Renal Artery Stenosis with Normal Angiotensin II Values

Relationship Between Angiotensin II and Body Sodium and Potassium on Correction of Hypertension by Captopril and Subsequent Surgery


SUMMARY The case is reported of a young woman with severe hypertension, unilateral renal artery stenosis, variously normal or marginally high plasma concentrations of active renin, angiotensin II, aldosterone, sodium, and potassium; and normal total exchangeable and total body sodium and potassium. Arteriograms and ureter catheterization showed the stenosis to be severe, but the unstimulated renal vein renin and angiotensin II differential to be modest. Captopril caused an initial fall in angiotensin II and arterial pressure. During prolonged captopril treatment, plasma angiotensin II and aldosterone remained depressed; exchangeable and total body sodium and potassium were unaltered. Blood pressure fell further to normal levels during prolonged captopril treatment, while subsequent surgical correction of the renal artery stenosis was curative; absolute values of blood pressure and plasma angiotensin II were similar in both situations. The findings support, without proving, the concept that chronic modest elevation of angiotensin II may be responsible for sustained hypertension in unilateral renal artery stenosis. Patients of this type contrast sharply with those, also with severe renal artery stenosis or occlusion, who have gross elevation of renin, angiotensin II, and aldosterone, with sodium and potassium deficiency. Captopril or surgery are effective in both syndromes, but the manner of response to treatment differs markedly. (Hypertension 3: 53-58, 1981)

KEY WORDS • renal artery stenosis • renin • angiotensin II • body composition • captopril

IMMEDIATE rise in blood pressure following unilateral renal artery constriction, with the opposite kidney and renal artery remaining untouched, can be explained by the initial consequent increase in circulating plasma angiotensin II. After the first few days, however, peripheral plasma levels of renin and of angiotensin II are lower than needed to sustain comparable hypertension in the first phase. It is in this second phase that hypertension due to renal artery stenosis is usually first encountered in humans. The role, if any, of the renin-angiotensin system in chronic hypertension with unilateral renal artery stenosis therefore remains uncertain.

Some workers have suggested that mechanisms independent of renin are responsible; others, that a slow pressor action of angiotensin II may come into play. For these reasons, it is important to analyze the renin-angiotensin system during chronic treatment with converting enzyme inhibitors, and compare results with the subsequent response to renal artery surgery. Assessment of concurrent changes in exchangeable and total body sodium and potassium could also yield valuable information.

We have previously reported in detail a patient with unilateral renal artery occlusion, intense, continued renin secretion from the affected kidney, sodium and potassium depletion, and secondary aldosterone excess. In that case, all the abnormal features were corrected by preoperative treatment with the orally active converting enzyme inhibitor, captopril, and by subsequent nephrectomy.

The present report concerns a markedly different syndrome. A severely hypertensive young woman with unilateral renal artery stenosis presented with predominantly normal peripheral venous plasma concentrations of renin and angiotensin II and normal serum electrolyte concentrations. Blood pressure was corrected initially by long-term treatment with captopril, and subsequently by renal artery reconstruction. Plasma angiotensin II concentrations have been related to mean arterial pressure (diastolic plus one-third pulse pressure) and to total exchangeable and total body sodium and potassium before treatment, and at various stages of therapy.

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Case Report

A 25-year-old married white woman with a 2-year history of severe headaches was found to have a blood pressure of 210/125 mm Hg. She had had one pregnancy 2 years previously during which blood pressure was said to have been raised in the last 3 months, but she went to full term and delivered normally. Subsequently, she was prescribed an oral contraceptive (ethinyl oestradiol, 50 µg, and nor-ethisterone acetate, 1 mg daily), which she was still taking at presentation. The oral contraceptive was then stopped, and she began taking metoprolol, 200 mg twice daily, with Moduretic (hydrochlorothiazide, 50 mg, plus amiloride, 5 mg) one tablet daily, and prazosin, 1 mg three times daily. Fourteen months later, however, blood pressure remained severely elevated (180/110 to 210/150 mm Hg). The prolonged interval after stopping hormonal contraceptive therapy suggested this was unlikely to be a direct contributor to the hypertension; in a series of 26 initially normotensive women who became hypertensive on oral contraceptives, blood pressure reverted to normal within 1 year of stopping treatment.* She was referred for further investigation to the Medical Research Council Blood Pressure Unit.

Excretion urography showed the right kidney to be 12.5 cm long and the left 15.0 cm long; the appearances were typical of right renal artery stenosis, with initial delay followed by marked increase in contrast density on the right. Selective right renal arteriogram showed a tight stenosis in the middle of the main renal artery, with collateral circulation via the lumbar arteries. Ureteric catheter studies (table 1) showed classical features of severe unilateral renal artery stenosis, with marked reduction of urine flow, urinary sodium, creatinine and para-amino hippurate (PAH) clearances, and increased urinary creatinine and PAH concentrations, on the right.

Antihypertensive therapy was changed to bethanidine only, 10 mg four times daily. This was to facilitate evaluation of the renin-angiotensin system because the drug is short-acting, and should not influence renin release for long after being withdrawn. Four weeks later, 14 hours after the last dose of bethanidine, simultaneous blood samples were obtained from right and left renal veins and the aorta and also (but not simultaneously) from the inferior vena cava below the renal veins, for renin and angiotensin assay. The results (table 2) showed slightly higher mean levels of both active renin and angiotensin II in the right as compared with the left renal vein. On these figures, net secretion of active renin by the right kidney, although present, was not marked; there was a similar indication of slight net extraction of active renin and of angiotensin II across the contralateral kidney.

The patient was admitted to the metabolic ward for detailed assessment before starting captopril. Bethanidine treatment was stopped, and the patient took a fixed diet containing 146 mEq sodium and 49 mEq potassium daily. All blood samples (except, where stated, after captopril) were taken between 0830 and 0930 hours, after overnight recumbency and fasting. Assays were made of plasma concentrations of active renin (normal range 10–50 µU/ml), angiotensin II (5–35 pg/ml), and aldosterone (<18 ng/dl), and blood levels of angiotensin I (10–90 pg/ml). Plasma angiotensin II values during captopril treatment were corrected for cross-reaction with angiotensin I. Total exchangeable sodium (NaE) and potassium (KE), together with total body sodium (TBNa) and total body potassium (T BK) were estimated; the coefficients of variation for duplicate estimations in the same person were 1.8%, 1.9%, 4.2%, and 3.1% respectively.

Detailed findings, and the effects of captopril treatment, are summarized in table 3 and figures 1 and 2. Untreated plasma sodium and potassium concentrations were normal, as were NaE and KE. Peripheral plasma concentrations of active renin and angiotensin II were variously within or marginally above the upper end of normal range, and plasma aldosterone was normal, except in the third set of samples (table 3) when all three measurements were slightly but distinctly high. Figure 1 and table 3 show the effect of an initial 25 mg dose of oral captopril. Plasma angiotensin II and arterial pressure fell in parallel, while circulating concentrations of active

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

**Figure 1.** Response of supine blood pressure, angiotensin I, and angiotensin II to the initial dose of 25 mg captopril.
renin and angiotensin I increased. Over the next 9 days, the captopril dose was increased to 150 mg three times daily; good control of blood pressure was achieved (fig. 2).

Six weeks later, the patient was readmitted for full assessment while taking captopril and the same fixed diet as before. The results (table 3) showed sustained reduction of plasma angiotensin II and aldosterone despite marked elevation of active renin. Plasma sodium and potassium concentrations, TBNa, NaE, and KE were not appreciably altered during captopril treatment, while TBK had risen slightly. The patient was referred for surgery, taking a final dose of 75 mg captopril 2 hours before operation. A pressure gradient of 22 mm Hg mean pressure was demonstrated across the stenosis. A dacron graft was inserted from the aorta to the distal renal artery, eliminating this gradient.

Four months after operation, in which time the patient needed no treatment, she was again admitted to the ward and assessed on the same diet as before. The results (table 3) showed sustained reduction of plasma angiotensin II and aldosterone despite marked elevation of active renin. Plasma sodium and potassium concentrations, TBNa, NaE, and KE were not appreciably altered during captopril treatment, while TBK had risen slightly. The patient was referred for surgery, taking a final dose of 75 mg captopril 2 hours before operation. A pressure gradient of 22 mm Hg mean pressure was demonstrated across the stenosis. A dacron graft was inserted from the aorta to the distal renal artery, eliminating this gradient.

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previously (table 3). Plasma concentrations of active renin, angiotensin II, and aldosterone were similar to values obtained before starting captopril; plasma electrolytes were normal, and body weight, NaE, and TBK had risen slightly. The patient remains well; her angiotensin II concentration and arterial pressure at various stages of her illness are shown in figure 3. The trolytes were normal, and body weight, NaE, and values obtained before starting captopril; plasma electrolytes were normal, and body weight, NaE, and TBK had risen slightly. The patient remains well; her angiotensin II concentration and arterial pressure at various stages of her illness are shown in figure 3. The upper regression line describes the correlation between plasma angiotensin II and mean arterial pressure in a group of untreated hypertensives with an associated renal lesion. The lower regression line describes this correlation in normal subjects infused for a short time with angiotensin II. All data were obtained under identical circumstances in recumbent subjects who had taken similar diets and fasted overnight. Before treatment, the present patient showed values, as expected, near the upper regression line. After the initial dose of captopril, both plasma angiotensin II and arterial pressure fell, but the relationship remained near the regression line of established renal hypertension. After 5 weeks of captopril treatment, while angiotensin II remained similarly depressed, the arterial pressure fell further, therefore approaching a normal relationship. After operation, normal values, and hence a normal relationship, persisted.

Discussion

The findings at renal venous sampling in the present patient are consistent with those reported in larger series from this department, in which only minor variations were usually encountered during the sampling procedure. Mean plasma concentrations of active renin and of angiotensin II were slightly higher in the right than in the left renal vein. Renin concentrations were also higher in the right renal vein than in the aorta, although the net renin secretion rate from the affected right kidney was modest in relation to the severity of the stenosis as assessed arteriographically and at ureter catheterization.

It is possible that the modest renal vein renin ratio may have been due to sampling from a segmental renal vein, as venography was not performed. This vein may not have been draining a markedly ischemic area. However, this possibility can be discounted as the renal artery stenosis was marked and occurred in the proximal portion of the single renal artery. As in some cases of unilateral renal disease in the earlier series, peripheral plasma angiotensin II concentrations were slightly higher than in either renal vein, indicating that angiotensin II generation in renal veins is incomplete. It is not clear why higher peripheral concentrations of active renin were found during renal vein sampling than subsequently, particularly as plasma angiotensin II levels were not greatly different. The modest renin secretion rate from the affected kidney accords with the finding of peripheral plasma concentrations of active renin and of angiotensin II variously slightly elevated or in the upper part of the normal range. Several procedures have been proposed with the aim of provoking renin secretion and thus enhancing both peripheral renin levels and the renal vein renin differential. However, we deliberately did not employ such maneuvers because we wanted quantitative data that could be related to similar measurements made in other recumbent patients and normal volunteers under comparable circumstances.

The present case appears analogous to experimental animals observed in the second, established phase of one-clip, two kidney “Goldblatt” hypertension. In that animal model, during the first phase, which follows immediately upon unilateral renal artery constriction, the rise in blood pressure is explicable by the initial rise in renin and the direct pressor effect of the consequent elevation of plasma angiotensin II. Within a few days, a second phase develops in which blood pressure remains high but plasma concentrations of renin and angiotensin II are proportionately lower. The renin-angiotensin system might still, however, be responsible for the hypertension in this second phase, because prolonged infusion of angiotensin II at a low dose has been shown in various species to cause a gradual increase in arterial pressure, and the plasma angiotensin/blood pressure dose-response relationship is demonstrably enhanced in these circumstances. Possible factors involved in long-term resetting of the angiotensin II/blood pressure dose-response curve have been discussed.

The relationship between plasma angiotensin II and arterial pressure during long-term captopril therapy changes progressively, eventually becoming very similar to that after renal artery surgery (fig. 3). This
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is consistent with the concept of reversal of a slow pressor action of angiotensin II. It does not constitute proof of such a mechanism, however, particularly because captopril may well lower blood pressure by mechanisms additional to angiotensin II reduc-

The present case reemphasizes that, at least in the recumbent unstimulated patient with renal artery stenosis, peripheral plasma concentrations of angiotensin II (or renin) do not require to be above the normal range, and the renal venous renin ratio does not need to be markedly raised for treatment either by reconstructive surgery or by captopril to be successful. This accords with several earlier instances that have been described of successful surgical intervention in renovascular hypertension with normal plasma renin. Moreover, Gavras and colleagues reported a good response to oral captopril in renal artery stenosis with normal peripheral renin levels, although few details were given. We are however, not aware of similar cases in which both surgery and captopril were separately beneficial, and in which plasma angiotensin II was measured at each stage.

The balanced pathophysiological and biochemical state seen before treatment in the present patient con-

stance that the markedly raised plasma angiotensin II concentration led to hypertension, natriuresis from the contralateral kidney, and thus to the observed sodium depletion, secondary aldosterone excess, and potassium depletion with severe hyponatraemia and hypokalaemia. There was evidence of progressively increasing renin secretion with rapidly worsening sodium and potassium deficiency. Despite advancing hypertension, the severity of the unilateral renal artery lesion apparently prevented a new steady state from being achieved. An immediate and pronounced fall in pressure was observed after the initial dose of captopril in this earlier patient; all the abnormal features were corrected by oral captopril and by subsequent unilateral nephrectomy.

In the present patient, by contrast, equilibrium was attained despite marked unilateral renal artery stenosis, with only marginal elevation of peripheral plasma renin and angiotensin II concentrations, and normal body sodium and potassium composition. Possibly severe systemic hypertension minimized the stimulus to renin secretion distal to the stenosis. If this was so, however, it was not sufficient to correct a markedly ischemic pattern at ureter catheterization. The case reported here represents a distinct, and much commoner, syndrome of renovascular hypertension, in which pathogenic involvement of the renin-angiotensin system, although likely, is less evident. The findings are consistent with, but do not prove, an important pressor action of angiotensin II, of slow onset and offset, in the established phase of hypertensive renal artery stenosis.

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