Development of Hypertension From Unilateral Renal Artery Stenosis in Conscious Dogs

Warwick P. Anderson, Debra E. Ramsey, and Masanobu Takata

The renal and systemic changes after stenosis of the left renal artery (n=5) or sham stenosis (n=6) in conscious dogs were studied sequentially over 25 days. Stenosis produced a prompt rise in arterial pressure, which was at all times due to reduced peripheral vascular conductance, with no increase in cardiac output despite initial evidence of mild fluid retention. The decrease in peripheral conductance was attributable to 1) the stenotic kidney (25% of the total and due to the mechanical effect of the stenosis itself), 2) the nonstenotic kidney (about 15% of the total and not caused by angiotensin II), and 3) the nonrenal vasculature (60%). The decrease in conductance in the nonrenal vasculature was due partly to angiotensin II, but there was also a gradually developing non-angiotensin II component. Acute administration of captopril caused significantly greater changes in arterial pressure and peripheral conductance throughout the period of stenosis than before stenosis (and greater than in sham-stenosis dogs), indicating that angiotensin II was constricting the peripheral vasculature even when plasma renin levels were no longer elevated. In the stenotic kidneys, captopril produced a fall in renal vascular resistance, but renal blood flow did not rise because there was an approximately equal rise in the resistance of the stenosis. There was no evidence for a role for the autonomic nervous system in the hypertension, as ganglion blockade (pentolinium) had similar hemodynamic effects before and after stenosis. Thus, the hypertension was due at all times to reduced peripheral conductance, with the two kidneys responsible for 40% of this reduced conductance. (Hypertension 1990;16:441-451)

Unilateral renal artery stenosis produces hypertension in humans and in experimental animals, including rats (see Reference 1), sheep,7 and dogs,2-5 provided that the stenosis is severe enough.4 Evidence from previous experiments suggests that both the renin-angiotensin system and the autonomic nervous system are involved in the development of this two-kidney, one clip (2K 1C) form of hypertension.1,3,6-8 However, gaining a complete understanding of the early stages of the hypertension has been complicated by the fact that stenosis has, with very few exceptions, been induced during surgery in anesthetized animals. Surgery itself disturbs the renin-angiotensin system, autonomic reflexes, and body fluid homeostasis,9 the very factors thought to be involved in the initiation and development of hypertension.

We recently published a comprehensive analysis of the hemodynamic events involved in the first hour of this form of renal hypertension in conscious dogs.10 This showed that the initial rise in arterial pressure was due entirely to decreased peripheral vascular conductance (increased resistance) and, remarkably, that the kidneys themselves were responsible for almost half of this fall in conductance. In the case of the stenotic kidney, its conductance was reduced by the mechanical effect of the stenosis, whereas the conductance of the contralateral nonstenotic kidney was reduced by angiotensin II (Ang II).

We have now extended this comprehensive analysis over a 25-day period. The systemic and both stenotic and nonstenotic renal hemodynamic responses to stenosis have been measured, the contributions of the renal responses to the hypertension have again been calculated, and the responses to acute pharmacological blockade of both Ang II formation (captopril) and neural transmission in autonomic ganglia (pentolinium) have been measured. The aim was to determine whether decreased renal conductances were responsible for a substantial portion of established hypertension, as they were during the first hour, and whether the renin-angiotensin or autonomic nervous systems were involved. The study was conducted entirely in conscious dogs (including during the induction of stenosis), and a separate sham-stenosis group was studied in an identical manner.
Methods

Preparation of Dogs

Greyhound dogs (30–38 kg body weight) were prepared as previously described. In brief, they were acclimatized to the laboratory and holding area over a 4–6-week period and trained to lie quietly on their right sides on a low padded table. The dogs underwent preparative surgery under halothane and nitrous oxide anesthesia, after induction with xylazine (Rompun, Bayer, Sydney, Australia) and ketamine (Ketalar, Parke-Davis, Sydney, Australia), or with propofol (Diprivan, ICI, Melbourne, Australia). Two catheters (1.5 mm o.d.) were placed in the aorta via a left flank retroperitoneal incision, and three catheters were inserted into the thoracic vena cava via the thoracolumbar vein. One of these catheters was advanced until its tip lay in the right atrium. Another catheter (0.96 mm o.d.) was placed in the distal renal artery. An inflatable cuff was placed around the renal artery and a Doppler flowprobe also placed around this artery, either upstream or downstream from the cuff. A thermodilution thermistor was placed in the aorta via the thoracolumbar artery. A Doppler flowprobe was also placed around the right renal artery via a right flank retroperitoneal incision. Each dog was given morphine (50 mg) at 4-hour intervals as required over the first 24 postoperative hours and amoxicillin trihydrate (500 mg/8 hr; Commonwealth Serum Laboratories [CSL], Melbourne, Australia) or sodium flucloxacillin (500 mg/8 hr; CSL) for 7 days. The dogs were allowed 3 weeks recovery from this surgery before the commencement of experiments. During this time, they were given a set amount of food each day, which gave them a resting daily Na+ excretion rate of about 70 mM/day.

Experimental Design

Two groups were studied: a stenosis group that was subjected to narrowing of the left renal artery and a sham-stenosis group that was studied and treated in an identical fashion to the stenosis group except that the left renal artery was not narrowed. Prestenosis measurements were made on three separate days at least 48 hours apart. One or two days later, the renal artery stenosis was established (or sham procedure performed). Further measurements were then made 1, 3, 7, and 14 days after stenosis (or sham) and on days 21, 23, and 25. The dogs were then killed by overdose of pentobarbitone.

Immediately before the establishment of the stenosis, and again 19 days after the stenosis, renal blood flow and glomerular filtration rate of the two kidneys were estimated in each dog by p-aminohippurate (PAH) and [3H]inulin clearance, respectively, over a 60–90-minute period. PAH was given as a 75 mg bolus followed by an intravenous infusion at 3.2 mg/min, and [3H]inulin was given as a 10 μCi bolus followed by an infusion of 0.3 μCi/min with 75 minutes allowed for equilibration. The PAH and [3H]inulin were both delivered in normal saline at 0.64 ml/min. Urine was collected via a canine bladder catheter inserted before the administration of PAH and [3H]inulin.

Method of Stenosis of Renal Artery

The cuff around the renal artery was inflated in a series of steps over 90 minutes. In the first step, the cuff was inflated to lower distal renal artery pressure to 60 mm Hg. After 30 minutes, the cuff was further inflated to lower distal pressure to 40 mm Hg and 30 minutes later to 20 mm Hg. Distal pressure was again lowered to 20 mm Hg after a further 30 minutes, and the cuff tubing was firmly clamped. One day later (after measurements had been made that day), the cuff was further inflated to reduce renal blood flow by an amount equivalent to 20% of the value measured previously on that day.

Measurements

Resting values. On each measurement day, the dogs lay on their sides throughout a 3½-hour protocol. After a 45-minute setting up period, continuous measurements of aortic pressure, renal artery pressure, heart rate, left and right renal blood flows, and central venous pressure were made over four consecutive 30-minute periods. The pressure transducers were balanced and the flowmeters tuned between each 30-minute measurement period. At the midpoint of each measurement period, cardiac output was measured two or three times by thermodilution.

After the fourth 30-minute measurement period, the dogs were given captopril or pentololinium or saline vehicle; 15 minutes were allowed for equilibration and then followed by a fifth 30-minute measurement period.

Aortic, renal artery, and central venous pressures were measured by connecting appropriate catheters to Gould P23iD transducers (Gould-Statham, Oxnard, Calif.). The Doppler flowmeters were used to measure left and right renal blood flows, and cardiac output was measured by thermodilution as described previously. All pressure and flow signals were displayed on a Neotrace recorder (Neomedix, Sydney, Australia) and monitored on line by computer. Plasma volume was measured (Evans blue, 5 mg) and arterial blood samples taken for later radioimmunoassay of plasma renin activity, vasopressin, and atrial natriuretic peptide (see References 11 and 12).

Vascular conductances, not resistances, were calculated in this study for arithmetic simplicity, as mainly changes in vascular beds in parallel have been compared. An exception is that resistances have been used for the series resistors of the left renal artery stenosis and the distal renal vascular bed.

Total peripheral conductance was calculated as cardiac output/(mean arterial pressure [MAP]–central venous pressure [CVP]) and renal conductances as left or right renal blood flow/(MAP–CVP). Total resistance of the stenotic kidney was calculated as (MAP–CVP)/renal blood flow.
Doppler flowmeter). The vascular resistance of the stenosis on the left renal artery was calculated as (MAP - distal renal artery pressure)/renal blood flow (Doppler), and the resistance of the renal vascular bed distal to the stenosis was calculated as (distal renal artery pressure - CVP)/renal blood flow (Doppler).

The combined conductance of the two kidneys was also calculated [PAH clearance rate/(MAP - CVP)] using the PAH clearance measurements made before and after stenosis. To calculate the contribution of the two kidneys to the change in total peripheral conductance, the difference in the combined renal conductances before and after stenosis was expressed as a percentage of the difference in total peripheral conductance (i.e., difference between the average of the three prestenosis days and the average of poststenosis days 21, 23, and 25).

Captopril (E.R. Squibb & Sons, Princeton, N.J.) was given as a 1.0 mg/kg bolus and a 0.5 mg/kg/hr infusion. Pentolinium (Sigma Chemical Co., St. Louis, Mo.) was given as a 6 mg/kg bolus and 3 mg/kg/hr infusion. Captopril, pentolinium, or saline were given in random order after the fourth measurement period on one of the 3 days before stenosis and again on day 21, 23, or 25 after stenosis. Captopril was also given on days 1, 7, and 14 after stenosis.

Analysis of Results

A single mean value for each variable was calculated from the four measurement periods (i.e., before captopril, pentolinium, or vehicle) for each day, and that mean value was entered into a two-way analysis of variance table. Orthogonal comparisons of the "between day" data were established, particularly the comparison of the values on the 3 days before stenosis with days 21, 23, and 25 after stenosis. When required, the significance of changes from prestenosis values on particular individual poststenotic days was calculated as a t value, using the mean difference from prestenosis values (averaged for all three prestenosis days) and the standard error of the difference.

The effects of captopril, pentolinium, or vehicle treatment were each calculated as the mean difference between the fourth 30-minute resting measurement period immediately before drug treatment and the fifth 30-minute measurement period. For captopril, the differences on the various days were entered into a two-way analysis of variance table with orthogonal comparisons established to allow comparison of the average effect of captopril over all the poststenosis days with the prestenosis effect, and the effect on day 1 with the effect on one of days 21-25. The main comparison for the effects of captopril, pentolinium, and vehicle was made by entering the changes due to these treatments in each dog on the days before stenosis and on days 21, 23, or 25 into a single two-way analysis of variance table.

For all analysis of variance comparisons, the effects in the stenosis and sham-stenosis groups were compared by calculating a t value, where t is the mean difference of the particular orthogonal comparison in the stenosis group minus equivalent mean difference in the sham group divided by the square root of the sum of the squared standard errors of each of those differences.

Results

Responses to Left Renal Artery Stenosis

Mean arterial pressure rose after stenosis of the left renal artery from an average of 104.2 ± 2.6 mm Hg (mean ± SEM) over the three prestenosis days to an average of 117.4 ± 3.8 mm Hg at 21-25 days after stenosis (average rise 13.2 ± 3.1 mm Hg, p < 0.01) (Figure 1). All dogs became hypertensive. The rise in blood pressure was prompt and pressure remained relatively stable throughout the 25 days of stenosis. In the sham-stenosis group, there was a small fall in mean arterial pressure over the corresponding period (−5.8 ± 1.9 mm Hg, p < 0.01) (Figure 1).
Cardiac output (Figure 1) fell by about 15% over the first 3 days after stenosis (e.g., −16.4±3.8% on day 3). Thereafter cardiac output was not significantly different from prestenosis values; it was −10.5±6.6% from average prestenosis on days 21–25 in the stenosis group (NS).

The rise in arterial pressure was therefore due to decreased total peripheral conductance (Figure 1), which fell immediately after stenosis (e.g., −18±6% on day 1, p<0.01). In the sham-stenosis group, total peripheral conductance did not change significantly (+1.3±13.5%, NS from pre- to sham-stenosis values on days 21–25).

Blood flow to the stenotic (left) kidney was significantly reduced throughout the stenosis: 32±10% and 20±7% below prestenosis values on day 1 and days 21–25, respectively (p<0.01) (Figure 2). Renal artery pressure beyond the stenosis was reduced to 20 mm Hg on establishment of the stenosis. It rose over the next 3 days but then remained at 65–80 mm Hg, significantly below prestenosis values (p<0.01) and 40–60 mm Hg below pressure in the aorta (Figure 2). The total vascular resistance of this kidney rose markedly after stenosis (Figure 2) and was about 50% greater than before stenosis throughout (e.g., on days 21–25 it averaged 47±12% above prestenosis values, p<0.01). Vascular resistance of the stenotic kidney has two components, the stenosis and the distal renal vasculature itself. The renal vasculature vasodilated initially (Figure 2), but vascular resistance then returned close to prestenosis values (e.g., −2±9% on days 21–25, NS). The resistance of the stenosis thus accounted for the rise in the total resistance of the kidney (Figure 2) and was directly responsible for about one third of the vascular resistance of the entire kidney.

Blood flow to the nonstenotic (right) kidney was reduced initially after stenosis (−18±6% on day 1, p<0.05) (Figure 2) but then gradually returned toward prestenosis values. At 21–25 days, flow was not significantly different from prestenosis values (−4.7±6%, NS). Averaged over the entire experiment, the resistance of this kidney was significantly elevated. The kidney hypertrophied during the experiment: 3.19±0.21 g/kg body wt at autopsy compared with 2.41±0.23 g/kg body wt for the left kidney. Respective values in the sham group were 2.38±0.27 g/kg and 2.35±0.24 g/kg body wt, respectively. When expressed per unit weight, blood flows to the right (nonstenotic) kidneys were similar in the stenosis and sham-stenosis groups, but resistance was about 25% greater in the stenosis group (p<0.05).

Central venous pressure was significantly elevated 24 hours after stenosis (Table 1) but then declined and was not significantly different from prestenosis values on days 21–25. Hematocrit fell significantly 24 hours after stenosis (by 4.7±1.4%), but the changes in hematocrit during the remainder of the stenosis were not significantly different from those seen in the sham group (Table 1). Neither blood volume (Table 1) nor plasma volume changed significantly in response to stenosis.

Plasma creatinine levels rose for the first week after stenosis and then declined to near prestenosis levels by 21–25 days (Table 1). Glomerular filtration rate measured by [3H]inulin clearance was 86.6±11.3
ml/min before stenosis and 96.4±10.0 ml/min 19 days after stenosis (NS). In the sham-stenosis group, these values were 95.8±5.9 ml/min and 94.7±9.1 ml/min, respectively.

Plasma renin activity rose in each animal in response to stenosis, peaking between days 1 and 7 and then declining gradually. Average rise on day 3, for example, was 2.3±1.53 ng angiotensin I (Ang I)/ml/hr. By days 21–25, plasma renin activity was 1.73±0.36 ng Ang I/ml/hr, not significantly different from the mean prestenosis value of 1.03±0.31 ng Ang I/ml/hr (mean difference +0.40±0.61 ng Ang I/ml/hr, NS). Plasma atrial natriuretic peptide levels had doubled 24 hours after stenosis, and although they fell slightly thereafter, they remained significantly elevated (Table 1). At 21–25 days, they were 9.0±3.6 pg/ml above prestenosis values (p<0.05). There were no significant changes in plasma levels of arginine vasopressin (Table 1).

**Contribution of Renal and Nonrenal Vasculature to Total Peripheral Conductance Changes**

Effective blood flow to both kidneys was measured by PAH clearance before and 19 days after stenosis or sham stenosis. This combined renal blood flow averaged 680±86 ml/min before stenosis and 517±96 ml/min after stenosis. Combined renal vascular conductance was 6.56±0.88 ml/min/mm Hg before stenosis and 4.43±0.79 ml/min/mm Hg after stenosis, a mean fall of 2.15±1.00 ml/min/mm Hg (Figure 3). Total peripheral conductance was 28.04±2.84 ml/min/mm Hg before stenosis and 22.60±3.27 ml/min/mm Hg after stenosis, a mean fall of 5.44±1.35 ml/min/mm Hg (Figure 3). Thus, the fall in renal vascular conductance was equivalent to 39.5% of the fall in total peripheral conductance (Figure 3).

Renal conductance changes calculated by Doppler flowmeter measurements indicated that conductance was reduced by 28±6% in the stenotic kidney and by 14±7% in the nonstenotic kidney (averaging the Doppler flowmeter measurements for days 14 and 21). When these figures are related to the combined conductances calculated from the PAH clearances, they indicate that the stenotic kidney was responsible for approximately 25% of the fall in total peripheral conductance and the nonstenotic kidney for approximately 15%.

Conductance of the nonrenal vasculature (calculated as total peripheral conductance minus the combined renal conductances) fell from 21.48±2.18 ml/min/mm Hg before stenosis to 18.19±3.49 ml/min/mm Hg after 19 days of stenosis, a fall of 3.29±1.58 ml/min/mm Hg (Figure 3).

In the sham-stenosis group, there were no significant changes in any of the above conductances. Combined renal blood flow measured by PAH clearance was 700±102 and 716±89 ml/min before and 21–25 days after sham stenosis, respectively (NS). Combined renal vascular conductance was 6.87±0.89 and 7.52±0.73 ml/min/mm Hg, respectively (+0.65±0.75 ml/min/mm Hg, NS), and total periph-
eral conductance was 27.92±2.05 and 27.70±3.21 ml/min/mm Hg, respectively (−0.22±3.54 ml/min/mm Hg, NS). Nonrenal conductances were 21.0±2.4 and 20.2±3.5 ml/min/mm Hg before and 21–25 days after sham stenosis, respectively (NS).

**Effects of Captopril**

Captopril was administered acutely after resting measurements on one of the prestenosis days and also again on each of days 1, 7, 14 and either 21, 23, or 25 days after stenosis (or sham stenosis).

Figure 4 is a pulsatile record of a typical poststenosis response to captopril in one dog, showing a greater fall in renal artery pressure distal to the stenosis than in arterial pressure with little change in flow to the stenotic kidney but an increase in flow to the nonstenotic kidney.

The group data showed that mean arterial pressure fell on all occasions in response to captopril in both stenosis and sham-stenosis groups (Figure 5). After stenosis, the average fall in pressure in response to captopril was 15.5±1.6 mm Hg (significantly greater than the fall of 9.4±1.5 mm Hg over the equivalent period in the sham-stenosis group, p<0.05). The fall was of similar magnitude on each poststenosis day tested, regardless of plasma renin activity (Figure 5) (e.g., captopril lowered MAP by 15.4±4.1 mm Hg 1 day after stenosis and by 17.1±3.3 mm Hg after 21–25 days). Pressure in the renal artery distal to the stenosis fell more than did aortic pressure in response to captopril. For example, the aorta–distal renal artery pressure gradient increased from 45.3 to 63.8 (SED 8.8) mm Hg on day 7 and from 59.2 to 71.4 (SED 5.2) mm Hg on day 14. The levels to which arterial pressure fell after captopril are plotted in Figure 6, showing that this level progressively rose during the stenosis.

Captopril caused significantly greater peripheral vasodilatation after stenosis than before (Figure 5). For example, the rises in total peripheral conductance on days 14 and 21–25 averaged 6.6±1.0 ml/min/mm Hg significantly greater than the rise before stenosis (2.78±1.61 ml/min/mm Hg, p<0.05), and significantly more than at the equivalent time after sham stenosis (Figure 5). The rise in conductance after stenosis remained about twice that before stenosis (Figure 5) despite renin levels falling back to near prestenosis levels (Figure 1).

The hemodynamic response of the stenotic (left) kidney to captopril was complex. After stenosis, the vasculature of the kidney vasodilated in response to captopril (Figure 7), and the magnitude of the vasodilatation was similar to before stenosis. However, the resistance of the stenosis rose in response to captopril (Figure 7). Because the magnitude of the rise in stenosis resistance was similar to the fall in the distal renal vascular resistance (Figure 7), the overall resistance of the stenotic kidney was little changed. Thus, captopril had little effect on blood flow to the stenotic kidney throughout the period of stenosis (see also Figure 4).

In contrast, the nonstenotic (right) kidney vasodilated in response to captopril at all times before and after stenosis and its blood flow increased significantly (Figure 7, see also Figure 4). However, the rises in blood flow and fall in resistance were not significantly greater than in the sham group except at 24 hours after stenosis.

The rise in plasma renin activity after captopril administration was significantly greater after stenosis than before (Figure 5) (e.g., captopril increased mean plasma renin activity from 1.19 to 3.56 ng Ang I/ml/hr before stenosis but from 3.15 to 16.38 ng Ang I/ml/hr 21–25 days after stenosis (p<0.01 for difference in response between the 2 days).

**Effects of Ganglion Blockade**

The effects of pentolinium before and 21–25 days after stenosis or sham stenosis are given in Table 2 and compared with the effects of vehicle and captopril. None of the responses to pentolinium 21–25 days after stenosis were significantly different from the responses before stenosis (Table 2) or from the responses seen in the sham-stenosis group (Table 2).

**Discussion**

In conscious dogs, unilateral renal artery stenosis increased mean arterial pressure promptly, the extent of the hypertension remained relatively constant over the 25-day study, and the hypertension was at all times mediated by a decrease in total peripheral conductance. There was no increase in cardiac output despite signs of fluid retention over the first few days of stenosis, including a brief fall in hematocrit and rise in central venous pressure. Indeed, cardiac output tended to decrease rather than increase over this initial period of stenosis.

The hypertension was due to 1) decreased conductance of the stenotic kidney caused by the stenosis itself, 2) decreased conductance of the nonstenotic kidney, and 3) decreased conductance of nonrenal vasculature due to Ang II and a gradually developing non-Ang II component. Each of these is discussed below.

**Decreased Conductance of Stenotic Kidney**

Stenosis increased this kidney's resistance by about 50%. The increase was due to the hydraulic resistance of the stenotic narrowing of the renal artery, not to increased resistance in the distal renal vasculature. The resistance of the stenosis was equivalent to about one third of the total resistance of the kidney in the established hypertensive state. In turn, as argued below, this resistance also accounted for a substantial proportion of the total decrease in peripheral conductance (about 25%). This is similar to the situation we have described for the stenosis on a single renal artery (i.e., one-kidney, one clip [1K1C] hypertension; see References 11, 13 and 14) and reflects the fact that a renal artery stenosis must be severe to produce hypertension.
The stenotic kidney was strikingly dependent on Ang II after stenosis. Captopril caused a pronounced fall in resistance of the renal vasculature but, surprisingly, this did not result in increased blood flow. Instead, the resistance offered by the stenosis increased by an amount approximately equal to the fall in distal vascular resistance, and thus the total resistance of the kidney (stenosis plus vasculature) was largely unchanged. This behavior of the stenosis, undergoing an increase in resistance in response to distal vasodilatation, occurs also in "one-kidney" hypertension and in stenoses on other arteries (e.g., the coronary artery). Any severe arterial stenosis has complex hydraulic properties and does not exert a fixed resistance to blood flow (see Reference 20). Instead, stenosis resistance varies with changing conductances of pressure and flow, particularly with changes in the resistance of the distal vasculature (see References 15,17-21).

The present experiments showed that pressure beyond the stenosis fell markedly as the kidney vasodilated under the influence of captopril. This may explain, at least in part, why converting enzyme inhibition frequently leads to renal failure in stenotic kidneys (see References 22-24). The effects of converting enzyme inhibition may also include actions within the glomerulus, however, and it should be acknowledged too that renal kinins may also be responsible for some of the distal renal vascular response to captopril especially as captopril has been shown to cause a pronounced increase in renal kinin excretion in dogs.

Even without converting enzyme inhibition, renal artery pressure distal to the stenosis was 30 mm Hg lower than before stenosis. Pressure distal to a stenosis will depend on the severity of narrowing of the artery, distal vascular tone, and the extent of changes in aortic pressure (see References 20 and 21). Na+ and K+ excretion rate and glomerular filtration rate remain low in the stenotic kidney, and this may be due to the reduced pressure distal to the stenosis. The low distal pressure is presumably also partly responsible for the increased renin synthesis and release from this kidney.

Decreased Conductance of Nonstenotic Kidney

The conductance of this kidney fell after contralateral stenosis. For the first 24 hours, this fall appeared to be due to Ang II-mediated vasoconstriction, as we have previously shown for the first hour after stenosis. By the third day of stenosis, however, there was no evidence that the conductance decrease was

---

**Figure 3.** Bar graph showing total peripheral and renal conductances before and 19 days after left renal artery stenosis. Renal portion of total peripheral conductance is shown as shaded, with the rest (nonrenal vascular beds) unshaded. On right of graph, differences between prestenosis and poststenosis values are shown for both total peripheral and renal conductances. Fall in renal conductance in response to stenosis is equivalent to 39.5% of fall in total peripheral conductance.

**Figure 4.** Representative recordings of effect of captopril (1 mg/kg bolus at vertical arrow, +0.5 mg/kg/hr infusion i.v.) in a conscious dog 7 days after induction of left renal artery stenosis. Note pronounced fall in pressure beyond stenosis and pronounced vasodilatation in nonstenotic kidney but not stenotic kidney.
EFFECT OF Captopril

Ang II–mediated (see References 1, 28–30). Increased vascular reactivity to other vasoconstrictors or increased levels of an unidentified vasoconstrictor are possible reasons for this decrease in conductance. With time, the decrease may have been due to structural changes in the vasculature of this kidney, and these changes reportedly include medial hypertrophy, increased wall-to-lumen ratio, increased vascular reactivity, and perhaps pathological changes such as focal arterial necrosis.31–33 The nonstenotic kidney also underwent considerable organ hypertrophy, increasing in weight by more than 30% in this study. Calculated per gram kidney weight, conductance was reduced by about 25% by 21–25 days. This kidney has also been reported to have increased Na⁺, K⁺, and water excretion and glomerular filtration rate (see References 1,3) and decreased glomerular K₁ (see References 34–36).

Reduction in Nonrenal Conductance

Ang II–mediated vasoconstriction was apparently responsible for much of the reduction in conductance in nonrenal vascular beds (60% of total conductance). Captopril produced a consistently greater rise in total peripheral conductance after stenosis than after sham stenosis, but the rise was not correlated with plasma renin levels. These were elevated initially after stenosis and then fell progressively over the next 3 weeks. The continuing large response to captopril despite the falling renin levels may reflect increased vascular sensitivity to all vasoconstrictors (see Reference 37), local vascular Ang II production at a rate unrelated to plasma renin (see Reference 38), or have been due to bradykinin potentiation (see Reference 27). Plasma renin levels varied considerably more between dogs after stenosis than we have noticed in 1K1C hypertension, possibly reflecting the more complicated situation for the control of renin release when the contralateral kidney is in situ. Renal artery pressure in the stenotic kidney remained below prestenosis values throughout the stenosis, presumably acting as a continuing stimulus to renin release, but renal artery pressure was increased in the contralateral kidney, tending to suppress renin release1 (though not necessarily intrarenal Ang II formation39). The instability of the renal artery pressure–renin release control system was exemplified on some days during measurements, when the pressure in the renal artery distal to the stenosis “spontaneously” rose and fell by as much as 30–40 mm Hg in irregular cycles of 5 minutes to 1 hour. Renal baroreceptor control of renin release was presumably also responsible for one other noticeable feature of the poststenosis period: the very large rise in plasma renin levels in response to captopril when distal renal artery pressure fell to values in the range of 40 mm Hg.

Although captopril reduced arterial blood pressure more after stenosis than before, the absolute level to which blood pressure fell after captopril was slightly higher each time captopril was given over the 25-day course of the hypertension. By the end of the experiment, the postcaptopril pressure was about 15 mm Hg higher than before stenosis. This suggests that there was a gradually developing non–Ang II component to the hypertension. The two renal vasculatures accounted for some of this non–Ang II–mediated rise in pressure, as outlined above. The present study provides no information as to the identity of the remainder of this non–Ang II, nonrenal component, but the gradual onset is compatible with its being due to hypertrophy of the walls of the resistance vessels (see References 37 and 40). The involvement of other vasoconstrictor substances can-

![Figure 5](http://hyper.ahajournals.org/)

**FIGURE 5.** Bar graphs showing mean effects of captopril administration before and on various days after the production of stenosis (crosshatched bars) or after sham stenosis (open bars). Bars show mean±SED in response to captopril Ang II-mediated (see References 1, 28-30). Increased vascular reactivity to other vasoconstrictors or increased levels of an unidentified vasoconstrictor are possible reasons for this decrease in conductance. With time, the decrease may have been due to structural changes in the vasculature of this kidney, and these changes reportedly include medial hypertrophy, increased wall-to-lumen ratio, increased vascular reactivity, and perhaps pathological changes such as focal arterial necrosis.31–33 The nonstenotic kidney also underwent considerable organ hypertrophy, increasing in weight by more than 30% in this study. Calculated per gram kidney weight, conductance was reduced by about 25% by 21–25 days. This kidney has also been reported to have increased Na⁺, K⁺, and water excretion and glomerular filtration rate (see References 1,3) and decreased glomerular K₁ (see References 34–36).

Reduction in Nonrenal Conductance

Ang II–mediated vasoconstriction was apparently responsible for much of the reduction in conductance in nonrenal vascular beds (60% of total conductance). Captopril produced a consistently greater rise in total peripheral conductance after stenosis than after sham stenosis, but the rise was not correlated with plasma renin levels. These were elevated initially after stenosis and then fell progressively over the next 3 weeks. The continuing large response to captopril despite the falling renin levels may reflect increased vascular sensitivity to all vasoconstrictors (see Reference 37), local vascular Ang II production at a rate unrelated to plasma renin (see Reference 38), or have been due to bradykinin potentiation (see Reference 27). Plasma renin levels varied considerably more between dogs after stenosis than we have noticed in 1K1C hypertension, possibly reflecting the more complicated situation for the control of renin release when the contralateral kidney is in situ. Renal artery pressure in the stenotic kidney remained below prestenosis values throughout the stenosis, presumably acting as a continuing stimulus to renin release, but renal artery pressure was increased in the contralateral kidney, tending to suppress renin release1 (though not necessarily intrarenal Ang II formation39). The instability of the renal artery pressure–renin release control system was exemplified on some days during measurements, when the pressure in the renal artery distal to the stenosis “spontaneously” rose and fell by as much as 30–40 mm Hg in irregular cycles of 5 minutes to 1 hour. Renal baroreceptor control of renin release was presumably also responsible for one other noticeable feature of the poststenosis period: the very large rise in plasma renin levels in response to captopril when distal renal artery pressure fell to values in the range of 40 mm Hg.

Although captopril reduced arterial blood pressure more after stenosis than before, the absolute level to which blood pressure fell after captopril was slightly higher each time captopril was given over the 25-day course of the hypertension. By the end of the experiment, the postcaptopril pressure was about 15 mm Hg higher than before stenosis. This suggests that there was a gradually developing non–Ang II component to the hypertension. The two renal vasculatures accounted for some of this non–Ang II–mediated rise in pressure, as outlined above. The present study provides no information as to the identity of the remainder of this non–Ang II, nonrenal component, but the gradual onset is compatible with its being due to hypertrophy of the walls of the resistance vessels (see References 37 and 40). The involvement of other vasoconstrictor substances can-

![Figure 6](http://hyper.ahajournals.org/)

**FIGURE 6.** Bar graph showing average values±SEM for arterial pressure during administration of captopril, before and after left renal artery stenosis (crosshatched bars) or sham stenosis (open bars).
not be discounted, but plasma levels of vasopressin did not change after stenosis, and plasma levels of the depressor atrial natriuretic peptide actually rose immediately after stenosis and remained significantly elevated throughout the experiment. The elevation in atrial natriuretic peptide levels may have been due to decreased clearance of atrial natriuretic peptide, as previous experiments from our laboratory have shown that renal artery narrowing in conscious dogs reduces both renal and nonrenal clearance of atrial natriuretic peptide acutely.12

Total Renal Contribution to Total Changes in Peripheral Conductance
The combined effective blood flow of the two kidneys was measured by PAH clearance before and about 3 weeks after stenosis and was used to calculate the contribution of the kidneys to the fall in total

### TABLE 2. Effects of Pentolinium, Captopril, or Saline Vehicle Before and After (21–25 days) Left Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Before stenosis</th>
<th>After stenosis</th>
<th>Before stenosis</th>
<th>After stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pent</td>
<td>V</td>
<td>Cap</td>
<td>Pent</td>
</tr>
<tr>
<td>MAP</td>
<td>0.1</td>
<td>2.8</td>
<td>-9.8</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>(6.3)</td>
<td>(3.8)</td>
<td>(3.1)</td>
<td>(7.2)</td>
</tr>
<tr>
<td>CO</td>
<td>-0.22</td>
<td>-0.25</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>(0.37)</td>
<td>(0.25)</td>
<td>(0.25)</td>
<td>(0.26)</td>
</tr>
<tr>
<td>TPC</td>
<td>-5.0</td>
<td>-3.2</td>
<td>2.8</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>(11.2)</td>
<td>(2.0)</td>
<td>(1.6)</td>
<td>(12.0)</td>
</tr>
<tr>
<td>RBF&lt;sub&gt;l&lt;/sub&gt;</td>
<td>-4.2</td>
<td>5.7</td>
<td>13.8</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>(5.3)</td>
<td>(6.8)</td>
<td>(10.3)</td>
<td>(4.0)</td>
</tr>
<tr>
<td>RBF&lt;sub&gt;r&lt;/sub&gt;</td>
<td>-6.6</td>
<td>4.2</td>
<td>15.2</td>
<td>-0.4</td>
</tr>
<tr>
<td></td>
<td>(2.7)</td>
<td>(5.5)</td>
<td>(6.8)</td>
<td>(10.0)</td>
</tr>
<tr>
<td>PRA</td>
<td>0.41</td>
<td>0.68</td>
<td>2.37</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>(0.83)</td>
<td>(0.7)</td>
<td>(1.26)</td>
<td>(0.73)</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure (Δmm Hg); CO, cardiac output (ΔL/min); TPC, total peripheral conductance (ΔmL/min/mm Hg); RBF<sub>l</sub>, blood flow to the stenotic left kidney (Δ%); RBF<sub>r</sub>, blood flow to the nonstenotic right kidney (Δ%); PRA, plasma renin activity (Δng/ml/hr). Values are mean change from the prepentolinium (Pent), vehicle (V), or captopril (Cap) measurement on each day (±SED). Pent, V, and Cap were given in random order both before and after stenosis. Doses are given in Methods.
peripheral conductance. The combined renal vascular conductance after stenosis was reduced by an amount equivalent to 40% of the fall in total peripheral conductance. This means that the decreased flow conductance of the two kidneys accounted for about 40% of the hypertension, as the hypertension was entirely due to decreased peripheral conductance. Relating the PAH clearance studies to the flowmeter findings, it may be surmised that the stenotic kidney was responsible for about 25% of the change in total peripheral conductance, and the nonstenotic kidney was responsible for about 15%. This figure was derived by relating the change in conductance measured separately by flowmeter for each kidney to the combined conductance changes measured by PAH clearance.

These findings are similar to those in our previous study of the first hour after stenosis when the two kidneys also contributed 40% of the fall in peripheral conductance. The only major difference is that the decreased conductance of the nonstenotic kidney was entirely due to Ang II–mediated vasoconstriction after 1 hour of stenosis but not due to Ang II after 3 weeks. For the stenotic kidney, the stenosis itself was the cause of the decreased conductance at both 1 hour and 3 weeks.

**Role of Autonomic Nervous System**

The apparent absence of an increase in sympathetic activity is at odds with several previous studies of 2K1C hypertension (See References 6–8, 41–43), particularly in rats. The autonomic nervous system could have been involved in the chronic responses to stenosis in at least two main ways: by its activity being modulated by Ang II either peripherally or centrally (See References 41–43) or by afferent neural input from the stenotic kidney. However, the results of the present study in conscious recumbent dogs did not reveal a significant role for the autonomic nervous system in the hemodynamic responses. Blockade of the autonomic nervous system with pentolinium gave no indication of significantly altered autonomic function after stenosis; arterial pressure, peripheral conductance, and cardiac output and flows to each kidney were affected similarly in dogs with and without unilateral stenosis. Thus, any increase or decrease in autonomic nervous function after stenosis must have been minor. Pentolinium has several advantages as a ganglion blocking agent in dogs: it has a short half-life and does not cause a profound hypotension in quietly recumbent, conscious dogs.

**Comparison With One-Kidney, One Clip Hypertension**

We have previously published results in which a similar degree of narrowing of the renal artery was performed in dogs with prior contralateral nephrectomy (1K1C hypertension). The increase in arterial pressure that was on average greater in the 1K1C dogs but was more variable than seen in the present 2K1C study, and plasma renin levels and distal renal artery pressure returned to prestenosis values sooner. In both forms, however, the hypertension was due to decreased conductance changes, not increased cardiac output, and in both forms the stenotic kidney contributed about 20% of the change in total conductance (see References 11, 13, and 14) due entirely to the mechanical resistance to blood flow of the renal stenosis on the renal artery.

**Acknowledgments**

We gratefully acknowledge the technical assistance of Jenny Lineham, Colleen Thomas, and Kerrie Lawrence, and thank Dr. Robyn Woods for helpful discussion and assistance. Captopril was generously donated by E.R. Squibb & Sons. The experiments were approved by the Alfred Hospital/Baker Institute Animal Experimentation Committee.

**References**


Key Words • angiotensin converting enzyme inhibitors • angiotensin • ganglionic blockers • pentolinium tartrate • cardiac output • vascular resistance • Goldblatt hypertension • renal circulation • renin
Development of hypertension from unilateral renal artery stenosis in conscious dogs.
W P Anderson, D E Ramsey and M Takata

Hypertension. 1990;16:441-451
doi: 10.1161/01.HYP.16.4.441

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/16/4/441