Telling Tails

Very High Plasma Renin Levels Prompt the Diagnosis of Renal Artery Stenosis, Despite Initial Negative Imaging

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The diagnosis of curable, secondary causes of hypertension is a satisfying but challenging aspect, for both patient and doctor, of the clinical management of hypertension. They are probably under-recognized, and the enthusiasm to look for causes is blunted by low pickup rates in unselected patients. Young age encourages a search more because the alternative is many decades of drug treatment than because of any good evidence that prevalence of secondary hypertension varies with age. Plasma renin is still not a routine measurement even in the younger patient. And although there is an increasing evidence that a low plasma renin is valuable in the detection of primary aldosteronism, a high plasma renin does not usually trigger investigations for renal artery stenosis. The cases we present here are not part of a formal prospective series. But they illustrate how valuable was the finding of an extremely high plasma renin, leading to re-evaluation of magnetic resonance (MR) and computed tomographic (CT) angiograms in the light of a high, rather than low prior probability. Our report is stimulated by the coincidence of 5 such patients being diagnosed within an 18-month period, and a parallel prospective study of plasma renin concentration’s prediction of treatment response, which enabled us to define the threshold for an extremely high plasma renin. We will discuss the significance of the log distribution of renin, of factors such as drug treatment influencing interpretation, and of reviewing reportedly normal radiology.

Plasma renin concentration was measured by the Diasorin Liaison automated immunoassay analyzer. Intra-assay coefficients of variation were 3.7%, 2.8%, 2.0%, and 1.2% at concentrations of 15.1, 33.8, 82.2, and 258.0 mU/L, respectively. Inter-assay coefficients of variation were 5.8% and 4.9% at concentrations of 25.6 and 101.3 mU/L, respectively. The lower limit of quantitation of the assay, as specified by the manufacturer, was 2.0 mU/L. Plasma renin activity is reported for 1 patient, in whom this was measured at the referring hospital.

Patient 1

A 24-year-old woman was referred in 2013 with a 2-year history of hypertension. Despite treatment with ramipril 5 mg daily and lercanidipine 20 mg daily, home systolic blood pressure readings often exceeded 140 mm Hg. Cardiovascular examination was normal with no abdominal bruits; ECG and echocardiogram were also normal, as were serum electrolytes and estimated glomerular filtration rate. An MR angiogram at the referring hospital noted normal renal arteries. However, her plasma renin was at least 50-fold above normal at 4220 mU/L (normal values 5.4–60), and aldosterone was 1130 pmol/L (normal values 100–450). The increase in renin was many-fold more than could be easily ascribed to treatment with an angiotensin-converting enzyme (ACE) inhibitor, and this should have reduced levels of aldosterone. On review of the MR angiogram at the Multi-Disciplinary Team meeting, no definite abnormality of the arteries was observed, but the right kidney looked hypoperfused (Figure 1A). Its length was 9.9 cm, and the left kidney was 11.0 cm. A formal renal angiogram was performed. This showed a tight stenosis in the midsegment of the right renal artery (Figure 1B), which was successfully treated by angioplasty (Figure 1C). One month later, average blood pressure was 122/75 mm Hg on ramipril 5 mg daily, which was then discontinued without rise in blood pressure. The plasma renin and aldosterone levels fell post angioplasty to 97 mU/L and 517 pmol/L, respectively.

Patient 2

A 26-year-old woman was referred in 2014 with a 2-year history of hypertension. She had presented with a blood pressure of 220/100 mm Hg during a follow-up visit for the prescription of a combined oral contraceptive pill. Serum electrolytes and estimated glomerular filtration rate were normal. Her blood pressure remained elevated, despite withdrawal of the contraceptive pill, and she was treated with doxazosin 8 mg, ramipril 5 mg, bisoprolol 5 mg, and amlodipine 10 mg, each daily. A CT angiogram had shown normal renal arteries, and because of the number of medications required in a young patient, she was referred for specialist review. This confirmed the report on the CT angiogram. Plasma renin concentration, on 2 visits, was increased at 385 and 764 mU/L, whereas plasma aldosterone was normal at 296 pmol/L. Renal vein renin sampling was performed, showing values of 500 to 600 mU/L in both veins, with no clear gradient between these.
Because the plasma renin concentrations were exceptionally high for a patient on β-blockade, a renin-secreting tumor was considered and a triple phase CT angiogram requested. This showed that the left kidney, at 9.0 cm, had diminished in size, and the right kidney increased, to 11.9 cm, since the previous CT angiogram 10 months earlier; on the arterial phase a tight stenosis was observed in the midportion of the left renal artery (Figure 2A). A left renal artery angioplasty was arranged (Figure 2B and 2C). Two months later, blood pressure was 128/67 mm Hg on ramipril 10 mg, and this was discontinued.

One year later, blood pressure was 146/96 mm Hg on no treatment, and candesartan 4 mg daily was commenced. Plasma renin and aldosterone concentrations while untreated were 17 mU/L and 94 pmol/L, respectively.

Patient 3
A 23-year-old woman was referred in 2015 with continuous, severe headaches and severe, refractory hypertension. She had been well until ≈1 year earlier, when she was hospitalized because of headache and blood pressure above 210/130 mm Hg. She was an ex-smoker with no family history of hypertension, and she had proteinuria but normal renal function and negative screening for renal vasculitis. On the echocardiogram, the left ventricle was mildly dilated with moderate systolic impairment. On 2 occasions, the serum potassium levels were slightly reduced (3.4 and 3.2 mEq/L; normal values 3.5–5.5), but other electrolytes and estimated glomerular filtration rate were normal. While on treatment with ramipril 2.5 mg and amlodipine 10 mg daily, her plasma renin activity and plasma aldosterone were raised at 21.2 nmol/L per hour (normal values: 0.5–3.5), and 1840 pmol/L. She was additionally prescribed doxazosin 12 mg, indapamide 2.5 mg, and bisoprolol 5 mg without effect on her blood pressure. Repeat plasma renin activity and aldosterone were 5.9 nmol/L per hour and 2010 pmol/L, respectively. A CT scan reportedly showed no evidence of renal artery stenosis or any adrenal lesion. Cardiac and aortic magnetic resonance imaging excluded coarctation. After referral, the plasma renin concentration was measured at 144 mU/L. Review of the original, axial CT images showed no abnormality of single renal arteries on each side. However, the several-fold elevation of plasma renin despite β-blockade, and our experience of the previous 2 patients, prompted further review with coronal reconstruction of the images. On these, a second renal artery was detected on the right, with a tight stenosis ≈2 cm from the origin, suggestive of fibromuscular dysplasia (Figure 3A). A renal artery angioplasty was performed (Figure 3B and 3C). A month later, her headaches had disappeared, blood pressure had fallen to 127/85 mm Hg, and plasma renin to 17 mU/L; aldosterone was 510 pmol/L. At 3 months, blood pressure was 137/88 mm Hg on no treatment.

Patient 4
A 56-year-old woman was referred in 2014 with refractory hypertension. She had been diagnosed with hypertension ≈30 years earlier and at the time of referral was on treatment with bisoprolol 5 mg, perindopril 8 mg, lercanidipine 20 mg, and spironolactone 25 mg, each daily. She complained of headaches and lethargy, and her blood pressure was 152/96 mm Hg. Serum electrolytes and creatinine were normal, but thyroid-stimulating hormone levels were slightly elevated at 5.6 mU/L (normal values: 0.35–5.5), together with marked elevation of
thyroid antibodies (antithyroid peroxidase 2147 IU/mL; normal values <60), leading to the diagnosis of Hashimoto thyroiditis. Plasma renin concentration was markedly elevated at 1230 mU/L. The CT scan at the referring hospital reported a large uncomplicated cyst on the right kidney. No abnormality was seen in the renal arteries, but the requested examination was not an angiogram. Multi-Disciplinary Team review prompted by the elevated renin noted calcification in the aorta (Figure 4A). A CT angiogram was performed which this time showed typical appearances of bilateral renal fibromuscular dysplasia (Figure 4B). There was only a small fall in blood pressure and plasma renin concentration after initiation of treatment with levothyroxine 50 μg,6 and so she proceeded to technically successful angioplasty of both renal arteries. Five months later, after discontinuation of spironolactone and lercanidipine, blood pressure was 146/95 mm Hg; the plasma renin fell to 130 mU/L and aldosterone to <70 pmol/L.

**Discussion**

Renovascular hypertension because of atherosclerosis or fibromuscular dysplasia is present in 1% to 4% of hypertensive patients, and it is probably the most common correctable cause of secondary hypertension after aldosterone-producing adenomas of the adrenal.1,9,10 Because these 2 conditions should, in theory, manifest plasma renin levels at opposite extremes of its distribution, this nowadays simple test might be considered a valuable addition to the routine investigation of patients with hypertension. However, there has been little

**Patient 5**

A 59-year-old man was referred in 2013 with a blood pressure of 191/101 mm Hg, despite prescription of ramipril, bisoprolol, amlodipine, indapamide, spironolactone, doxazosin, and methyldopa. Serum electrolytes and estimated glomerular filtration rate were normal, as were plasma renin concentration, 41 mU/L, and plasma aldosterone, 198 pmol/L. The recently introduced Hypertensive Compliance Screen showed that none of his 7 drugs were detectable in a spot urine sample.7,8 His treatment was changed to a single tablet containing olmesartan, amlodipine, and hydrochlorothiazide, on which his blood pressure fell to 125/72 mm Hg, and he was discharged. A year later, he was re-referred with blood pressure 175/110 mm Hg. His medication was detectable, and plasma renin had risen to 1068 mU/L. Nebivolol was added, on which plasma renin fell to 102 mU/L, with little improvement in blood pressure. Review of the CT angiogram performed at the referring hospital in 2013 found no abnormality, and a repeat was requested in view of the refractory hypertension and rise in plasma renin. This demonstrated a tight ostial stenosis on the left (Figure 5A). In view of uncontrolled hypertension despite compliance with therapy, and frequent episodes of angina despite coronary stenting, he proceeded to renal artery stenting (Figure 5B and 5C). Preprocedure, he was admitted with angina and a blood pressure of 246/132 mm Hg. Within 24 hours, he was asymptomatic and blood pressure was 122/78 mm Hg. Plasma renin at 24 hours was 13 mU/L. His blood pressure continued to fall to 80/53 mm Hg, at which point all treatment was stopped. Blood pressure rose to 164/87 mm Hg, and olmesartan/amlodipine combination was restarted. Plasma renin off treatment was 7 mU/L.

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** A 3-dimensional reconstruction of a computed tomographic angiogram (A) showing the presence of a second renal artery on the right, with a tight stenosis of the principal right renal artery (arrow). Pre- and postangioplasty right renal artery angiograms (B and C, respectively).

![Figure 4](http://hyper.ahajournals.org/)

**Figure 4.** Axial computed tomographic (CT) scan of the abdomen (A) showing liver cysts and calcification of the aorta (arrow). Three-dimensional reconstructions of the arterial phase of a repeated CT scan of the abdomen showing the tortuous trajectory and beaded appearance of the right and left renal arteries (B and C, respectively).
evidence to support its use in diagnosis of renal artery stenosis, and plasma renin can be reduced when bilateral disease results in sodium retention.\textsuperscript{10,11} In addition, an initially high plasma renin might be expected to fall toward normal because the development of systemic hypertension returns the poststenosis pressure from low to normal. Indeed, plasma renin levels are normal in \(\approx\)50\% of patients with renovascular hypertension while, conversely, increased levels may be found in \(\leq\)10\% of patients with essential hypertension.\textsuperscript{12} Although a tissue diagnosis is rarely made, the renal artery stenosis of younger patients is most likely because of fibromuscular dysplasia, as in patients 1 to 4, rather than the atherosclerosis of older patients, and studies of captopril renography suggest renin dependence in such patients.\textsuperscript{13}

Across all ages, fibromuscular dysplasia (FMD) accounts for a minor proportion of all patients with renovascular disease, but intervention is more likely to achieve sustained cure both of the renal artery stenosis and the resulting hypertension.\textsuperscript{10,14} Its management should not be influenced by the neutral outcomes in the large trials of revascularization, Angioplasty and Stent for Renal Artery Lesion (ASTRAL) and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), which generally excluded patients with FMD.\textsuperscript{15,16} Moreover, the primary outcome of these trials was renal function, and the eligible patients were those in whom clinicians were unsure of management. One trial required good blood pressure control at entry.\textsuperscript{17} The trials do not exclude continued search for patients with atherosclerotic renovascular disease in whom percutaneous revascularization may substantially improve blood pressure control. However, the outcome of intervention in both FMD and atherosclerotic renal artery disease may depend on how early the diagnosis is made, with the 30-year delay in patient 4 probably leading to some irreversibility of her hypertension. Initiation of medical treatment is also not hazard-free. The risk for renal function of treatment with ACE inhibitors or angiotensin receptor blockers in atherosclerotic renal artery stenosis is well recognized and ascribed to their greater effect on efferent than afferent arteriolar tone.\textsuperscript{18} Their risks in FMD are less studied, but we wondered whether initiation of treatment in patient 2 may have contributed to the tight stenosis and reduction in kidney size during a short period of time. The deterioration of patient 5 was less surprising, but still an illustration why not to rely on a recently normal angiogram if blood pressure and plasma renin concentration have risen substantially in the interval.

Although systematic screening for renovascular hypertension is not recommended, several clinical indications should alert the clinician to look for lesions in the renal artery. Young age, severe or refractory hypertension, diffuse atherosclerosis, incidental finding of asymmetrical size of the kidneys are just some of the conditions that should make the clinician suspicious for renovascular hypertension.\textsuperscript{19} Such conditions were variously present in the 5 cases reported here and led the diagnostic clinician to perform early imaging procedures to assess the morphology of the renal arteries. Strikingly, these investigations were reported as normal, even in some instances on review after referral. In each case, the decision to either question or repeat the initial investigation was the greatly increased prior probability (of an abnormality being present) consequent on measurement of a high plasma renin. The value of noninvasive (CT or MR) angiography in detection of renal artery stenosis, especially the more distal lesions of FMD, was challenged in the Renal Artery Diagnostic Imaging Study in Hypertension (RADISH), but this in turn has been questioned.\textsuperscript{20,21} It may be that in some centers, the initial failures of diagnosis in our patients would not have occurred, but the 5 patients came from 5 different secondary centers, and even review in a tertiary center did not always detect an abnormality.

The distribution of plasma renin is unusually broad, compared with most hormones, spanning 4 logarithmic units.\textsuperscript{2} There are many stimuli to renin secretion, and appropriate increases in plasma renin occur after salt depletion, sympathetic activation, or interruption of the negative feedback by angiotensin II.\textsuperscript{22} Although each of diuretics, calcium-blockers or \(\alpha\)-blockers, and ACE inhibitors or angiotensin receptor blockers, may cause 50\% to 100\% elevation of plasma renin through, respectively, one of these mechanisms, this rarely results in a log-unit (10-fold) increase in plasma renin, even when the drugs are combined. In the Prevention and Treatment of Hypertension With Algorithm-Based Therapy (PATHWAY)-2 study, comparing mineralocorticoid with \(\alpha\)- and \(\beta\)-adrenergic blockade in 285 patients already treated with each of diuretics, calcium-blockers and ACE inhibitors or angiotensin receptor blockers, only 3\% of patients had a plasma renin >660 mU/L, and only in these 3\% of patients was renin suppression (by \(\beta\)-blockade) as likely to reduce blood pressure as the spironolactone.\textsuperscript{3} This prospective evaluation of renin concentration as a predictor of drug response quantifies the frequency of elevated plasma renin concentrations in multi-treated patients, and offers some evidence that hypertension at the most extreme values of

**Figure 5.** Left renal artery stenosis (arrow) demonstrated on a 3-dimensional reconstruction of the arterial phase of the computed tomographic angiogram (A). Pre- and poststenting angiograms of the left renal artery (B and C, respectively).
plasma renin may have a different pathogenesis from hypertension in other patients. At the least, the plasma renin concentrations in our 5 patients, of 1130, 764 (despite β-blockade), 144 (despite β-blockade), 1230, and 1068 (102 on β-blockade) mU/L, seem unlikely to be due solely to the pharmacological actions of their treatment. Rather, we considered them to be probable evidence of the fourth stimulus to renin production—a low pressure within the afferent renal arterioles at the site of renin secretion. In such patients, an elevated renin is more likely to be the cause of hypertension, rather than consequence of treatment. The potential for additive, logarithmic increases in plasma renin in response to multiple stimuli was not fully appreciated when renin was measured via its enzyme activity—because at high levels the assay runs out of renin substrate in the patient’s plasma. The patients illustrate how plasma renin can be interpreted, despite concurrent antihypertensive treatment, but also the importance of recognizing the substantial impact of β-blockade on expected levels. This class lowers blood pressure by blocking the sympathetic activation of renin, and its impact is illustrated by the 10-fold fall in case 5, after introduction of nebivolol.

The final patient illustrates a possible new clue to the presence of a secondary cause. The Leicester urine compliance test has led to recognition that a substantially elevated blood pressure despite prescription of multiple drugs is often, even usually, because of complete noncompliance. However, if blood pressure is unresponsive to all the major drug classes, and compliance is confirmed, then expectations of a secondary cause become high.

It is important to emphasize that this is a retrospective report of 5 individual cases, too numerous, we suggest, for the high plasma renin concentration to have been a false pointer to diagnosis, but too few for us to comment on the overall sensitivity and specificity of plasma renin as a diagnostic test. We are not suggesting that all patients with extremely high plasma renin concentrations have an anatomic cause. Addition of high-dose diuretic to an ACE inhibitor or angiotensin receptor blocker was associated, in a prospective study, with rises to similar concentrations of plasma renin in ≈2% of patients, but we do not know how often underlying renal ischemia contributes to such reactive rises. We have also not examined reasons why initial CT angiograms may have been misleading, but suggest that timing of films after injection of contrast may be critical.

In conclusion, we have presented 5 patients with severe hypertension because of renal artery stenosis, in whom the diagnosis was not appreciated on the initial CT or MR angiogram. Recognition of a plasma renin that is many-fold higher than the normal range, after accounting for background drug treatment, led to further evaluation and investigation. These cases may stimulate systematic prospective evaluation, and meanwhile encourage greater measurement of plasma renin in young patients with hypertension, and patients with uncontrollable hypertension, despite treatment with multiple drugs.

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Disclosures

M.J. Brown conceived the analysis, and designed the report. M. Petruzelli and M.J. Brown wrote the article. B. Koo undertook renovascular imaging, angioplasty and stenting, and advised on image presentation for the article. K.P. Taylor undertook renin estimations for the 5 patients, and all other patients contributing to recognition of the renin distribution, and advised on interpretation. All authors approved the final version of the article.

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