosis was tested by analysis of variance. The effect of 2 weeks of renal artery stenosis was determined by comparing the average difference between measurements at Weeks 1 and 2 with the average of the control values. Results are expressed as the mean or the difference between the means ± standard error of the mean (SEM).

The effect of enalapril on the responses to stenosis was determined by comparing the analyses of variance from each group (i.e., with and without enalapril) and calculating the t statistic as (mean difference between groups)/(standard error of the difference between groups).

Results
Three of the nine dogs that did not receive enalapril treatment (untreated) developed malignant hypertension and were excluded from all analyses. These three dogs showed a rapid decline in physical condition that was associated with a rapid rise in mean arterial pressure to values in excess of 150 mm Hg, vomiting and
diarrhea, blood in urine and feces, weight loss, and very high levels of plasma renin activity in two of the three dogs. Benign Goldblatt hypertension developed in the remaining six untreated dogs and was associated with good physical condition and a return of plasma renin levels to normal within 1 to 2 weeks after renal artery stenosis. One of the eight enalapril-treated dogs was excluded from the study because the balloon cuff burst during the second week of stenosis. Since there were no significant differences between any of the variables measured on the two control days, all results from Days C1 and C2 have been pooled to a single average control value.

**Systemic Hemodynamics**

Individual and mean values for mean arterial pressure, cardiac output, and total peripheral resistance are shown in Figure 1. Average mean arterial pressure in untreated dogs with benign hypertension rose by 17.1 ± 2.0 mm Hg (p < 0.01) during the 2 weeks after renal artery stenosis. The responses of cardiac output and total peripheral resistance were somewhat variable particularly during Week 1, but by the second week, cardiac output was normal in all dogs except one and total peripheral resistance was elevated in four of the six dogs.

In the enalapril-treated dogs mean arterial pressure rose by an average of 23.0 ± 2.7 mm Hg (p < 0.01); this increase was not significantly different from that in untreated dogs. Both cardiac output and total peripheral resistance were elevated significantly during the 2 weeks after renal artery stenosis (11.6% and 10.1% respectively; p < 0.05), although the individual responses were varied. One dog was solely dependent on a rise in total peripheral resistance for the blood pressure elevation, as his cardiac output fell by 40%; three other dogs had no changes in total peripheral resistance but large increases in cardiac output. Total peripheral resistance and cardiac output increased in the remaining dogs. There were no significant changes in heart rate or central venous pressure in either enalapril-treated or untreated dogs during the 2 weeks of stenosis.

**Renal Hemodynamics**

In the untreated dogs, distal renal artery pressure, renal blood flow, and renal vascular resistance had recovered to prestenosis levels within 1 to 2 weeks after renal artery stenosis (Table 1). Before stenosis, renal vascular resistance was significantly lower and renal blood flow significantly higher (p < 0.01) in enalapril-treated dogs (see Table 1). After stenosis in these blocked dogs, renal artery pressure remained below prestenosis levels and averaged almost 30 mm Hg less than that in untreated dogs. This reduction in distal renal artery pressure was not accompanied by a fall in renal blood flow, because renal vascular resistance values remained lower than those recorded before stenosis (p < 0.05; see Table 1). Total renal resistance was significantly elevated in both groups of dogs throughout the 2 weeks of renal artery narrowing.

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

**Figure 1.** Changes from prestenosis control (C) values of mean arterial pressure, cardiac output, and total peripheral resistance 7 and 14 days after renal artery stenosis in individual dogs (thin lines) either untreated or treated continuously with enalapril, 2 to 3 mg/kg/day. Mean change from control for each group is represented by the thick line. The dotted horizontal lines represent the mean prestenosis (C) levels; the absolute values are given in parentheses; n.s. = not significant.
TABLE 1. Plasma Renin Activity, Renal Hemodynamics, and Plasma Vasopressin Levels During Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Group</th>
<th>Plasma renin activity (ng ANG I/ml/hr)</th>
<th>Renal artery pressure (mm Hg)</th>
<th>Renal blood flow (kHz)</th>
<th>Renal vascular resistance (mm Hg/ml min⁻¹)</th>
<th>Total renal resistance (mm Hg/ml min⁻¹)</th>
<th>Plasma vasopressin (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated dogs (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C1</td>
<td>0.55</td>
<td>93.3</td>
<td>2.67</td>
<td>0.43</td>
<td>0.45</td>
<td>4.1</td>
</tr>
<tr>
<td>C2</td>
<td>0.54</td>
<td>93.6</td>
<td>3.11</td>
<td>0.38</td>
<td>0.41</td>
<td>4.1</td>
</tr>
<tr>
<td>W1</td>
<td>0.88</td>
<td>83.5</td>
<td>2.72</td>
<td>0.40</td>
<td>0.59</td>
<td>4.1</td>
</tr>
<tr>
<td>W2</td>
<td>0.53</td>
<td>94.3</td>
<td>2.91</td>
<td>0.41</td>
<td>0.50</td>
<td>4.0</td>
</tr>
<tr>
<td>SEM</td>
<td>±0.27</td>
<td>±4.3</td>
<td>±0.23</td>
<td>±0.04</td>
<td>±0.05</td>
<td>±0.1</td>
</tr>
<tr>
<td>Enalapril-treated dogs (n = 7)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>2.62</td>
<td>80.6</td>
<td>3.48</td>
<td>0.30</td>
<td>0.31</td>
<td>3.5</td>
</tr>
<tr>
<td>C2</td>
<td>3.62</td>
<td>82.0</td>
<td>4.11</td>
<td>0.25</td>
<td>0.28</td>
<td>3.6</td>
</tr>
<tr>
<td>W1</td>
<td>7.06</td>
<td>50.3</td>
<td>3.85</td>
<td>0.15</td>
<td>0.35</td>
<td>4.4</td>
</tr>
<tr>
<td>W2</td>
<td>5.49</td>
<td>71.3</td>
<td>3.50</td>
<td>0.265</td>
<td>0.39</td>
<td>5.7</td>
</tr>
<tr>
<td>SEM</td>
<td>±0.98</td>
<td>±5.4</td>
<td>±0.24</td>
<td>±0.03</td>
<td>±0.03</td>
<td>±0.7</td>
</tr>
</tbody>
</table>

ANG I = angiotensin I; C1, C2 = individual control days; W1, W2 = Weeks 1 and 2 after stenosis; SEM refers to orthogonal comparison of W1 and W2 values with C1 and C2 values.

*p < 0.05, †p < 0.01, orthogonal comparison of W1 and W2 values with C1 and C2 values.

The difference between total renal resistance and renal vascular resistance corresponds to the resistance of the renal artery stenosis itself and was very similar in the two groups (0.19 ± 0.06 and 0.09 ± 0.03 mm Hg/ml min⁻¹ at Weeks 1 and 2, respectively, in untreated dogs; 0.20 ± 0.04 and 0.13 ± 0.04 mm Hg/ml min⁻¹, respectively, in enalapril-treated dogs).

Glomerular Filtration Rate

In dogs not receiving enalapril, the GFR was slightly but not significantly reduced at Week 1 and had recovered to prestenosis levels by Week 2 (Figure 2). In enalapril-treated dogs, the GFR was markedly reduced throughout the 2 weeks of renal artery stenosis, by an average of 44.2% (p < 0.01; Figure 2). Plasma creatinine concentrations mirrored the changes in GFR and were significantly correlated with creatinine clearance (p < 0.001) such that creatinine clearance and the reciprocal of plasma creatinine concentration had a regression line of y = 8.37 + 40.52x with a correlation coefficient of r = 0.772 (n = 39). Mean plasma creatinine levels were significantly elevated at Weeks 1 and 2 only in the enalapril-treated dogs (see Figure 2).

Fluid and Electrolyte Balance

The responses in fluid and electrolyte balance to renal artery stenosis varied somewhat in both groups of dogs. As a whole, the untreated group showed no significant changes in water intake, urine output, or urinary Na⁺ excretion, while the enalapril-treated dogs had significant increases in water intake and urine out-

FIGURE 2. Changes from prestenosis control (C) values of glomerular filtration rate 7 and 14 days after renal artery stenosis in individual dogs (thin lines) either untreated (NO DRUG) or treated with enalapril. The thick lines represent the mean change from control; the dotted horizontal lines represent the mean prestenosis (C) levels: the absolute values are given in parentheses. Mean plasma creatinine levels during control period and 1 and 2 weeks after stenosis are given in parentheses. Significance levels are from comparison of stenosis versus control: n.s. = not significant.
put with no change in Na⁺ excretion (Table 2). Urinary K⁺ excretion was unchanged in both groups of dogs. Plasma volume and hematocrit were not significantly altered by renal artery stenosis in the untreated dogs. Plasma volume was also unchanged in enalapril-treated animals, but there was a significant fall in hematocrit (34.1% to 30.6 ± 1.4%; p < 0.05). Plasma Na⁺ and K⁺ concentrations did not change significantly in either group of dogs (see Table 2).

### Plasma Renin Activity and Plasma Vasopressin Concentration

In untreated dogs, plasma renin activity and plasma vasopressin concentrations were not significantly different from prestenosis levels after either 1 or 2 weeks of renal artery stenosis (see Table 1). In enalapril-treated dogs, inhibition of angiotensin converting enzyme resulted in a substantial rise in resting plasma renin activity levels when compared with that in unblocked dogs (p < 0.01), and the levels continued to rise after renal artery stenosis (see Table 1). Plasma vasopressin levels were modestly but significantly elevated after renal artery stenosis in the enalapril-treated dogs (see Table 1). One dog in particular showed a large rise in plasma vasopressin levels: an increase of 10.6 pg/ml 2 weeks after stenosis. This dog also had the large decrease in cardiac output and increase in total peripheral resistance (see Figure 1).

### Discussion

Our results indicate that ANG II does not determine the degree to which blood pressure rises in chronic benign hypertension after renal artery stenosis, because after 2 weeks, the average rise in blood pressure was similar in converting enzyme-inhibited dogs and in untreated dogs. Previous studies from our laboratory have shown that ANG II was not essential for the development of hypertension during the first 2 days of renal artery stenosis, although the absolute rise in blood pressure was less when ANG II formation was prevented. Our results therefore do not support the hypothesis that ANG II is an essential trigger factor for Goldblatt hypertension. This conclusion is in accord with other studies in dogs and in rats with renal artery clips, which have shown that neither short-term nor long-term inhibition of the renin-angiotensin system affects the degree of hypertension.

The chronic hypertension in dogs with an intact renin-angiotensin system was mainly due to an increase in total peripheral resistance, although there was some variability in the responses of both cardiac output and total peripheral resistance. The initial rise in total peripheral resistance was primarily due to increased circulating levels of ANG II, which vasocostricted the nonrenal vasculature. Later, when plasma renin levels had returned to normal, most of the rise in total peripheral resistance was likely to be due to secondary amplifying factors such as vascular hypertrophy, changes in vascular membrane properties such as suppressed Na⁺-K⁺ transport, or autonomic alterations.

The hypertension in the enalapril-treated dogs was due to increases in either cardiac output or total peripheral resistance, or to both. We have previously measured even larger increases in cardiac output (up to 50%) over the first 24 hours of renal artery stenosis in dogs with converting enzyme inhibition. The causes of these rises in output were not apparent but were not associated with changes in blood volume or central venous pressure. The rise in total peripheral resistance, which seemed to occur progressively in enalapril-treated dogs, also may have been due to the development of vascular hypertrophy secondary to the elevated blood pressure.

It is possible that increased plasma levels of vasopressin contributed to the increased total peripheral resistance in these dogs, although with one exception the increases in vasopressin were very small and under normal circumstances these levels are not pressor in conscious dogs with intact autonomic reflexes. Furthermore, in previous experiments, when plasma vasopressin was shown to be elevated in chronic one-kidney Goldblatt hypertensive rats, its effect on blood pressure was related to its antidiuretic rather than its vasoconstrictor properties. The elevated plasma vasopressin concentrations in hypertensive dogs treated with enalapril are puzzling, because the animals were normovolemic, plasma Na⁺ levels were normal, and, if anything, the inhibition of ANG II formation should have reduced rather than raised circulating levels. Renal clearance is one of the major pathways for removal of vasopressin from the circulation, and this removal is largely related to the GFR. Thus, we suggest that, in these enalapril-treated dogs with low

### Table 2. Fluid and Sodium Balance During Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Group</th>
<th>Water Intake (ml/day)</th>
<th>Urine Output (ml/day)</th>
<th>Urinary Na⁺ Excretion (mmol/day)</th>
<th>Plasma Na⁺ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated dogs (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control*</td>
<td>1089</td>
<td>975</td>
<td>68.5</td>
<td>144</td>
</tr>
<tr>
<td>W1</td>
<td>1061</td>
<td>826</td>
<td>60.0</td>
<td>147</td>
</tr>
<tr>
<td>W2</td>
<td>1131</td>
<td>972</td>
<td>66.3</td>
<td>146</td>
</tr>
<tr>
<td>SEM</td>
<td>±195</td>
<td>±98</td>
<td>±6.1</td>
<td>±3</td>
</tr>
<tr>
<td>Enalapril-treated dogs (n = 7)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control*</td>
<td>1004</td>
<td>935</td>
<td>70.3</td>
<td>143</td>
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<tr>
<td></td>
<td>†</td>
<td>†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td>1422</td>
<td>1231</td>
<td>53.3</td>
<td>142</td>
</tr>
<tr>
<td>W2</td>
<td>1584</td>
<td>1369</td>
<td>60.6</td>
<td>142</td>
</tr>
<tr>
<td>SEM</td>
<td>±162</td>
<td>±170</td>
<td>±8.1</td>
<td>±2</td>
</tr>
</tbody>
</table>

See Table 1 for key to abbreviations.

*Metabolic collection averaged over 2 days between Days C1 and C2.

†p < 0.01, ‡p < 0.05, orthogonal comparison of W1 and W2 values with C1 and C2 values.
GFR, reduced renal clearance of vasopressin resulted in elevated plasma levels.

Although ANG II blockade did not affect the level of blood pressure achieved after 2 weeks of renal artery stenosis, GFR remained low in enalapril-treated dogs, averaging only about half the filtration rate measured before stenosis. In untreated dogs GFR recovered to prestenosis values within 2 weeks. Thus, ANG II was responsible for the recovery of GFR in the latter group of dogs, most likely through intrarenal actions because circulating levels in plasma had returned to normal by this time. The main action of this intrarenal ANG II is presumably efferent arteriolar vasoconstriction, but it may also have an effect on some nonvascular component affecting GFR (e.g., ultrafiltration coefficient).

We have previously shown that in both untreated and enalapril-treated dogs, water and Na+ excretions fell immediately after renal artery stenosis but returned toward normal levels within 48 hours. The return to normal Na+ excretion in enalapril-treated dogs was surprising in view of their markedly reduced GFR. Similarly, in the present study of chronic renal artery stenosis, Na+ excretion was normal in enalapril-treated animals, even though the GFR was reduced by 44%. Presumably, the absence of ANG II lowered Na+ reabsorption, which, when combined with the lower GFR, resulted in normal Na+ excretion.

Water turnover was normal in the untreated dogs after 2 weeks of renal artery stenosis, but urine flow and water intake were significantly increased in enalapril-treated dogs. Other workers have demonstrated that converting enzyme inhibition causes a diuresis that is independent of the level of circulating vasopressin. The proposed mechanism for this action is that converting enzyme inhibitors increase free water clearance by preventing antidiuretic and antinatriuretic effects of ANG II on renal tubules. Kinin-induced water loss also may contribute to this action when normal breakdown of bradykinin is prevented. Although the mechanisms responsible for the increased water turnover are not certain, this effect of enalapril appears to overwhelm any effects of the increased plasma vasopressin levels.

Converting enzyme inhibitors also inhibit the degradation of kinins and thus may raise circulating and intrarenal kinin levels. An interpretation of our results could therefore include the effects of enalapril on kinins as well as on ANG II. On the other hand, other workers have shown that quantitatively similar cardiovascular and renal responses are elicited by the ANG II receptor antagonist saralasin and the converting enzyme inhibitor captopril, including in renal artery stenosis. This finding suggests that the effects of enalapril in the present study are predominantly due to blockade of ANG II formation.

In studies of this type, all animals must be subjected to the same degree of narrowing of the renal artery. This may not necessarily be achieved if changes in distal pressure or in renal blood flow are used as the criteria for vessel narrowing. Earlier experiments from our laboratory have shown that the tone of the distal renal vasculature greatly alters the relationship between the degree of artery narrowing and the reduction in distal pressure or flow. For example, these experiments showed that a more severe stenosis was needed to reduce distal pressure to a given level when the renal vasculature was vasoconstricted than when it was vasodilated. Hence, the degree of renal artery stenosis is unlikely to be the same in animals with and without ANG II inhibition because the latter alters renal vascular tone.

Differences in narrowing will be further exaggerated if the severity of the stenosis is adjusted over time to achieve a given reduction in distal pressure, because ANG II actively affects renal vascular resistance over the first hours and days of stenosis. We circumvented these problems by inflating the cuff around the renal artery to a fixed percentage of the volume needed to totally occlude the artery. Confirmation of the degree of inflation, by measuring the volume of saline recovered when the cuff was deflated, ensured that all dogs received the same severity of renal artery narrowing.

Arterial stenoses are now known to exhibit complex hydraulic behavior. This behavior has been studied most extensively in coronary stenoses. Of relevance to the present study, a fixed degree of narrowing of an artery does not exert a fixed effective resistance to blood flow. Instead, the effective resistance to blood flow varies with changes in upstream (aortic) pressure and with the downstream vascular resistance. Furthermore, it has recently been proposed that part of the renal circulation acts as a Starling resistor and that changes in external compressive forces may alter the relationship between pressure and flow. All these factors complicate the interpretation of the renal blood flow responses to stenosis.

Nevertheless, the renal vasculature clearly remained vasodilated after stenosis when ANG II formation was blocked and was reflected in lower distal renal artery pressure, whereas it returned to prestenosis values in untreated dogs. This restoration of renal vascular resistance and of GFR following stenosis suggests that the vasoconstrictive effect of ANG II was postglomerular.

It should be noted that Dzau et al. and Ayers et al. have reported that short-term blockade of the renin-angiotensin system in chronic hypertension does not reduce renal vascular resistance. The reasons for the difference between the results of short-term versus long-term converting enzyme inhibition are not clear, although the activation of baroreflexes may complicate analysis of short-term changes (e.g., see Reference 18). Furthermore, the methods used to narrow the renal artery differed in the two experiments. In our experiments, the renal artery was narrowed in two steps on the first day, whereas Dzau et al. frequently adjusted the cuff to maintain distal pressure below control levels. Similar to our findings, Ferrario and McCubbin reported that mean renal blood flow was not reduced in chronic hypertension following a single narrowing of the renal artery.

A second important observation regarding the stenosis is that the effective resistance to blood flow that it
exerted was substantial and increased the kidney’s total resistance to blood flow by about 30%. The kidney received approximately 20% of the cardiac output in our dogs, which represents a significant proportion of the increase in peripheral resistance in both untreated and enalapril-treated dogs.

Our experimental findings support recent clinical studies with converting enzyme inhibitors in patients with renovascular hypertension. In these studies, short-term and long-term treatment with captopril or enalapril was associated with a marked decline in renal function.

Finally, we should comment on the occurrence of malignant hypertension in this study. Malignant hypertension developed in three of the nine untreated dogs subjected to renal artery stenosis. This development was characterized by rapidly increasing blood pressure, large fluid and electrolyte disturbances, and a progressive decline in physical condition. In contrast, none of the seven dogs receiving enalapril showed signs of malignant hypertension, which may implicate ANG II in the pathogenesis of this condition.

In summary, our results indicate that ANG II is not essential for the development and maintenance of chronic one-kidney Goldblatt hypertension in dogs. However, this hormone is important for the maintenance of GFR in both the chronic and acute phases following renal artery constriction. Since plasma renin levels are normal in the chronic benign phase, intrarenal ANG II is probably responsible for maintaining GFR at normal levels.

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