Acute Angiotensin II-Mediated Restoration of Distal Renal Artery Pressure in Renal Artery Stenosis and its Relationship to the Development of Sustained One-Kidney Hypertension in Conscious Dogs

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SUMMARY The effects of graded renal artery stenosis on renal and systemic hemodynamics and plasma renin activity (PRA) were studied in conscious, chronically instrumented dogs. In mild and moderate stenosis (following rapid reduction in distal renal artery pressure to 60 or 40 mm Hg) there was initial vasodilatation followed by prompt restoration within 5–30 minutes of renal artery pressure and vascular resistance; changes in mean aortic pressure (MAP) were minimal. Both Δ PRA and Δ renal artery pressure were reciprocally related, the relationship reflecting renal “barostat” control of renin secretion in the conscious dog. Pretreatment with converting enzyme inhibitor before induction of stenosis prevented restoration of renal artery pressure during stenosis. With more severe stenosis, after lowering renal artery pressure to 20 mm Hg, the latter took 2 to 3 days to become fully restored. The MAP rose 18.2 ± 2.5 by the end of 30 minutes but had declined to control by the second or third day. The Δ PRA during the first hour of stenosis was greater than accounted for by the fall in renal artery pressure, but by Days 2–7 PRA appeared to be predominantly under renal “barostat” control.

With even more severe stenosis, systemic MAP remained elevated and after 7 days was 39 ± 14 mm Hg above control levels; PRA also stayed above control levels despite restoration of renal artery pressure, suggesting that it was controlled by factors additional to the “barostat” mechanism. The rise in renal artery pressure was now mainly determined by the increase in systemic MAP. Renal “barostat”-mediated increase in renin-angiotensin activity appears to be the main mechanism that restores renal artery pressure with mild stenosis, while in severe stenosis this is accomplished by development of systemic hypertension.

(Khypertension 1: 292–298, 1979)

KEY WORDS • critical stenosis • renin • renal blood flow • renal hypertension • renal barostat • renal hemodynamics

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There has been relatively little analysis of the hemodynamic events following acute renal artery stenosis in conscious animals, since this requires instrumented preparations in which arterial pressures and renal blood flow can be measured simultaneously and continuously. We have recently performed such an analysis in conscious dogs and have found that immediately upon induction of stenosis there was renal vasodilatation which was followed within minutes by angiotensin II-mediated restoration of renal vascular resistance and renal artery pressure. Plasma renin activity (PRA) was only transiently elevated.

In this present investigation we have studied the relationship between the above renal effects and the development of systemic hypertension in four grades of renal artery stenosis. The results indicate that in the conscious dog it is only with very severe stenosis that restoration of distal renal artery pressure is slow and that systemic hypertension develops.
Methods

The experiments were performed on conscious male mongrel dogs (18-32 kg). At a preliminary operation at least 2 weeks before the first experiment, one kidney was removed and the other kidney was exposed through a flank incision. An inflatable saline-filled silastic cuff, 5 mm in diameter (Hazen Everett Co, Mahwah, NJ) was placed around the renal artery. In some experiments a wire snare, similar to that used by Harris and Ayers was placed around the artery instead of the cuff. A catheter was inserted through the wall of the renal artery distal to the cuff or snare. A Doppler ultrasonic flow probe (cuff type, 5 mm in diameter) was also placed around the renal artery.

The flowmeter wires and catheters were exteriorized on the chest and protected by a canvas jacket. Postoperative management and precautions to remove any small air bubbles from the inflated cuff over the next few days were as described previously. Dietary sodium intake was about 110 mEq/day, and all dogs in our experiments maintained a good appetite and ate normal meals during this period.

During each experiment the dog lay on its side on a padded table in a quiet laboratory. The dogs had been trained before operation and visited the laboratory daily after the operation for flushing of catheters. Phasic and mean aortic and renal artery pressures (Statham P23Dc transducers) and phasic and mean renal blood flows were recorded on a Devices recorder. After chronic implantation of cuff-type Doppler flowmeter probes, the Doppler shift (kHz) and volume flow (ml/min) are linearly related over a wide range of pressures. Results of blood flow have been expressed as Doppler shift (kHz). An approximate conversion factor is 160 ml/min/kHz Doppler shift. Renal vascular resistance was calculated as distal renal artery pressure (mm Hg)/renal blood flow (kHz).

The dogs rested for 30 minutes before the start of the experiment. They were then under observation for 20 minutes. The renal artery was then narrowed by inflating the cuff (or tightening the snare) over a period of 30 seconds to lower renal artery pressure to a predetermined value (60, 40 or 20 mm Hg). The cuff tubing or snare was then clamped to maintain the stenosis. In some experiments inflation was maintained for 30-60 minutes and in others for 7 days. The volumes of 0.9% NaCl initially added to the cuff were compared with the volume recovered upon release of the cuff after the 7-day inflation period (recovery: 100.0 ± 1.3%).

In some experiments the dogs received angiotensin I converting enzyme inhibitor (CEI; SQ20,881, Squibb) into the renal artery (20 μg/kg/min bolus and continuous infusion, 0.5-1.0 μg/kg/min) before and after renal artery stenosis.

Both PRA and plasma renin concentration (PRC) were measured enzymatically by radioimmunoassay of generated angiotensin I. For measurement of PRC additional dog substrate was added. Evans blue (5 mg, I.V.) was used to measure plasma volume in the 7-day experiments. Plasma creatinine was measured by a modification of the method of Brod and Sirota. The statistical significance of the various changes were assessed mostly within dogs by analysis of variance.

Results

Resting Values

Before stenosis the resting mean pressure (MAP) in the 33 dogs used in the study was 97.7 ± 1.8 (SEM) mm Hg (range 80-110 mm Hg). In the absence of stenosis PRA was 0.37 ± 0.046 ng/ml/hr (range 0.15-0.50 ng/ml/hr).

Acute Renal Hemodynamic Changes

Restoration of distal renal artery pressure during stenosis occurred rapidly in 15 dogs when renal artery pressure was reduced to 40 mm Hg by inflating the cuff or tightening the snare over a period of 30 seconds and then maintaining stenosis by clamping the cuff tubing or the snare (fig. 1, right). Renal artery pressure began to rise within 1-5 minutes after the
start of stenosis and by 30 minutes was at 93 ± 2% of prestenosis control. Renal blood flow (RBF) reached minimum values at the end of the 30-second period of cuff inflation. The RBF recovered more rapidly at first than the renal artery pressure but then declined again, and by 25-30 minutes it was 91 ± 3.8% of control (fig. 1). Renal vascular resistance (RVR) fell markedly during cuff inflation to 47.5 ± 3.5% of resting. Because of the differences in recovery rates of renal artery pressure and RBF, RVR remained low for several minutes after the start of stenosis. Then it too began to recover and had become almost completely restored by 30 minutes (fig. 1). Systemic mean arterial pressure (MAP) rose only slightly, (8.7 ± 2.0 mm Hg; \( p < 0.01 \)) during the first few minutes of stenosis; by 30 minutes it was 6.6 ± 1.4 mm Hg above initial control and by 1 hour averaged only 1.3 ± 0.2 mm Hg (n = 10) above control.

Pretreatment with CEI in five dogs abolished the restoration of distal renal artery pressure and RVR during stenosis (fig. 1, right). After renal artery pressure was lowered to 40 mm Hg by stenosis as above, there was a further reduction in pressure over the next few minutes followed by a small rise to 49 ± 4 mm Hg at 25-30 minutes. The RBF first fell during induction of stenosis but then gradually rose close to the prestenosis level or even above it. The flow reached after stenosis was significantly higher than in dogs not pretreated with CEI (\( p < 0.05 \)). Renal vascular resistance remained low in these experiments reaching a value of 43.6 ± 11.3% of control at the end of 30 minutes; MAP did not change significantly.

Relationship Between PRA and Renal Artery Pressure in Mild and Moderate Stenosis

In normal dogs PRA had increased by 1.13 ± 0.29% ng/ml/hr above resting levels \( (p < 0.01) \) 15 minutes from the start of stenosis, but had fallen again significantly from the peak value at 30-45 minutes by 0.58 ± 0.12 ng/ml/hr, pari passu with the restoration of renal artery pressure. This pattern occurred not only after initially lowering renal artery pressure to 40 mm Hg (fig. 2a) but with even milder stenosis following pressure reduction to 60 mm Hg where MAP had not changed at all during stenosis \( (n = 9) \) (fig. 2b). The relationship between renal artery pressure and \( \Delta \) PRA at 15 minutes and at 30-45 minutes obtained from the data of individual dogs in the two grades of stenosis was approximately linear (fig. 2c).

For every 10-mm Hg reduction in renal artery pressure, PRA increased by 0.6 ± 0.1 ng/ml/hr, that is, by more than 150% of the resting PRA. The greater average rise in PRA in the course of stenosis in CEI pretreated dogs (in which systemic MAP did not rise either) was slightly greater than predicted from the regression line calculated from the data from normal dogs, but the difference was not statistically significant (fig. 2c). It thus mainly reflected the effects of greater and more sustained reduction in renal artery pressure over the observation period.

Effects of Lowering Renal Artery Pressure to 40 mm Hg

After acutely lowering renal artery pressure to 40 mm Hg neither PRA or MAP were significantly elevated after 1 hour. In two dogs studied for 7 days no elevation in MAP was observed.

Reduction of Renal Artery Pressure to 20 mm Hg

Greater stenosis than in the above experiments was induced by: 1) a single reduction of renal artery pressure to 20 mm Hg by cuff inflation in the usual way over a period of 30 seconds, followed by maintained inflation for either 1 hour (13 dogs) or 7 days (five dogs); or 2) repeated reduction to 20 mm Hg, in which renal artery pressure was relowered four times at 15, 30 and 60 minutes during the first hour of
stenosis with cuff inflation, and then maintained without further adjustment for the next 7 days (six dogs).

**Single Reduction to 20 mm Hg**

Recovery of distal renal artery pressure after reduction to 20 mm Hg was slower than with milder stenosis (fig. 3). After 40-60 minutes, renal artery pressure had risen to only about 75 mm Hg, despite the fact that systemic MAP was 18.2 ± 2.5 mm Hg above control (fig. 3, left). Again RBF initially rose more rapidly than renal artery pressure.

The rise in PRA was greater than with the milder grades of stenosis (fig. 3, left). However, the relationship between changes in PRA and renal artery pressures at 15 minutes was similar to that predicted from the milder stenoses, but by 45 minutes the rise in PRA was significantly greater than expected from the reduction in renal artery pressure (p < 0.05, fig. 4).

In five dogs cuff inflation was maintained for 7 days (fig. 5, left). The MAP declined from the maximum observed at 30 minutes after inflation and by Day 7 was only 4.3 ± 2.5 mm Hg above control. Renal artery pressure had become almost fully restored by Day 7, when only a small MAP-renal artery pressure gradient (7.5 ± 1.4 mm Hg; p < 0.01) remained. Renal blood flow was significantly below control from Days 1 to 7 (−11 ± 3%; p < 0.05) and RVR had become restored by Day 1 or 2 and remained at that value or slightly increased (fig. 5, left).

Both PRA and PRC had returned to control by Day 2 when MAP was only slightly raised and renal artery pressure had nearly recovered. Between Days 2–7 the results from individual dogs relating Δ renal artery pressure to Δ PRA was close to the origin of the regression line obtained from the data in milder grades of stenosis (fig. 4).

Plasma volume was elevated on all days in three of five dogs and on some days in the others, but the rise was statistically significant only on Day 3 after stenosis, i.e., a rise of 17%, from 1.84 to 2.17 liters, SED 0.145; p < 0.05. Plasma volume fell significantly by about 10% 24 hours after recovery (p = 0.05).

**Repeated Reduction to 20 mm Hg over 1 Hour**

The increase in stenosis after relowering renal artery pressure to 20 mm Hg four times during the first hour of stenosis raised systemic MAP to 42 ± 5 mm Hg, more than twice the value as obtained by a single narrowing (fig. 3, right). Renal blood flow partly recovered between adjustments and RVR remained low.

By 24 hours MAP had fallen slightly from the 1-hour value but then increased gradually (i.e., 39 ± 14 mm Hg) above control by Day 7 (fig. 5, right). Renal artery pressure from Day 1 rose in parallel with MAP over the next few days and reached prestenosis control by Day 7. The MAP-renal artery pressure gradient remained approximately constant between Days 2–7 at 40 ± 9 mm Hg (fig. 5, right). By Day 1 RVR had returned to control value and then increased by a

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**Figure 3.** Average effects of renal artery stenosis over 1 hour. Left: Distal renal artery pressure lowered to 20 mm Hg at vertical arrow (n = 13). Right: Renal artery pressure lowered initially to 20 mm Hg, with additional cuff inflations at 15, 30 and 60 minutes to relower pressure to 20 mm Hg (n = 6). Abbreviations as in figure 1.

**Figure 4.** Relationship between change in renal artery pressure (RAP) and change in plasma renin activity (PRA) in five dogs after renal artery pressure was reduced to 20 mm Hg at various times after stenosis induction. Line is regression of Δ RAP on Δ PRA from figure 2 produced during mild and moderate levels of stenosis with only minimal changes in systemic MAP.
Further $35 \pm 15\%$ of control by Day 7 ($p < 0.05$).

PRA was highest at 1 hour, with an average rise of $4.51 \pm 1.02$ ng/min/hr, only slightly greater than after a single narrowing (fig. 3). By Day 1 this had fallen by about 50% but remained about 2.5 times higher than control for the next 7 days, falling toward prestenosis values only after release of the cuff (fig. 5).

In these dogs, plasma volume changes were more variable with some rises occurring in all dogs. Since these rises occurred on different days, the average changes on any one day were not statistically significant. Plasma creatinine rose from an average 0.106 mM/liter to 0.165 mM/liter on Days 3 and 7 (SED 0.020; $p < 0.05$).

**Discussion**

The possibility that the rapid recovery of distal renal artery pressure is artifactual (i.e., due to leakage of saline from the cuff) has been excluded in the short-term experiments by 1) previous demonstration of constancy of stenosis resistance when tested in vitro over several hours; 2) in vivo demonstration of well-maintained resistance by the stenosis after pretreatment of the dogs with CEI (fig. 1) or Sarcosine, Isoleucine AII, and 3) identical hemodynamic effects following stenosis by cuff and wire snare. The effective resistance of a critical stenosis depends to a large extent on the resistance to flow in the distal vascular bed. Thus, when the recovery of renal vascular resistance after stenosis was prevented by CEI pretreatment effective stenosis resistance remained high (fig. 1). However, if the renal vasculature was constricted under these circumstances by intrarenal infusion of exogenous AII, effective stenosis resistance fell but rose again when AII infusion stopped. In the 7-day stenosis experiments, leakage cannot be absolutely excluded, but is unlikely in view of the complete recovery of the saline used to inflate the cuff. Moreover, the pressure in the inflated perivascular cuff is very high (between 700-800 mm Hg) and the inflated cuffs are taut and fairly rigid. The amount of extra fluid is about 25% greater after repeated reduction to 20 mm Hg in the distal renal artery pressure over the first hour of stenosis than after a single reduction of pressure. In neither group was there any further cuff adjustment over the next 7 days of stenosis and it is difficult to postulate whether the cuff would leak in the latter group, but not the former in which systemic MAP remained elevated and the MAP-renal artery pressure gradient approximately constant.

After acute stenosis there is rapid restoration of distal renal artery pressure and RVR, which, if the stenosis is relatively mild, occurs without change in systemic MAP. The restoration cuts short the initial renal vasodilator response to acute stenosis. The restorative phase involves constriction of the renal vasculature and is prevented by pretreatment with CEI and with Sar; Ile AII, indicating that it is due to the intrarenal constrictor effects of AII. The opposing effects on RBF of the initial vasodilatation and the subsequent AII-mediated vasoconstriction are most obvious at the mildest levels of stenosis, where no changes in systemic arterial pressure were detected. Thus, during reduction of renal artery pressure to only 60 mm Hg, RBF first falls slightly as described in detail previously, then returns to control levels over the next few minutes as further renal vasodilation occurs, and finally falls again as renal vascular resistance and renal artery pressure rise. These early phase differences in the pressure and flow changes are also present at the moderate and severe levels of stenosis of the present study, although in the latter case they are confounded by the immediate rise in systemic arterial pressure.

Most vascular beds vasodilate in response to stenosis-induced reduction in perfusion pressure and this is also the initial response of the renal bed. However, the kidney is unique in that reduction in renal artery pressure provides a stimulus to the renin secretion and AII production which constricts the
dilated bed and restores distal renal artery pressure. Although the site of action of AII has not been investigated here, it most probably constricts the efferent renal arterioles. This action may help to maintain glomerular filtration rate during reduction in renal artery pressure.

After mild or moderate stenosis, the rapid restoration of distal pressures and/or the restoration of renal vascular resistance appears to be the main factor that turns off the renin-angiotensin system after the initial stimulation (fig. 2). Previous experiments in which CEI was infused later have shown that once distal renal artery pressure has become restored, mechanisms other than AII contribute to its continued maintenance.

Our results extend the observations of Ayers and colleagues who showed that in renal artery stenosis that is sufficiently severe to produce systemic hypertension, AII caused renal vasoconstriction which was a factor in turning the renin-angiotensin system off over a period of several days. The present findings with mild and moderate stenosis, where renin release can be turned off within minutes, indicate that this mechanism is part of a more general renal response that occurs regardless of whether the stenosis is severe enough to produce hypertension. With these levels of stenosis the turning off of renin release appears to be secondary to the restoration of renal artery pressure, although our study cannot exclude that the direct feedback action of AII on the juxtaglomerular cells could not have played an additional role.

The relationship between change in renal artery pressure and PRA is most easily interpreted in the experiments with less severe stenosis in which systemic arterial pressure changed only slightly or not at all. Under these conditions of stenosis the renal artery pressure depends almost exclusively on RVR changes rather than changes in systemic MAP. Thus, the relationship between PRA and renal artery pressure in fig. 2c probably depends on renal "barostat" control of renin secretion in the conscious dog. More severe stenosis, however, causes a rise in arterial pressure, and this in turn raises renal artery pressure. The rise in PRA is now greater than that predicted from the reduction in renal artery pressure (fig. 4), suggesting that a mechanism additional to the renal "barostat" is responsible for renin release.

In the second most severe level of stenosis (single lowering of renal artery pressure to 20 mm Hg), restoration of renal artery pressure was slower than after milder stenosis. However, after 2–3 days of stenosis, PRA had fallen to normal, renal artery pressure had become fully restored and MAP was only slightly raised. While factors other than the renal "barostat" contributed to the control of renin secretion during the first hour of stenosis (fig. 4), it seems likely that subsequently the "barostat" mechanism was the major factor involved. By Day 7 this more severe stenosis resembles the milder stenosis at 1 hour, i.e., no hypertension, normal PRA, and restoration of renal artery pressure. Thus, this level of stenosis appears to be close to the limit of the renal "barostat" mechanism's capacity to restore renal artery pressure.

With even more severe stenosis, the elevation of systemic MAP appears to be the major determinant of restoration of renal artery pressure. The systemic hypertension had still not stabilized by Day 7, and despite restoration of renal artery pressure and increased RVR, renal function was still abnormal as judged by the elevation in plasma creatinine. The elevation of PRA at Day 7, despite normal renal artery pressure, suggests that renin release was now predominantly under the control of mechanisms other than the renal "barostat." Had the observations been continued longer, it is likely that systemic arterial pressure would have increased further and PRA would have fallen eventually.

At first it might appear that in the present study more severe stenosis was required to produce chronic hypertension than reported by other workers. However, a given degree of arterial narrowing will produce a much greater fall in the distal pressure or blood flow when the vascular bed is dilated than when it is constricted. Thus, although other workers have reduced distal renal artery pressure less in anesthetized dogs (in which MAP is elevated and RBF reduced) it is likely that the arterial narrowing was considerably greater than would have been required to achieve the same pressure drop as in the conscious quietly resting dogs reported here.

In conclusion, these results show that distal renal artery pressure is restored rapidly following its reduction by mild or moderate stenosis. This is mediated through the renal vasoconstrictor action of AII, which compensates for the initial vasodilatation. The release of renin seems to be almost entirely mediated through the renal "barostat." This mechanism can be regarded as a local action of AII that, because it rapidly restores renal function, is in a sense an antihypertensive mechanism. More severe stenosis initiates greater renin-angiotensin system activity with resultant systemic effects on arterial pressure. The renal "barostat" mechanism thus makes a progressively smaller contribution to the eventual restoration of renal hemodynamics and function.

Acknowledgments

We thank E. Anderson, M. LeDuc, J. Dixon and D. Casley for their excellent assistance, and Dr. Z. P. Horowitz of E. R. Squibb & Sons, Inc., for the gift of SQ30,881.

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Hypertension. 1979;1:292-298
doi: 10.1161/01.HYP.1.3.292

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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