

Unilateral "Page Kidney" Hypertension in Man

Studies of the Renin-Angiotensin-Aldosterone System Before and After Nephrectomy

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• Hypertension developed in a 17-year-old boy one year after a flank injury. Intravenous pyelography showed a slightly smaller kidney on the injured side. Renal arteriography demonstrated unilateral decreased vascular filling. Renal vein renin ratios suggested an ischemic kidney, as did split-function studies. Nephrectomy cured the hypertension. Detailed studies before and after nephrectomy suggested that hyperactivity of the renin-angiotensin-aldosterone system may participate in the pathophysiology of this unusual cause of hypertension in man.

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FIBROUS encapsulation of the kidney is a rare, curable cause of hypertension in man.¹⁻⁶ The present report describes a detailed investigation into the renin-angiotensin-aldosterone system before and after removal of an encapsulated kidney that resulted in the cure of hypertension.

METHODS

All studies were performed in the Clinical Research Center. Our methods and normal values for measuring plasma renin activity, plasma aldosterone, and urinary aldosterone have been described in detail elsewhere,⁷ as have the details of examining the circadian rhythm of plasma renin activity and plasma aldosterone.⁷

Renal vein samples were obtained

while the patient was supine, and he was then tilted to 45° for 20 minutes, at which time repeat samples were taken.⁸ All medication had been discontinued at least two weeks before the study. The renal vein study was performed the day following a low-salt diet (10 mEq/day for one day) and the administration of furosemide at 10 AM, noon, and 4 PM.^{9,10} Right and left ureteral urine samples were obtained during a time when the patient was ingesting a normal sodium intake.

REPORT OF A CASE

In August 1970, at age 16 years, this white young man had a blood pressure of 120/72 mm Hg on a routine physical examination prior to participation in football. In September 1970, he received a blow to the right flank during football practice. For several days he noted pain and a large bruise in this area. No gross hematuria was noted. In November 1970, the patient began to notice an intermittent, dull, right flank aching. In June 1971, he noted headaches and a sense of fatigue. On a routine

prefootball physical examination in August 1971, his blood pressure was recorded as 160/90 mm Hg, and treatment with methyldopa and hydrochlorothiazide was begun. An intravenous pyelogram showed some delayed filling of the right kidney. He was referred to our institution for further evaluation of his condition. The patient's father and two uncles had a history of hypertension. The blood pressure of the patient was now 150/95 mm Hg. Otherwise, the physical examination gave normal findings. Laboratory tests gave the following results: sodium, 139 mEq/liter; potassium, 4.3 mEq/liter; chloride, 91 mEq/liter; bicarbonate, 26 mEq/liter; blood urea nitrogen (BUN), 13 mg/100 ml; and creatinine, 1.2 mg/100 ml. The urine had pH of 7, a specific gravity of 1.015, and no protein; microscopic examination showed normal findings.

Contrast Media Studies and Renin Determinations

A rapid-sequence intravenous urographic study showed equal appearance of contrast media bilaterally. A tomogram (Fig 1) demonstrated calyceal distortion of the upper pole of the right kidney. The left kidney was normal. There was no appreciable difference in renal size. A retrograde aortogram (Fig 2) demonstrated normal single renal arteries bilaterally. There was early branching of the left renal artery without luminal narrowing. However, the intrarenal vasculature on the right had a definite decrease in arborization. On the nephrographic phase (Fig 3), the outer contour of the kidney was smooth, but there was a reduced and nonuniform cortical opacification with contrast media.

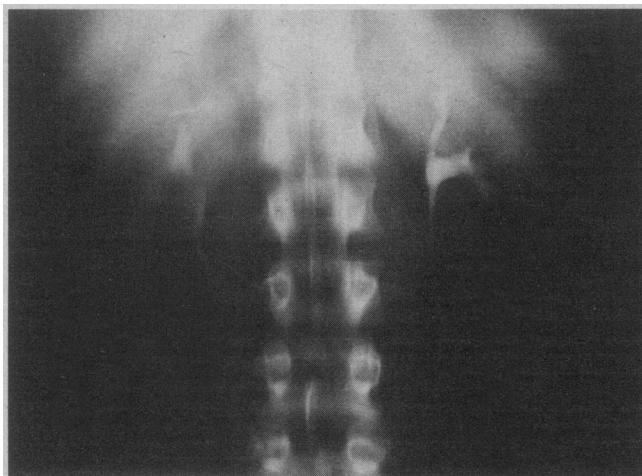


Fig 1.—Tomogram of rapid-sequence urogram. Prompt appearance of contrast media bilaterally with distortion of right upper pole calyx demonstrated.

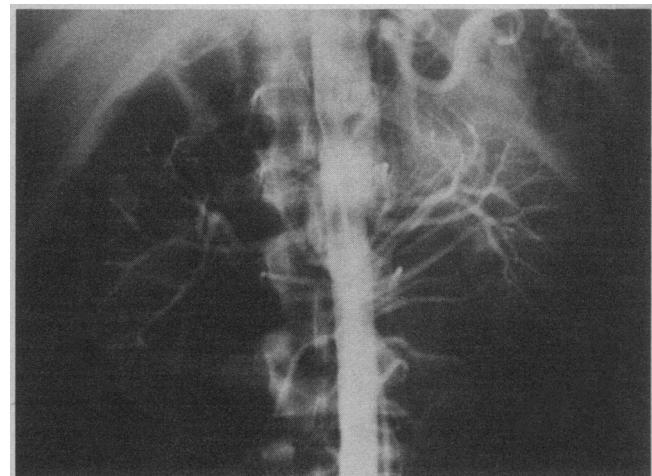


Fig 2.—Retrograde aortogram. There are normal renal arteries bilaterally with early branching on left. Branching of intrarenal vessels on right is markedly decreased.

Renal vein renin measurements following sodium depletion with furosemide (Table) demonstrated that renin was being released in increased quantities from the right kidney. Antihypertensive therapy was attempted with hydrochlorothiazide, propranolol hydrochloride, and hydralazine hydrochloride without much change in blood pressure. The patient continued to feel fatigued and had frequent headaches. All medication was therefore discontinued for one month, and he was admitted in November 1972 to the Clinical Research Center for the studies of the circadian rhythm of renin and aldosterone. Right and left ureteral urine samples were also collected. The right urinary sodium concentration was 27 mEq/liter, and that of creatinine was 0.13 mg/100 ml. The values from the left side were 45 mEq/liter and 0.08 mg/100 ml, respectively. This was evidence of an "ischemic kidney."¹¹

Because of the unusual nature of these findings in a patient with decreased perfusion as shown by aortogram of this kidney, open renal biopsy was performed on the right. The posterior aspect of the kidney was surrounded by a dense fibrous capsule that could not be removed. It was only after the patient had recovered from this surgery that he recalled, on careful questioning, the history of flank trauma. Treatment with propranolol hydrochloride and hydrochlorothiazide was again resumed, and the dosages were increased to 400 mg/day and 100 mg/day, respectively. However, blood pressure readings taken at home continued to average 150/95 mm Hg, and the patient did not feel well. Therefore, after nine months of treatment, it was decided to proceed with nephrectomy. After nephrectomy, blood pressure rapidly

returned to normal and has remained so for one year. The repeat study of the circadian rhythm was done three months after nephrectomy.

Pathologic Examination

The kidney measured 11×6.5×5 cm. The posterior surface was encased in a thick fibrous capsule (Fig 4). No involvement of the hilus was noted. The anterior surface was entirely normal. On cross section only the posterior aspect showed the areas of scarring. The scarring appeared to encapsulate certain segments of the renal cortex. On microscopic examination, no difference between the encapsulated and nonencapsulated areas was noted. No arteriolar nephrosclerosis was apparent.

RESULTS

Blood pressure before surgery averaged 140/98 mm Hg; after surgery, it was 121/72 mm Hg ($P=.005$) (average of six days' blood pressure readings during the circadian rhythm study). The results of the detailed measurements of peripheral plasma renin activity and plasma aldosterone, under controlled conditions of sodium intake, before and after nephrectomy, are shown in Fig 5. Prior to surgery, peripheral plasma renin activity was in the normal range at all times, except at 8 PM on day 5. Following surgery, results of seven of the nine determinations were lower than preoperative determinations. With use of the Wilcoxon match-pairs signed-ranks test, the distribution

Renin Studies		
Sample Site	Renin by Angiotensin I, ng/ml/hr	
Recumbent		
Right renal vein	30.7	
Left renal vein	19.6	
Tilt		
Right renal vein	51.6	
Left renal vein	24.3	
Inferior vena cava	34.1	

of plasma renin activity after surgery was lower than before surgery ($P=.025$). Similarly, all of the preoperative peripheral plasma aldosterone values were in the normal range, except for the 8 PM value on day 5 that was above the upper limit of normal observed at that time. Following surgery, peripheral plasma aldosterone level decreased in seven of the eight time periods studied ($P=.05$), and all values were in the normal range.

Urinary aldosterone excretion prior to surgery was 10.2 μ g/24 hr, and 2.6 μ g/24 hr after surgery.

When taken together, these results suggested that the level of activity of the renin-angiotensin-aldosterone system was greater before than after cure of hypertension.

COMMENT

In 1939, Page¹ first produced hypertension in the dog by wrapping one kidney in cellophane; wrapping led to



Fig 3.—Right kidney has smooth cortical margin and decreased accumulation of contrast medium.



Fig 4.—Two cross sections of kidney. Left section was from lower half of kidney and right section from upper half of kidney. Hilus is on the right in each section. Areas of fibrous capsule are to the left of each section.

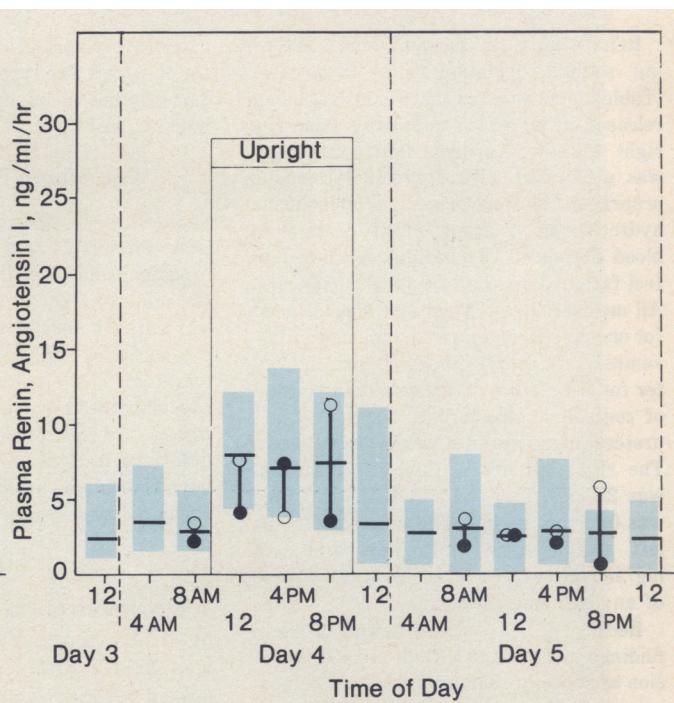
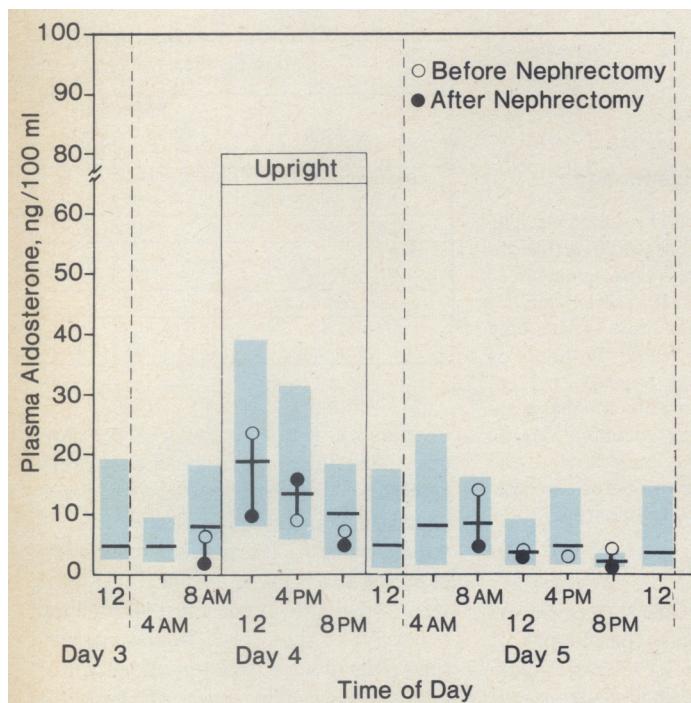


Fig 5.—Plasma renin activity (right) and plasma aldosterone (left) in patient before and after nephrectomy. Shaded bars represent the absolute range of values found in normal subjects. Horizontal line in each bar represents mean value of normal subjects at that sampling time.

formation of a dense fibrocollagenous hull that encased the kidney. Plasma obtained from these animals contained a substance compatible with what is now called renin.

From more recent animal studies¹²⁻¹⁴ that make use of unilateral encapsulation with the contralateral kidney untouched, it is evident that the encapsulated kidney contains and releases more renin than its un-

touched mate. Furthermore, the peripheral renin level tends to be "normal."

In man, we could find only two reports of renal vein renin determinations^{4,15} in this disease. Both patients had a higher renal vein renin concentration on the involved side. Abnormal results of split-function tests have also reported to be present in several such patients.^{3,4,15}

Mechanisms Influencing Levels of Plasma Renin

The clinical characteristics of this type of curable hypertension have been reviewed.⁵ In brief, these patients tend to be young men, the causative trauma may or may not be recalled by the patients, and the hypertension tends to be mild.

The present report demonstrates

that the level of activity of the renin-angiotensin-aldosterone system decreased in a patient when the encapsulated kidney was removed. The failure to find frankly increased circulating levels of plasma renin activity would seem to militate against any role for this pressor system in the continuance of the hypertension. However, it has been demonstrated that the renin content of the contralateral kidney is subnormal in this form of experimental hypertension, and normal to increased on the "wrapped" side.¹² The suppression of renin secretion in the contralateral (normal) kidney probably results from the effects of circulating renin released from the ischemic kidney. As renin is released by the ischemic kidney, peripheral angiotensin II levels increase. An increase in angiotensin II can directly suppress renin release¹⁶ as well as cause sodium retention.¹⁷ The sodium retention would result in volume expansion that would suppress renin secretion from both kidneys. Finally, the cumulative effects of volume expansion and increased levels of angiotensin II would raise the perfusion pressure to the normal kidney, which would also tend to decrease its renin release. Assum-

ing no changes in the rate of metabolic clearance of renin, this combination of events would tend to minimize increases in level of peripheral renin produced by a unilateral source of renin; ie, as renin production by the ischemic kidney increases, the renin production by the contralateral kidney would decrease, so that the peripheral level (the sum of the production by the two kidneys) might remain in the "normal" range, although greater than what the level had been before the ischemia developed. The identification of "hyperactivity" of the renin-angiotensin-aldosterone system in such a physiological disturbance would then rely on demonstrating that when the source of the disturbance was removed, the level of activity would decrease—perhaps from high "normal" level to a low or mid—"normal" level of activity. We have previously reported¹³ similar changes in plasma renin activity and plasma aldosterone following correction of unilateral renal artery stenosis.

The results of the renal vein renin determinations support the concept that the contralateral kidney is secreting no renin.¹² The renin level in the sample obtained from the inferior

vena cava was higher than in the uninvolved renal vein (Table). This demonstrated that the contralateral kidney added no renin to blood passing through it (and indeed, appeared to be extracting renin). This finding was emphasized by Stockdit, et al¹⁸ as being suggestive of contralateral hypersecretion of renin. Others have recently confirmed this finding.¹⁹

A diligent search for a history of flank trauma in patients with hypertension should always be performed. A normal intravenous pyelogram does not exclude this diagnosis. Peripheral plasma renin activity will most likely be normal. The combination of history, renal arteriography, and renal vein renin measurements should allow one to make this diagnosis.

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The patient was referred by R. John Torontow, MD, Nevada, Mo.

Nonproprietary Names and Trademarks of Drugs

Propranolol hydrochloride—*Inderal*.
Furosemide—*Lasix*.

References

- Page IH: The production of persistent arterial hypertension by cellophane perinephritis. *JAMA* 113:2046-2048, 1939.
- Engel WJ, Page IH: Hypertension due to renal compression resulting from subcapsular hematoma. *J Urol* 73:735-739, 1955.
- Hellebusch AA, Simmons JL, Holland N: Renal ischemia and hypertension from a constrictive perirenal hematoma. *JAMA* 214:757-759, 1970.
- Marshall WH, Castellino RA: Hypertension produced by constricting capsular renal lesions ("Page" kidney). *Diagnos Radiol* 101:561-565, 1973.
- Massumi RA, Andrade A, Kramer N: Arterial hypertension in traumatic subcapsular perirenal hematoma ("Page" kidney): Evidence for renal ischemia. *Am J Med* 46:635-639, 1969.
- Grant RP, Gifford RW, Pudvan WR, et al: Renal trauma and hypertension. *Am J Cardiol* 27:173-176, 1971.
- Grim CE, Keitzer WF: Circadian rhythm of renin and aldosterone in unilateral renovascular hypertension: Pre and Postoperative studies. *Ann Intern Med* 80:298-304, 1974.
- Michelakis AM, Simmons J: Effect of posture on renal vein renin activity in hypertension: Its implications in management of patients with renovascular hypertension. *JAMA* 208:659-662, 1969.
- Marshall SJ, Grim CE: A rapid method to detect low renin hypertension. *Clin Res* 21:699, 1973.
- Strong CG, Hunt JC, Sheps SG, et al: Renal venous renin activity enhancement of sensitivity of lateralization by sodium depletion. *Am J Cardiol* 27:602-611, 1971.
- Rapoport A: Modification of the "Howard test" for the detection of renal-artery constriction. *N Engl J Med* 263:1159-1165, 1960.
- Gross F, Lichtlen P: Pressor substance in kidneys of renal hypertensive rats with and without adrenals. *Proc Soc Exp Biol Med* 98:341-345, 1958.
- Masson GMC, Yagi S, Kashii C, et al: Further observations on juxtaglomerular cells and renal pressor activity in experimental hypertension. *Lab Invest* 13:321-330, 1964.
- Biddal J, Masson GMC, McCubbin JW: Renin-like activity in kidneys of dogs with neurogenic and nephrogenic hypertension. *Am J Physiol* 208:1078-1082, 1965.
- Schroeder KF, Correa RJ: Hypertension resulting from an unusual pararenal pseudocyst. *J Urol* 96:119-121, 1966.
- De Champlian J, Genest J, Veyrat R, et al: Factors controlling renin in man. *Trans Assoc Am Physician* 78:135-148, 1965.
- Fourcade JC, Navar LG, Guyton AC: Possibility that angiotensin resulting from unilateral kidney disease affects contralateral renal function. *Nephron* 8:1-16, 1971.
- Stockdit JR, Noakes CA, Collins RD, et al: Renal vein renin in various forms of renal hypertension. *Lancet* 1:1194-1197, 1972.
- Vaughn ED Jr, Buhler FR, Laragh JH, et al: Renovascular hypertension: Renal measurements to indicate hypersecretion and contralateral suppression, estimate renal plasma flow and score for surgical curability. *Am J Med* 55:402-414, 1973.