What Is Critical Renal Artery Stenosis? Implications for Treatment

Geza Simon

Renovascular disease due to progressive atherosclerotic renal artery stenosis is being diagnosed with increasing frequency in the elderly. At what degree of renal artery stenosis should intervention be recommended is not clear. To answer this question, unilateral or bilateral activation of the renin-angiotensin system or its absence were detected by captopril-stimulated renal vein renin measurements in 49 hypertensive patients, aged 63 years, with normal or near-normal renal function (serum creatinine concentration < 2.0 mg/dL), and the information was matched against radiographic measurements of the extent of renal artery stenosis. With few exceptions, unilateral or bilateral hypersecretion of renin was associated with 80% or greater reduction of renal artery lumen diameter. In contrast, normal secretion or suppression of renin production in a kidney contralateral to an ischemic one was associated with either normal caliber renal artery or renal artery stenosis less than 80%. These findings suggest that renal artery stenosis less than 80% should be monitored rather than treated because improvement of renal function and amelioration of hypertension are not expected unless the renin-angiotensin system has been activated in the affected kidney. Renoprotection by early intervention is uncertain because progression of renal artery stenosis is unpredictable. Normal captopril-stimulated renal vein renin measurements in hypertensive patients obviate the need for further work-up or interventional therapy of renovascular disease. Am J Hypertens 2000; 13:1189–1193 © 2000 American Journal of Hypertension, Ltd.

KEY WORDS: Hypertension, renovascular, renal vein renins, angioplasty, stenting.

Progressive atherosclerotic renal artery stenosis, termed renovascular disease or ischemic nephropathy, is an important cause of end-stage renal disease in the elderly. It is estimated that about 15% of patients entering chronic hemodialysis programs have renovascular disease as the principal cause of renal failure. In the very old, this figure may be higher. With timely diagnosis and successful surgical repair or intraluminal angioplasty and stenting, renovascular disease is an eminently preventable cause of renal failure. Noninvasive and minimally invasive screening tests, in the form of duplex Doppler ultrasonography and magnetic resonance angiography, are now available and have facilitated the diagnosis of renovascular disease. An increasing number of patients undergoing evaluation for hypertension or unexplained renal insufficiency are being diagnosed as having renal artery stenosis ranging from 50% to 100% (complete occlusion) of luminal diameter. Many of these patients will be treated with intraluminal angioplasty with or without stenting without evidence that the observed lesion is hemodynamically significant and a reasonable assurance that the intervention will ameliorate the hypertension or improve and protect renal function. By hemodynamically significant or critical renal artery stenosis we mean a lesion that is sufficiently severe to
formed on the same day.17 Renal vein sampling, using sive medications up to the time of testing. In dogs, acute reduction of renal artery perfusion pressure begins with 60% to 65% reduction of the luminal diameter, but due to autoregulation of blood flow luminal diameter has to be reduced 75% or more before a reduction of renal blood flow is registered.11,13 The relevance of these acute experiments to renal artery stenosis in patients is not clear. The available clinical information is sparse and inconclusive.12 What constitutes critical renal artery stenosis in the clinical setting remains to be determined. We have attempted to do this in the present study by using captopril-stimulated renal vein renin (RVR) measurements to detect activation of the RAS,14–17 and then matching this information with radiographic measurements of the extent of stenosis. To improve our chances of detecting the minimal stenosis that is necessary for activating the RAS, we have limited our investigation to patients with normal or near-normal renal function and to patients with a single renal artery per kidney. For radiographic measurements of the extent of renal artery stenosis, the official reports filed by the examining radiologists were used as representative of the clinical information on which the internists and vascular surgeons base their decisions.

PATIENTS AND METHODS

Patients undergoing abdominal aortography and captopril-stimulated RVR measurements to rule out renovascular disease at our institution between 1989 and 1998 were included in the study. The indications for the procedures were refractory or difficult-to-treat hypertension or unexplained renal insufficiency (serum creatinine >1.5 mg/dL) in a hypertensive patient. The majority of patients also had an asymetrically abnormal renal scintigram before further testing. Except for angiotensin I converting enzyme inhibitors, which were discontinued 4 to 7 days before RVR measurements, patients continued to take their antihypertensive medications up to the time of testing.

Renal vein sampling and aortography were performed on the same day. Renal vein sampling, using the Seldinger retrograde femoral technique, preceded aortography and was performed 30 min after the oral administration of 25 mg of captopril to the patient. A single catheter was used to sample left in duplicate and right renal vein and vena cava blood sequentially within 1 and 4 min of one another. Vena cava blood was sampled upstream to the kidneys as representa-tive of peripheral blood plasma renin activity (PRA). A small amount of contrast medium (5 mL) was used to confirm placement of catheter in the left and right renal vein.

For aortography a percutaneous femoral artery approach was used. Using local anesthesia, the femoral artery was punctured with an angiographic needle, followed by placement of a 5F pigtail catheter in the abdominal aorta with the side holes at the level of the renal arteries. Aortography was performed by injecting 40 to 50 mL of contrast medium at 20 to 25 mL/sec with a filming rate of 2/sec for 3 sec followed by 1/sec for 4 sec. If necessary, oblique views were taken using digital subtraction angiography. Since 1997 digital subtraction angiography was used exclusively. On the films, the prestenotic arterial lumen diameter was measured in millimeters; the percentage of stenosis, if any, was determined at the site of the greatest degree of narrowing as the ratio (percentage) between normal minus stenotic lumen and normal lumen diameter.

Plasma renin activity was measured by radioimmunoassay of angiotensin I (125I-Angiotensin I Radioimmunoassay Kit, DuPont, North Billerica, MA) as previously described and validated.17

Data Analysis The following question was posed: How severe does the renal artery stenosis have to be to trigger hypersecretion of renin from the affected kidney?

The kidney with the numerically higher PRA in its venous effluent was identified as ipsilateral (I), and the other kidney as contralateral (C). Ipsilateral-kidney-to-renal (vena cava) blood (I/P) and contralateral-kidney-to-renal blood (C/P) renin ratios were calculated. Three diagnostic patterns of postcaptopril RVRs were defined on the basis of published reports: 1) normal (I/P and C/P <2.0); 2) unilateral hypersecretion (I/P >2.0) and contralateral suppression (C/P <1.25); and 3) bilateral hypersecretion (I/P >2.0, C/P >1.25).14–17

To improve the chances of detecting the minimal renal artery stenosis that is necessary for triggering the RAS, the investigations were limited to patients with normal or near-normal renal function (serum creatinine ≤2.0 mg/dL), patients with a single renal artery per kidney, and patients without prior renal artery surgery, angioplasty, or stenting. Patients with renal insufficiency were excluded because the salt and water retention accompanying this condition may suppress renin release from one or both kidneys. Patients with low-renin hypertension (postcaptopril systemic blood PRA <1.0 ng/mL/h) were excluded because when PRA is low, the calculation of RVR and systemic blood renin ratios becomes unreliable. A total of 26 patients were excluded from the study for these various reasons.
Statistical Analysis  Data are listed as mean ± SD. A posteriori, the diagnostic utility (sensitivity, specificity, and positive predictive value) of hypersecretion of renin from the ipsilateral or contralateral kidney in predicting 80% or greater renal artery stenosis was calculated.

RESULTS

All patients were white and male. The duration of hypertension was 10 years or longer in the large majority of patients (data not shown), indicating that renovascular disease, if present, was a complication of longstanding essential hypertension. Patients were categorized as having normal secretion or unilateral or bilateral hypersecretion of renin. Their ages, serum creatinines, and RVR measurements are shown in Table 1. Two of the 9 patients with “normal” secretion of renin had high postcaptopril systemic PRA (50.9 and 45.4 ng/mL/h, respectively), but the two kidneys contributed equally to the high circulating levels of renin (I/P and C/P, 2.0). (This type of response may be seen in patients with intact kidneys who were dehydrated at the time of captopril administration and had a major decrease in their blood pressure.)

In Fig. 1, the renin secretory status of kidneys is plotted against the extent of renal artery stenosis. On the basis of RVR measurements, 45 kidneys (solid circles) were predicted to have normal caliber renal artery or noncritical renal artery stenosis. The average artery stenosis of these kidneys was 20%, and all kidneys but two had artery stenosis less than 80%. Fifty-three kidneys were judged to have critical artery stenosis (open circles). The average artery stenosis was 85%, with all kidneys but eight having artery stenosis 80% or greater. Of the eight kidneys with less than 80% artery stenosis, four kidneys were reported as having 70% to 80% stenosis, which was plotted as 75%.

There were four major departures from the predicted results, numbered 1 to 4 in Fig. 1. On the basis of RVR measurements, these kidneys were predicted to have critical renal artery stenosis, but on aortography turned out to have mild stenosis (kidney 1) or no stenosis (kidneys 2, 3, and 4). Kidney 1 was a small kidney (10 cm), compared to the contralateral kidney (15 cm), with extensive small vessel disease. Kidney 2 had a normal artery and extensive, tortuous perirenal

![FIG. 1.](https://academic.oup.com/ajh/article-abstract/13/11/1189/145151)

**TABLE 1. CLINICAL CHARACTERISTICS AND RENAL VEIN RENINS OF PATIENTS WITH “NORMAL” SECRETION AND UNILATERAL OR BILATERAL HYPERSECRETION OF RENIN**

<table>
<thead>
<tr>
<th>Renin Secretion</th>
<th>Age (y)</th>
<th>Serum Creatinine (mg/dL)</th>
<th>Renal Vein Renins (ng/mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Normal (n = 9)</td>
<td>61 ± 8</td>
<td>1.5 ± 0.4</td>
<td>20.9 ± 14.3</td>
</tr>
<tr>
<td>Unilateral hypersecretion (n = 27)</td>
<td>63 ± 8</td>
<td>1.7 ± 0.6</td>
<td>150.9 ± 194.2</td>
</tr>
<tr>
<td>Bilateral hypersecretion (n = 13)</td>
<td>66 ± 7</td>
<td>1.7 ± 0.7</td>
<td>106.2 ± 143.1</td>
</tr>
</tbody>
</table>

*IVC = inferior vena cava. Means ± SD.*
venous circulation, including a dilated left gonadal vein; the diagnosis was recanalized renal vein thrombosis. Kidneys 3 and 4 had normal arteries despite failure to suppress renin secretion contralateral to a hypersecreting kidney.

Using 80% stenosis as the cutoff between critical and noncritical renal artery stenosis, the sensitivity, specificity, and positive predictive value of hypersecretion of renin or failure to suppress renin release by negative feedback inhibition in the contralateral kidney were 85%, 84%, and 96%, respectively, in predicting a critical renal artery lesion.

**DISCUSSION**

In the present study, captopril-stimulated RVR measurements were used to detect activation of the RAS. By inhibiting angiotensin II production, captopril attenuates the negative feedback inhibition of renin release by circulating angiotensin II, thereby accentuating the differences that exist in renin production between the ischemic and nonischemic kidney. The administration of captopril also helps to evaluate blood flow to the kidney contralateral to the ischemic kidney. During chronic elevation of circulating plasma angiotensin II levels an intact kidney turns off renin synthesis, but renin production is only partially inhibited in a kidney with reduced blood flow due to renovascular disease. Captopril accentuates this latent capacity of the contralateral ischemic kidney to secrete renin, thereby facilitating the detection of bilateral disease.

The findings of the present study indicate that with few exceptions unilateral or bilateral hypersecretion of renin was associated with renal artery stenosis of 80% or greater of the luminal diameter. In the majority of patients renal artery stenosis was 90% or greater. In contrast, normal secretion of renin or suppression of renin production in a kidney contralateral to an ischemic one were associated with either normal-caliber renal arteries or renal artery stenosis less than 80%. Critical stenosis in patients with atherosclerotic renovascular disease appears to be 80% or greater. In acute dog experiments, there is activation of the RAS with 65% reduction of renal artery lumen diameter. However, due to autoregulation, reduction of renal blood flow does not occur until renal artery diameter has been reduced to 75% or more. The degree of renal artery stenosis required for the long-term activation of the RAS in dogs is not known.

The published literature suggests that a significant proportion (≈30%) of angioplasties and stent placements are performed in renal arteries with less than 80% reduction of luminal diameter. This practice is difficult to justify for several reasons. When the RAS is not activated, it is unreasonable to expect that angioplasty or stent placement will ameliorate the hypertension in patients with normal or near-normal renal function. The difficulties encountered in demonstrating an antihypertensive effect of these interventions support this suggestion. Similarly, improvement of renal function is not expected unless the stenosis is severe enough to activate the RAS because this requires less severe stenosis than reduction of renal blood flow and glomerular filtration. In cases of stenoses less than 80%, renal artery angioplasty and stenting for the protection of renal function is also open to criticism because the rate of progression of renovascular disease is difficult to predict. Progression of atherosclerotic renovascular disease occurs in about 10% of patients per year (range: 4.5% to 18.0%). In a recent prospective study using sequential duplex Doppler ultrasonographic measurements, only 4% of renal arteries with luminal diameter stenosis greater than 60% progressed to complete occlusion in 3 years. Finally, stenting of the renal artery is not an innocuous procedure; major complications occur in about 4% of patients.

With the availability of noninvasive or minimally invasive monitoring techniques, it seems more prudent to closely follow renal artery stenosis less than 80% in luminal diameter than to intervene unnecessarily. The life expectancy of these elderly patients with systemic atherosclerosis is short due to multiple other vascular complications; the chances are favorable that moderate renovascular disease will not complicate their clinical course. At our institution, we rely on annual serum creatinine measurements and renal scintigrams to follow patients with known but not critical renal artery stenosis. In comparison to a baseline study, obtained at or around the time when renal artery stenosis was diagnosed, progressive reduction of function of one or both kidneys can be easily detected by follow-up renal scintigrams. If deterioration of renal function is supported by the serum creatinine measurements, repeat RVR measurements or aortography with the option of intervention may be indicated. The role of newer diagnostic techniques, such as Doppler ultrasonography and magnetic resonance angiography, in the long-term follow-up of patients with renal artery stenosis needs to be defined. Doppler ultrasonography is technically difficult and is unsuccessful in about 20% of patients. Magnetic resonance imaging may overestimate the degree of renal artery stenosis; calibration studies in comparison with conventional arteriography are needed to determine the degree of stenosis detected by magnetic resonance angiography that represents a critical lesion as defined in this study.

In summary, amelioration of hypertension or improvement in renal function by interventional therapy of renal artery stenosis are not expected unless the stenosis is severe enough to activate the RAS. This
requires a luminal diameter stenosis of 80% or greater. Normal captopril-stimulated RVR measurements obviate the need for further work-up or interventional therapy of renovascular disease.

REFERENCES


