Renin-Dependent Hypertension Caused by Nonfocal Stenotic Aberrant Renal Arteries

Proof of a New Syndrome

David C. Kem, Daniel F. Lyons, James Wenzl, Donald Halverstadt, Xichun Yu

Abstract—We have identified 2 relatively young patients with significant hypertension, an elongated single aberrant renal artery supplying blood to a renal segment, and evidence for localization of the elevated plasma renin activity to the side and vein draining the affected kidney. Furosemide-induced diuresis and acute oral captopril stimulated the renal vein/contralateral renin ratios to 4.3:1 and 6.5:1 in patients 1 and 2, respectively. These renal vein ratios are significantly higher than normal (>3:1 under similar conditions). Partial resection of the portion of the kidney affected by the aberrant tortuous artery led to a marked reduction in blood pressure in patient 1. Patient 2, not an operative candidate, responded satisfactorily to use of a converting enzyme inhibitor, which helped to confirm the dependency of the blood pressure on the abnormal flow relationship existing within that aberrant artery and the kidney. We believe these 2 patients are representative of a small but distinct subgroup within the larger number of patients with elongated single or multiple renal aberrant arteries. Each aberrant artery had no focal stenosis, although a decrease in flow relative to the tissue perfusion demands was apparent from the marked activation of the renin-angiotensin system in the venous system draining that artery. The increased length of such vessels may contribute to their decreased flow, although their average diameter may reside just above such a critical value for a normal length vessel. This new syndrome, involving more than one component of the flow/resistance relationship, has been overlooked when renin-dependent forms of hypertension are considered. (Hypertension. 2005;46:380-385.)

Key Words: angiotensin □ arteries □ hypertension, renal □ renin □ vessels

A possible association between accessory renal arteries and hypertension has been suspected over a long time. However, this relationship has received comparatively little attention in terms of its existence because of conflicting or inconclusive data, and many texts do not assign it pathophysiologic significance. It is not surprising that little literature exists as to possible etiologic factors.

Accessory renal arteries, like hypertension, are common. Variations of renal arteries are recorded from the mid-nineteenth century,1 and the frequency varies from 25% to 61% of cadavers.2–5 The association of hypertension with multiple renal arteries first appeared in the 1930s and included anomalies involving the renal pelvis as well.6–9 Since 1951, Marshall10 and other authors reported an increased presence of multiple renal arteries in hypertensive patients compared with normotensive patients.11–15 Within this population, some had focal stenosis of an aberrant artery and were identified as having a variant of classical renal artery stenosis and hypertension.

A persuasive literature supports a dominant role for activation of the renin-angiotensin system in maintaining the elevated systemic pressure in patients with unilateral renal artery stenosis.16–20 Recently, 2 reports21,22 have attempted to attach specific etiologic significance to the copresence of nonstenotic multiple renal arteries and a modest elevation of systemic renin activity discovered during evaluation of hypertensive subjects but failed to demonstrate a causal relationship.

We have examined this issue and identified a pathophysiologic relationship of the renin-angiotensin system to the tissues supplied by a single aberrant renal artery in 2 young patients. These aberrant arteries, with no radiographic evidence for a focal lesion, limited the effective perfusion in their respective renal segments and are etiologic in the pathogenesis of their hypertension.

Case Reports

The institutional review board has ruled that these case reports fall within its norms for protection of patient identity.

Patient 1

A 5-year-old boy with learning difficulties in kindergarten had a blood pressure of 190/130 and was referred to a local...
medical center. His blood pressure was partially controlled with propranolol, a diuretic, and spironolactone. An arteriogram was performed and no stenosis of renal vessels was observed. A nonstenotic aberrant artery arose from the common iliac artery near the aortic bifurcation and fed the lower pole of the right kidney. Nonstimulated renal vein renins were reported with a 2:1 right/left ratio. A renal biopsy was “normal.” The patient was reported as having “essential” hypertension and treated with diuretics and various antihypertensives including minoxidil with moderate reduction in blood pressures.

He was referred to the University of Oklahoma Health Sciences Center for a second opinion because his blood pressure was still elevated and he faced a lifetime of medical therapy. By this time he was 8 years old, his admission blood pressure was 154/104 on propranolol 50 mg twice per day and hydrochlorothiazide 50 mg/d. He demonstrated normal development and his physical examination was normal. There was I/VI systolic murmur over the aortic region and a physiological split first sound. There was no bruit over the abdomen or flank.

An arteriogram demonstrated an elongated, nonstenotic aberrant artery arising from the common iliac artery leading to the lower pole of the right kidney (Figure 1, upper panel). An ultrasound demonstrated the right kidney to be 9.4×3.5 cm, whereas the left was 8.8×3.8 cm. A 99mTc-DTPA flow study demonstrated perfusion to the left lower pole to be 66% compared with 33% for the right (Figure 1, lower panel). Overall function was 55% on the left and 45% on the right 3 minutes after injection. Sequential images after injection of 1 mCi of 131I-hippuran demonstrated symmetrical uptake bilaterally. Medications were discontinued for 24 hours and he was given 10 mg furosemide orally on the afternoon before bilateral renal vein catheterization. After baseline samples were obtained from the renal veins and a peripheral vein, he was given 25 mg of captopril orally. Samples were then obtained at 15-minute intervals. Plasma renin activity and plasma aldosterone concentration values are shown in Table 1. The basal plasma aldosterone/plasma renin activity (PA/PRA) ratio was relatively low at 1.8. The renal vein renin ratio peaked at 30 minutes after oral captopril with a (right/left) ratio of 4.3:1, compatible with that observed in patients with renin-dependent renovascular stenosis (>3:1 under similar conditions). The rapid decrease in the plasma aldosterone concentration confirmed that angiotensin II blockade was achieved by the captopril. The patient’s blood pressure decreased concurrently with administration of the captopril and remained suppressed for 4 to 6 hours.

After consideration between the physicians and the parents, a decision was made to perform a partial nephrectomy to eliminate the source of the apparent renin-dependent hypertension. During this operative procedure, the aberrant artery was carefully dissected to its junction with the right iliac artery. No thrill or abnormal thickening was palpable in its length. It was injected with methylene blue and then ligated and resected at its origin. The renal capsule was reflected and the blue-stained lower renal segment resected. The reflected capsule was subsequently used to cover the remaining renal surface tissue. Pathological examination demonstrated changes consistent with chronic intermittent ischemia with some fibrosis and focal sclerosis of glomeruli. No abnormality of the aberrant artery was observed. Postoperatively he did well and was discharged 7 days later. His blood pressure was 130/90 at the time of discharge while off of all medications. It was anticipated that this blood pressure was a residual of acquired vascular and renal changes from the marked hyper-
tension and would improve with time. A follow-up visit 1 month later demonstrated a peripheral blood pressure of 120/70 off of all medications. He was to be followed-up by his local physicians and was not seen again in our pediatric clinic. Subsequent attempts at follow-up were frustrated by the patient and his family moving on several occasions and recent attempts at a computer-based name/birth date search in the USA have been unsuccessful in locating him.

**Patient 2**

A 16-year-old girl had a difficult childhood with variable periods of alienation from her family. She was followed in the adolescent clinic and observed to have significant hypertension with values as high as 220/115. This was occasionally brought under reasonable control when contact with the physician was maintained over a few months. Physical examination before her studies demonstrated a blood pressure of 140/100 on metoprolol 50 mg twice per day and hydrochlorothiazide 50 mg/d. She had Keith Wegener (KW) retinal changes. Her heart and lungs were normal. An arteriogram revealed a nonstenotic aberrant artery arising from the lower aorta feeding the lower pole of the left kidney (Figure 2, upper panel). A $^{99m}$Tc-DTPA flow study demonstrated perfusion to be equal in both kidneys with no differential to the lower poles (Figure 2, bottom). Sequential images after injection of 1 mCi of $^{131}$I-Hippuran demonstrated symmetrical uptake bilaterally.

The metoprolol and hydrochlorothiazide were withdrawn 4 days before her selective renal vein studies and she was given 10 mg furosemide orally on the afternoon before the study. Baseline samples were obtained from the renal veins and a peripheral vein, followed by 25 mg of captopril orally. Similar samples were obtained at 15-minute intervals. The plasma renin activity and plasma aldosterone values are shown in Table 1 and the appropriate ratios are calculated as defined. The basal PA/PRA ratio was 1.3. The renal vein renin ratio peaked at 15 minutes after oral captopril with a (right/left) ratio of 8:1. Her plasma aldosterone decreased to its lowest value at 30 minutes and her blood pressure decreased concurrently and remained suppressed for 4 hours.

It was decided that the patient was not in a position to give informed consent, because of her psycho/social status, for a possible left partial nephrectomy and she was followed in the pediatric adolescent outpatient clinic. Her blood pressures were generally well-controlled when she took medications

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>MAP</th>
<th>L Renal Vein PRA</th>
<th>R Renal Vein PRA</th>
<th>Ratio</th>
<th>Peripheral PRA</th>
<th>Peripheral PA</th>
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MAP indicates mean arterial pressure; PA, plasma aldosterone expressed in ng/dL [conversion factor to SI (pmol/L) = 27.741]; PRA, plasma renin activity expressed in ng/mL per hour [conversion factor to SI (ng/L per second) = 0.2778].
that included captopril, a diuretic, and a β-blocker. She was lost to follow-up after age 19 and subsequently died at age 24 of an unknown cause. A postmortem examination failed to establish any cause for her death other than some nonspecific acute cardiac changes. Although various drug-related issues were present over the years, no specific relationship was established at the time of the postmortem examination. Only casual reference to the kidneys was made in the postmortem report.

**Discussion**

These 2 patients demonstrated the onset of relatively severe hypertension at a young age and were examined carefully. Both had a relatively long and tortuous aberrant renal artery with no arteriographic evidence for stenosis in either the aberrant or main renal arteries. Both were subsequently found to lateralize renin secretion, with high values coming from the renal vein serving the aberrant vessel. The elevated blood pressure in both patients was related to elevated angiotensin II levels, as evidenced by an acute response to blockade of angiotensin I-converting enzyme. Each was presented to our bimonthly hypertension ground rounds where evaluation of the angiograms and other relevant data were made by hypertension, vascular, radiological, and surgical specialists in a critical atmosphere. Additionally, patient 1 had a marked reduction in blood pressure after resection of the portion of the kidney dependent on blood flow from the elongated aberrant artery and he was able to be taken off of all medications. Although a renal segmental resection was not attempted in patient 2, the circumstances are quite similar to those in patient 1. These data support our contention that there was relative ischemia in the tissues served by these elongated but not focally stenotic aberrant renal arteries.

We believe these 2 patients represent a subset of patients with elevated blood pressure who have one or more aberrant arteries that are not sufficient to supply their respective renal tissues adequately. This resultant ischemia is comparable to that observed in renal artery stenosis and is capable of inducing a hypertensive state comparable to that observed with renovascular hypertension. Support for this thesis has been presented by Glodny et al who measured peripheral plasma renin activity in a group of hypertensive patients with a concurrent aberrant renal artery(s) and compared this to a matched control group of hypertensive patients without aberrant renal arteries. The peripheral plasma renin activity was higher in the group with aberrant arteries and the authors suggested there might be some relationship between these observations but could offer no specific proof of this concept.

There was a marked unilateral renin release in our 2 patients despite the relatively small contribution the venous effluent from the affected segment would make to the combined venous effluent from the other 4 of the 5 segments normally found in the kidney. These studies were performed while the patient was recumbent, making it unlikely that "ptosis" of these arteries was a factor in the altered ratios. Additionally, demonstration that surgical resection of the affected ischemic area and/or reduction of blood pressure using a relatively specific pharmacological agent (captopril) provides a reasonable expectation that this syndrome may be also present in a subset of other hypertensive patients with associated aberrant renal arteries. Attempts to validate this concept are difficult because this subgroup is probably a minority of those patients with aberrant renal arteries. Radiologists routinely consider aberrant vessels to be a normal variant and describe them as such. The cost and risks for such invasive procedures make it unlikely that these will be pursued as a sole object of further studies. One of our 2 patients demonstrated an abnormal renal flow study, but these have been difficult to interpret and if we did not have the concurrent arteriogram and renal venous renin results, it is likely that it would have been overlooked.

Future diagnostic efforts to identify such patients might include use of the lower end of patients screened with a PA/PRA ratio. Each had a peripheral PA/PRA ratio of <2.0 with an absolute PRA value of >5 ng/mL per hour despite being on a combination of a β-blocker and a diuretic. This would support a renin-dependent hypertension. The use of spiral CT or MRI angiogram technology modified to provide renal tissue flow capability would provide a noninvasive examination to identify the renal arteries for stenosis, and these generally demonstrate the presence of an aberrant artery. An additional advantage resides in their ability to demonstrate venous effluent, so an aberrant vein draining this region also could be identified with reasonable accuracy. Confirmation would then be performed by measuring stimulated renal vein renins as previously published. Because of dilutional effects from the ipsilateral normally perfused segments, it would be important to either obtain segmental venous effluent renins and/or use efforts to maximally stimulate the abnormal segment while the renin released from the normal segments is still suppressed. This may be difficult to achieve in those patients on long-term diuretic therapy. However, we have reported that the acute administration of furosemide on the day preceding the study and an oral converting enzyme inhibitor immediately after obtaining the baseline values followed by sampling renal vein renins and a peripheral renin at 15 and 30 minutes led to differentiation and accurate prediction of a successful operative outcome in 15 of 17 patients with conventional unilateral or bilateral renal artery stenosis. Several of these patients had been on a diuretic before the study. Our 2 patients demonstrated a relatively sharp and transient increase in the renal venous ratio and would have been missed if not for multiple sampling. The application of other techniques and criteria for this diagnosis would need to take these issues into consideration.

The Poiseuille equation rearranged to $R = \frac{8\mu L}{\Delta P \pi R^4}$ (where $R =$ resistance, $\mu =$ viscosity, $L =$ length of vessel, $8 =$ constant, $P =$ pressure, $\pi =$ constant, and $R =$ radius of the vessel) suggests that both the radius and the length of the vessel may be operative in our patients. The average diameter of aberrant arteries in infants is $\approx 1.0$ to $1.5$ mm, whereas those in the early teens may be $1.5$ to $2.0$ mm despite growth and the expected increased demand for tissue perfusion consequent to that growth. It is therefore possible that some combination of restrictive average diameter and abnormal length of such aberrant vessels may lead to critical underperfusion of the affected renal segment and activation of the
renin-angiotensin system and its consequent impact on systemic blood pressure.

We have made theoretical estimates of the resistance (R) for the arterial supply of the right kidney in patient 1. These are based on measurements of the diameter and length of the major trunk of the right kidney and for the aberrant artery. The renal artery resistance associated with a series comprised of a normal segment, stenosis, and normal segment can be treated as resistances in series: $R_{\text{total}} = R_{\text{Segment}} + R_{\text{Pathologic}} + R_{\text{Segment}}$.

For the present purpose, the increased resistance associated with a focal stenosis would be:

$$R_{\text{Pathologic}} = 8 \mu L_{\text{Stenosis}} / \pi R_{\text{Stenosis}}^4$$

Assuming the radius of a stenosis ($R_{\text{Stenosis}}$) of 0.125 cm (50% stenosis) in a normal renal artery having a radius R ($R_{\text{normal}}$) of 0.25 cm, a stenosis length ($L_{\text{Stenosis}}$) of 0.5 cm, and a blood viscosity ($\mu$) of 0.05 poise, the calculated additional resistance necessary for manifestation of the pathology is 261 (dyn/cm²)/(cm³/s). To predict what added length of a relatively large aberrant artery with a radius $R = 0.25$ cm would result in the same increased resistance:

$$R_{\text{Pathologic}} = 8 \mu L_{\text{Incremental Length}} / \pi R^4$$

Solving for the incremental length, we have:

$$L_{\text{Incremental Length}} = \pi R^4 \times R_{\text{Pathologic}} / 8 \mu (0.25 \text{ cm})^4 \times (261 \text{ dyn/cm}^2)/(\text{cm}^3/\text{s}) / 8(0.05) = 8 \text{ cm}$$

Adding this incremental length to the normal length of 4.5 cm, we predict a total length of $\approx 12.5$ cm. This is the estimated length of the aberrant artery of 12 to 13 cm in patient 1, despite using a theoretical radius larger than existed for the aberrant artery in that patient. We have provided theoretical estimates of the length of an aberrant vessel, which are summarized in Table 2, with the assumptions that the actual length of the aberrant artery would be capable of increasing the R to a degree that is at least equal to a $>50\%$ reduction in the diameter of the main arterial trunk. The length of the aberrant vessel is therefore capable of contributing to the increased vascular resistance and reduced vascular flow, with all other components remaining unchanged.

Another possibility is an additional small and difficult to measure reduction in the overall radius of the aberrant vessel relative to the pressure–flow requirements of that perfused renal segment. Such a combination would be likely to contribute to a significant decrease in perfusion pressure and resultant release and activation of the renin-angiotensin system without a focal abnormality that would alert the radiologist to this circumstance. It is not clear whether these aberrant vessels had a general diameter that would not allow for sufficient flow, or whether some other component(s) were operative. It is possible that these segments, identified by an associated aberrant renal artery, have a diminished number of glomeruli or other vascular features leading to increased intrarenal resistance and/or diminished perfusion leading to an exaggerated production of renin.

Whatever the pathophysiologic mechanism(s), these patients constitute a small but distinct subgroup within the larger number of patients with single or multiple renal aberrant arteries. We believe these patients and data provide strong support for a new clinical syndrome within the hypertensive population.

**Perspectives**

This study raises 2 important questions. First, how do we identify and establish the prevalence of this entity? Use of a low PA/PRA ratio should identify patients with a renin-dependent hypertension that characterizes this syndrome. CT or MRI technology would noninvasively identify those with either an arterial stenosis or a suspicious aberrant artery that could be confirmed by lateralization of renal vein renins. Second, What etiologic component(s) contribute to the pathophysiology of this new syndrome? Emerging studies support both genetic and epigenetic bases for development of structural deviations. Genetic determinants, ranging from mutations and/or abnormal methylation of genes, probably alter normal renal angiogenesis during fetal development. Samples of vascular tissue obtained from future patients will permit identification of genetic mutations by genetic techniques including SNP and/or gene subtraction methodology. Epigenetic factors affecting renal vascular development in a time-specific manner may be operative. These could include nutritional, infectious, and cytokine-related changes that are tissue-specific. Primary changes in the affected renal segment may also be operative and the aberrant artery might only be a marker. A recent study demonstrated that acute stress and associated application of glucocorticoids to a fetal model led to decreased glomeruli and subsequent development of hypertension. A segmental expression could produce some equivalent to this. Although we believe that present evidence favors a relative decrease in segmental perfusion from a relative restriction of flow from these narrow and elongated aberrant arteries, further studies will be needed to provide answers to these questions.

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References

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