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Selective Reduction of Renal Perfusion Pressure and Blood Flow in Man: Humoral and Hemodynamic Effects

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SUMMARY We studied the renin and the circulatory responses to unilateral reduction of the renal perfusion pressure (RPP) in seven normotensive subjects and 17 patients with primary hypertension who required diagnostic renal angiography. A balloon-tipped catheter was used for occlusive arteriography; the same catheter was also used to reduce, through appropriate inflation of the balloon, the RPP by 50% of control. In preliminary observations, this stimulus was shown to be safe and strong enough to activate renin release maximally. The reduction in RPP (either right or left) was maintained for 60 minutes. Plasma renin activity was determined after 1 hour of recumbency (baseline), at various periods during occlusion of the vessel, and after release. Cardiac output was measured at the same periods, and systemic arterial pressure and heart rate were monitored continuously.

As regards the renin response, we observed that (1) systemic (arterial) renin was already significantly augmented at 5 minutes, reached a peak at 15 minutes and then tended to decrease, although the mean values continued to be markedly higher than the baseline values; (2) soon after the stimulus, venous renin and venous arterial difference of the occluded kidney became definitely elevated and remained elevated for the duration of the occlusion; (3) on the contralateral side, the venous arterial difference decreased progressively until 30 minutes after occlusion, when it was almost abolished, indicating that renin release from the nonoccluded kidney was suppressed; and (4) the response was quantitatively and qualitatively similar in normotensive and hypertensive subjects. Despite this humoral reaction, in no case did systemic arterial pressure, heart rate and cardiac output change throughout the studies.

We conclude that in man, either normotensive or hypertensive, unilateral RPP reduction duplicates the renin pattern of the Goldblatt kidney, but does not duplicate the circulatory response. This evidence applies to 1-hour renal artery occlusion and does not exclude the possibility that renin may have a role in the blood pressure elevation after long-standing renal arterial stenosis.

HIGH BLOOD PRESSURE associated with stenotic lesions of the renal artery is regarded as a sort of duplication in man of the hypertension induced experimentally by renal artery clipping.1 Although activation of the renin-angiotensin system probably represents the link between the altered hemodynamics of the kidney due to stenosis and the pressure rise, the role of renin in the pathogenesis of hypertension remains uncertain both in animals and in humans. After constriction of a renal artery, in animals, blood pressure rises within 1 hour or less,2,3 and can be explained quantitatively by the direct vasoconstrictor effect of the concomitant increase in circulating angiotensin II.4 Later in the course of hypertension, peripheral plasma levels of renin and renin activity5,6 and angiotensin II concentration7 become normal or only slightly increased, whereas hypertension persists or worsens. Clearly, other mechanisms are involved in the later stages. Renal vascular hypertension is usually first encountered clinically in the second phase. Information concerning the humoral and the circulatory response and the relation between the two shortly after development of a renal stenotic lesion in man is not available.

Recently, balloon-tipped catheters that hold preset curves and enable selective placement of the balloon...
were introduced for renal occlusion phlebography and arteriography. These catheters were regarded as a means by which selective reduction of the renal perfusion pressure could be accomplished and modulated in man through an appropriate inflation of the balloon after placement into a renal artery. We used these catheters in the present study to test whether an acute diminution of the renal perfusion pressure in man duplicates the circulatory and humoral responses that characterize the very early stage of experimental renovascular hypertension.

Materials and Methods

Subjects

These studies were performed in normotensive and hypertensive subjects who required diagnostic renal arteriography. The normotensive group included one woman and six men in whom renal disorders (solitary cyst, malformations) were suspected and later excluded through angiographic evaluation. Renal arteriography was part of the diagnostic work for the elevated blood pressure in the hypertensive group, which included 14 men and three women, ages 25–58 years, suffering from moderate-to-severe primary hypertension. Patients who had multiple arteries supplying the kidneys or stenotic lesions of the renal artery were not included in this report.

Endovascular Techniques

A #7F double-lumen balloon-tipped radiopaque polyethylene catheter (Medi-Tech OB/7/2/65 occlusion balloon catheter) curved suitably to allow selective placement in the renal artery was introduced percutaneously through the right femoral artery by the Seldinger technique.* The same catheter was used to inject dye for arteriography through the distal lumen and to produce partial occlusion of the main renal artery by inflation of the balloon (proximal lumen) with Renografin-60, diluted 50% with 5% dextrose in water.

A preshaped polyethylene radiopaque catheter placed in the renal vein through femoral introduction was used for selective bilateral blood sampling.

A thermodilution catheter positioned in the renal vein by the Seldinger technique was used in a few subjects to measure renal venous blood outflow. The reliability of the method has been validated previously.16 In brief, we used a triple-lumen, pigtail catheter adapted for local thermodilution: The first lumen houses the wire of the thermistor; the second has an orifice of 0.6 mm set on the catheter curve at an angle of 40° for injection of the cold solution; the third is at the tip of the catheter and allows pressure monitoring and percutaneous introduction. The thermistor is located in the wall of the catheter beyond the second lumen. Absolute thermal isolation of the thermistor from the cold dye injected and a constant relative position between injecting and sampling sites were assured.

A Teflon catheter needle was introduced into the brachial artery to monitor arterial pressure and to sample blood for renin and indocyanine green for cardiac output determinations.

Procedures

After admission to the hospital and discontinuance of any treatment (hypertensive patients in urgent need of therapy were not included), patients were observed for 10 days, while they were kept on a standard hospital diet (100 mEq sodium) and the routine clinical and laboratory evaluation was performed. To minimize the possible interference of emotion or tension, they were familiarized with the investigators and the catheterization room before the studies, which were carried out in the morning, 3 hours after breakfast, with the patients in the supine position, and without premedication. After catheter positioning, the patients lay quietly and comfortably for at least 1 hour. Then blood was collected from the brachial artery and from either renal vein for baseline renin determinations; cardiac output was measured by dye-dilution curves after injection of indocyanine green into the right atrium and withdrawal from the brachial artery. For dye injections the venous catheter was advanced to the right atrium and then pulled back to the renal vein. Subsequently, the balloon, which was placed either in the right or in the left renal artery, was inflated so as to reduce the mean renal perfusion pressure by 50%. The distal lumen of the catheter was connected to a transducer for pressure monitoring. Inflation was maintained for 60 minutes, with a 30-second deflation every 10 minutes. Blood samples (5 ml) were withdrawn from the brachial artery and both renal veins for renin determinations at 5, 15, 30 and 60 minutes after balloon inflation, and at 5 and 15 minutes after removal of the renal artery obstruction. In no case did blood loss exceed 120 ml. Cardiac output was repeated at the same intervals, with immediate reinfusion of the blood withdrawn during inscription of the indicator dilution curves. Systemic pressure and renal perfusion pressure (by Statham P23Db strain-gauge transducers) and the ECG were continuously monitored on an eight-channel ink recorder (Gould-Brush, model 480). At the end of the study, bilateral renal arteriography was performed in each patient through the same arterial catheter.

Great care was taken to uncover any possible injury to the kidney subjected to ischemia, which could make the procedure unjustified for investigative purposes. We performed preliminary partial occlusion of the renal artery (reduction of the mean perfusion pressure by 50% of control) in five patients for 10, 20, 30, 40 and 50 minutes, respectively. Blood urea nitrogen, serum electrolyte, creatinine, glutamic oxalacetic transaminase and lactic dehydrogenase concentrations, and urinalyses were determined 12, 24 and 48 hours after the procedure in each subject, and we found no changes in these variables from the prestudy period. The harmlessness of the procedure was confirmed through the same tests in all of the patients who were investigated subsequently.
To elucidate the renal hemodynamic and renin responses to arterial occlusion, a pilot study was performed in which the balloon was inflated by stages in five subjects to reduce the mean perfusion pressure by 10%, 30%, 50% and 70% of the baseline.

After each 15-minute occlusion, renal blood flow of the occluded side was measured by the thermodilution technique, and blood was collected from the brachial artery for renin determinations.

Plasma renin activity was measured by radioimmunoassay of angiotensin I in plasma samples and calculated as the difference between immunoreactive angiotensin I formed during 3-hour plasma incubation at 37°C and that present in an unincubated plasma sample at 4°C. Plasma renin activity was expressed as nanograms of angiotensin I formed per milliliter of plasma per hour.

**Statistical Analysis**

Results were treated statistically by analysis of variance with comparison between control and stimulus values.

**Results**

Figure 1 shows the average percentage variations from control of renal blood flow and vascular resistance (ratio of the driving pressure to flow) in two normotensive and three moderately hypertensive subjects who underwent graded reduction of the renal perfusion pressure. The averages of systemic plasma renin activity in the control and at the end of each 15-minute occlusion are shown. Examples of original strips of records of the renal perfusion pressure during graded occlusion in one of these patients are also given. At each stage of pressure reduction, renal blood flow is diminished, although proportionally less than the decrease in pressure; this reflects a progressive reduction in flow resistance distal to the occlusion (renal vascular resistance). The vasodilating response persists after removal of the obstruction and reversion
of the renal artery pressure to the control levels; in fact, at 15 minutes, renal blood flow exceeded the baseline flow by an average of 24%.

In regard to the renin response, the average plasma renin activity increased from 0.85 ng/ml/hour in the control state to 1.25 and 2.55 ng/ml/hour at, respectively, 10% and 30% diminution of the renal perfusion pressure, and subsequently stabilized despite further pressure diminution by 50% and 70% of control. Fifteen minutes after release of the obstruction, plasma renin activity had almost reverted to the control level. On the basis of these findings we considered a 50% reduction of the renal artery pressure safe and strong enough to induce maximal effects on renin. This stimulus was used in the subsequent studies.

The time course of the response of renin and systemic circulation to 50% reduction of the perfusion pressure of one kidney (either right or left) in seven normotensive and 17 hypertensive subjects is shown in figure 2. Averages of the systolic and diastolic arterial pressure, heart rate, cardiac output and arterial and venous renin activity of both kidneys in the control state and in the 60 minutes after renal artery occlusion are reported. Baseline renin values were similar in the two groups, but heart rate and cardiac index were higher in the normotensive group. Arterial renin activity was already significantly augmented at 5 minutes after the beginning of renal artery occlusion and reached a peak at 15 minutes. Subsequently, arterial renin levels tended to decrease, although the mean values were still markedly elevated over baseline. In the control period, renal venous

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Systolic and diastolic arterial pressure (AP), heart rate (HR) and cardiac index (CI) in seven normotensive and 17 primary hypertensive subjects at various periods before, during and after 60-minute unilateral renal artery occlusion that reduced the mean perfusion pressure by 50% of the baseline. The black symbols refer to the hypertensive patients; the white symbols represent the normotensive group. Plasma renin activity (PRA) for the two groups in the arterial (solid bars) and in the venous blood of the occluded kidney (dashed bars, on the left) and of the contralateral side (dotted bars, on the right) at the various periods, are also reported. Asterisk indicates differences from the preocclusion period significant at p < 0.01. All values are mean ± SEM.
Renin and the venous arterial difference in renin activity were comparable on both sides. Soon after the stimulus, venous renin and venous arterial difference of the occluded kidney became definitely elevated and remained elevated for the duration of the occlusion. On the contralateral side, the venous arterial difference decreased slightly and progressively until, 30 minutes after occlusion, it was almost abolished, indicating that renin secretion from the nonoccluded kidney was suppressed.

Despite the significant elevation in systemic renin, arterial pressure, heart rate and cardiac output did not vary from control throughout the studies in either hypertensive or normotensive subjects.

Discussion

Our data show that renal artery occlusion is associated with an increase in systemic renin. The distinct increment in renal vein renin and venous arterial difference in renin activity on the occluded side, although suggestive, cannot be taken as a proof that it is the source of the extra renin, since, as Hosie and co-workers12 noted, the venous arterial difference reflects both the secretion rate and renal plasma flow, and changes in renal vein renin do not necessarily reflect changes in the secretion rate of renin. In our study, simultaneous renal vein renin and plasma flow determinations were not performed. There is however, valid evidence that the occluded kidney is the source of the excessive renin: The increment in systemic renin is, within certain limits, proportional to the degree of occlusion; suppression of renin release from the contralateral kidney parallels the increment in systemic renin activity; and renin approximates the baseline within 15 minutes after the release of the occlusion.

The fact that renin measurements were commenced when patients felt comfortable, after prolonged recumbency and at least 1 hour after catheter positioning, and also that renin changes were strictly time-related to the arterial occlusion, rules out the intervention of factors other than the occlusive stimulus, such as posture and emotion. Volume depletion due to blood sampling can also be reasonably excluded because in no case did total blood loss exceed 120 ml and because comparable renin responses were seen in patients in the pilot study who had very small bleeding, as in those who were later thoroughly investigated.

The ability of the kidney to autoregulate blood flow during an acute reduction in perfusion pressure is poorly understood. Our results confirm the occurrence of acute autoregulation, but they do not shed any new light on the mechanisms responsible. Vasodilatation persists even when plasma renin becomes definitely elevated (fig. 1), which suggests that renal autoregulation mechanisms, at least in a very early stage of renal perfusion pressure reduction, are not affected by the renin-angiotensin system. This introduces a reverse consideration of the problem, i.e., the role of the renal vasodilatation in the promotion of renin release. The finding that systemic renin activity clearly tended to revert toward normal within 15 minutes after release of the occlusion, when renal vascular resistance was still reduced and blood flow augmented, strongly contrasts with the concept that renal vasodilatation is the primary mechanism for the enhanced renin secretion. This is in agreement with experimental findings in dogs.13 Based on studies of Tobian et al.,14 Skinner et al.,15 and Blaine et al.,16-18 we believe that stimulation of the vascular receptors in the afferent arteriole, caused by changes in the transmural pressure gradient, is responsible for the augmented release of renin.

The excessive renin secretion from the occluded kidney resulted in almost complete suppression of renin secretion from the contralateral kidney (fig. 2), duplicating the classic Goldblatt hypertension.19, 20 However, systemic blood pressure did not vary during the studies in either normotensive or hypertensive subjects, and neither heart rate nor cardiac output changed significantly. This makes unlikely the possibility of an intervention of buffer mechanisms, such as baroreceptor activation, restraining or preventing the tendency of arterial pressure to increase; it also proves, more convincingly than the measurement of blood pressure alone, that an acute increase in circulating renin has no circulatory effects in normotensive or hypertensive man. These findings are very puzzling.

Conversion of angiotensin I to the vasoactive angiotensin II is an obvious requirement for the blood pressure to increase in response to augmented release of renin. Although angiotensin II was not measured, we would not support the interpretation that the time elapsed was insufficient for all angiotensin I generated by renin to be converted to angiotensin II, because conversion takes place rapidly and suppression of renin release from the contralateral kidney probably reflects angiotensin II's inhibition of renin from that kidney.

The hypothesis that the subjects selected for this study were incapable of reacting to angiotensin II seems inconsistent considering that none of the 24 subjects showed appreciable pressure variations during renal artery occlusion.

Therefore, selective reduction of renal perfusion pressure in man duplicates the quality of the renin response to the same stimulus in animals, but does not duplicate the circulatory response. This evidence, of course, applies only to a narrowing of the renal artery for 1 hour and does not apply to the increase in blood pressure that might occur after the renal artery has been narrowed for a longer duration. It is not known if enhanced renin secretion per se can elevate the blood pressure, or if the subsequent intervention of additional factors is required to induce chronic Goldblatt hypertension in humans.

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