Prospective Analysis of Strategies for Diagnosing Renovascular Hypertension


Renovascular hypertension is a potentially curable form of high blood pressure. However, it is unclear how best to select patients who are likely to have renovascular hypertension, what diagnostic strategy to use in these selected patients, and how to predict the hemodynamic significance of a renal artery stenosis. We determined the prevalence of renovascular hypertension in adults who exhibited suggestive clinical features. In these clinically selected patients, we then determined the test characteristics of various diagnostic and potential screening tests. Renovascular hypertension was diagnosed if correction of renal artery stenosis resulted in decreased blood pressure. Of the 66 hypertensive adults evaluated, 11 (16.7%) had renovascular hypertension. Captopril-stimulated peripheral renin activity detected renovascular hypertension with 73% sensitivity, 72% specificity, 38% positive predictive value, and 92% negative predictive value. Less optimal combinations of sensitivity and specificity were found for differential glomerular filtration rate renography, differential effective renal plasma flow renography, and selective renal vein renin ratios, each performed after a single dose of captopril. Intravenous digital subtraction renal angiography detected all patients with renovascular hypertension and was normal in 71% of patients with essential hypertension. To evaluate potential screening tests for renovascular hypertension, we calculated predictive values applied to a low prevalence population. If the observed sensitivities and specificities apply to a population with 5% prevalence of renovascular hypertension, captopril-stimulated peripheral renin would have a positive predictive value of 12% and a negative predictive value of 98%. In 16 patients with known renal artery stenosis, neither the captopril-stimulated renal vein renin ratio nor captopril-stimulated differential renography accurately predicted blood pressure response to correction of the stenosis. We conclude that clinical criteria can identify a subgroup with 16.7% prevalence of renovascular hypertension. In this high prevalence group, intravenous digital subtraction renal angiography will identify virtually all patients with renovascular hypertension, and a normal study will be sufficient to exclude renovascular hypertension. In unselected hypertensive patients, screening with captopril-stimulated peripheral renin activity may be the most useful and efficient procedure for identification of patients with renovascular hypertension. Functional tests do not accurately predict the hemodynamic significance of a renal artery stenosis. (Hypertension 1989;14:247-257)
data concerning the sensitivity and specificity of each of these tests are inconsistent, and it is unclear which is most useful. For instance, intravenous digital subtraction renal angiography (IV-DSRA) is widely recommended as an alternative to conventional renal arteriography for defining renal vascular anatomy, but it is unclear if IV-DSRA is sufficiently accurate to justify this recommendation.

Other diagnostic tests for renovascular hypertension include peripheral renin activity to distinguish "renin-dependent" renovascular hypertension from "non-renin-dependent" essential hypertension,6,7 differential renography,8-10 and selective measurement of renal vein renin activity.9,11-14 While the diagnostic accuracy of each of these tests is clearly improved by pretreatment with angiotensin converting enzyme inhibitor,6,7,9,10,12,14 previous evaluations of these diagnostic modalities have been inconclusive. In some studies, only patients with known renal artery stenosis were evaluated.10,11,13 In others, the investigators identified renal artery stenosis but could not draw conclusions about blood pressure response to correction of the stenosis.8,9,12,13 Other studies were retrospective6 or did not uniformly use converting enzyme inhibition.6,9,11,13 Standardized, prospective comparisons among the available diagnostic tests are needed.

Third, currently only patients with suggestive clinical features are thoroughly evaluated for the presence of RVH, but the true prevalence of RVH in hypertensive patients without these clinical features is unclear.19-22 A sensitive and specific screening test is needed to identify unselected patients likely to have RVH.

Fourth, although renal artery stenosis is a necessary precondition for the diagnosis of RVH, it is frequently found coincidentally with essential hypertension.23 Our ability to predict the hemodynamic significance of a stenosis is unclear.13,24-26 Once renal artery stenosis is detected, functional tests are needed to accurately predict the blood pressure response to correction of that stenosis.

We performed a prospective study with the following goals: to confirm that clinical criteria can be used to identify a population with high prevalence of renovascular hypertension; to compare IV-DSRA to conventional renal arteriography in its ability to detect hemodynamically significant renal artery stenosis; to define the sensitivity, specificity, and predictive values of peripheral renin activity, differential renography, and selective renal vein renin activity, each performed after a single oral dose of captopril; to compare these tests as potential screening tools in unselected populations; and to evaluate the ability of functional tests to predict blood pressure response to correction of a renal artery stenosis.

**Subjects and Methods**

Ambulatory hypertensive adults were recruited from the Duke Hypertension Center and the Durham Veterans Administration Medical Center Hypertension Clinic. The diagnosis of hypertension was confirmed if untreated systolic blood pressure was greater than 145 mm Hg or diastolic blood pressure was greater than 90 mm Hg on two separate occasions. Patients were eligible to enter the study if one or more of the following clinical features, suggestive of the diagnosis of RVH, was present: 1) severe hypertension (history of diastolic blood pressure greater than 115 mm Hg, malignant hypertension or hypertensive encephalopathy, or physical examination revealing grade III hypertensive retinopathy); 2) uncontrolled hypertension (systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 95 mm Hg on maximum tolerated doses of three antihypertensive agents); 3) onset of hypertension within 2 years; 4) onset of hypertension at age less than 25 years or at age greater than 45 years; 5) acceleration of hypertension by at least 15% within the previous 6 months; 6) presence of abdominal or flank bruit; or 7) previous rapid-sequence intravenous pyelogram suggestive of renal artery stenosis.

Subjects were excluded from entry if they had experienced a myocardial infarction or cerebrovascular accident within the previous 3 months or if there was evidence on history, physical examination, or routine laboratory evaluation of other secondary forms of hypertension. Subjects were also excluded if renal insufficiency (creatinine greater than 2.0 mg%) or iodine allergy precluded multiple contrast studies.

This study was approved by the Institutional Review Boards and the Human Use Committees of Duke University Medical Center and the Durham Veterans Administration Medical Center, and written, informed consent was obtained from each subject. Before hospitalization, β-blockers and angiotensin converting enzyme inhibitors were discontinued for at least 2 weeks, and diuretics were discontinued for at least 48 hours. Other antihypertensive agents were discontinued whenever possible. No changes in diet were prescribed before admission, and all patients were given a 4 g sodium/day diet in the hospital.

Subjects were admitted to the Durham Veterans Administration Hospital or to the Clinical Research Unit of Duke University Medical Center. During a 5-day hospital stay, each subject underwent the following sequence of tests:

1. **Captopril-stimulated peripheral plasma renin activity.** Captopril (25 mg) was administered orally. After 30–60 minutes in the supine position, a peripheral venous specimen was obtained for measurement of plasma renin activity by radioimmunoassay. A supine measurement was made since captopril increases plasma renin threefold in supine subjects.27 A captopril-stimulated peripheral renin activity greater than 4 ng/ml/hr was considered elevated. In a recent report,6 the peripheral renin both before and after administration of captopril, as well as the
degree of change in peripheral renin activity, were used to define criteria for “hyperresponsiveness of renin secretion in renovascular hypertensive patients”. This retrospective report suggested that these combined criteria improve the ability of peripheral renin activity to distinguish RVH from essential hypertension. We chose, however, to evaluate a single postcaptopril renin in an attempt to develop and characterize a simple screening procedure easily performed in the general practice setting. A cut-off value of 4 ng/ml/hr was chosen because it is well above the upper limit of normal for our laboratory but low enough to maximize sensitivity for detection of RVH.

2) Captopril-stimulated selective renal vein renin activity. Captopril (25 mg p.o.) was administered just before catheterization for IV-DSRA. After performing IV-DSRA (see below), we exchanged the pigtail catheter (Cook, Inc., Bloomington, Indiana) for a preformed end-hole catheter (Cook, Inc.), and selective main renal vein and inferior vena cava blood samples were obtained for renin assay. The position of the catheter was confirmed by small hand injections of contrast material. Care was taken to avoid the left gonadal vein and to clear the catheter of contrast material before drawing the venous sample. Selective renal vein and inferior vena cava samples were obtained within 5 minutes of each other, approximately 60 minutes after captopril was ingested.

Plasma renin activity was measured by radioimmunoassay. The renal vein renin ratio was calculated by dividing the higher renal vein renin value by the lower. We considered a renal vein renin ratio of 1.5 or greater evidence for lateralization of renin secretion. In a second analysis, the Vaughan ratio was calculated for each renal vein according to the method previously described. When the inferior vena cava renin is at least 1 ng/ml/hr, the Vaughan ratio is considered lateralizing if the ratio for one renal artery is at least 0.48 and the ratio for the other renal artery is less than 0.23 or if the ratio on both sides is greater than 0.23 (suggesting bilateral hypersecretion of renin). When the inferior vena cava renin is less than 1 ng/ml/hr, the Vaughan ratio is considered nonlateralizing regardless of the calculated ratio.

3) Differential glomerular filtration rate and effective renal plasma flow by renography. Radionuclide renography was performed 60 minutes after the subject ingested 25 mg captopril. After an intravenous injection of 3 mCi technetium-99m DTPA, glomerular filtration rate (GFR) for each kidney was estimated by an Anger-type scintillation camera (General Electric MaxiCamera II, General Electric Company, Milwaukee, Wisconsin), using a modification of the method developed by Gates. Immediately after this measurement, 50 μCi [131I]iodohippurate was injected intravenously. The kidneys were then imaged with a scintillation camera for at least 5 minutes. Exactly 44 minutes after the injection of [131I]iodohippurate, a blood sample was obtained for determination of tracer activity. Effective renal plasma flow (ERPF) in each kidney was determined from these data by the method described by Tauxe et al. Renal artery stenosis was inferred if there was more than a 6% difference between the right and left kidneys in total function (GFR) or in total perfusion (ERPF).

4) Intravenous digital subtraction renal angiography was performed with commercially available units (ADAC DPS-4100, ADAC Labs, Milpitas, California or GE 3000, General Electric Medical Systems, Milwaukee, Wisconsin). A 5F pigtail catheter was positioned in the right atrium and conventional ionic contrast material (Renografin 60, ER Squibb and Sons, Princeton, New Jersey) was injected at 20 ml/sec for 2 seconds. The initial series of roentgenograms was performed in the anteroposterior projection. If both renal arteries were not clearly seen, additional views in the left or right anterior oblique projections were obtained. Each study was interpreted by a senior vascular radiologist without knowledge of the results of any other diagnostic test. Luminal narrowing of 50% or greater was considered significant renal artery stenosis. For the purpose of this analysis, we assumed that in a clinical setting patients with inconclusive or technically inadequate IV-DSRA would be evaluated further with conventional arteriography. Therefore, inconclusive or inadequate intravenous digital angiograms were considered abnormal (i.e., positive studies).

5) Conventional renal arteriography. On the fourth hospital day each subject was pretreated with atropine, demerol, and local anesthetic. A 5F pigtail catheter was passed percutaneously via the femoral artery into the abdominal aorta. Conventional ionic intravascular contrast material (Renografin 60) was injected at 25 ml/sec for 2 seconds, for a total infusion of 50 ml contrast material. Roentgenograms were obtained in the anteroposterior projection at 3 frames/sec. If the main renal arteries were not clearly seen, additional views were obtained in oblique projections. Occasionally selective renal artery injections were required. In such cases, a preformed end-hole catheter was used and the injection rate varied with the size of the renal artery. Fifty percent or greater luminal narrowing of a main renal artery was considered significant renal artery stenosis. On the fifth day, subjects were discharged from the hospital.

Treatment decisions were based solely on the results of conventional renal arteriography. Subjects without significant renal artery stenosis on arteriography were treated with antihypertensive medications. Patients with 50% or greater luminal narrowing of a main renal artery on conventional arteriography were advised to have percutaneous transluminal angioplasty. Subjects with complete occlusion of a main renal artery were evaluated on an individual basis. In these patients, surgical revascularization was recommended if there was signifi-
renal function distal to the occlusion, as assessed by kidney size and differential GFR renogram. If there was minimal or no renal function distal to an occluded renal artery, the patient was advised to undergo nephrectomy. Regardless of treatment, each patient was examined by an investigator (L.P.S. or S.I.H.) within 2 weeks of discharge. Patients who had been treated with percutaneous transluminal angioplasty or surgery were examined in the clinic approximately every month thereafter. At each clinic visit, three seated blood pressure measurements were obtained. Antihypertensive medication was adjusted to attain a goal blood pressure of 140/90 mm Hg.

Renovascular hypertension was diagnosed if correction of a renal artery stenosis by percutaneous transluminal angioplasty, revascularization, or nephrectomy, resulted in cure or improvement in the patient's hypertension, based on criteria set by the Cooperative Study of Renovascular Hypertension.32 "Cure" was defined as blood pressure of 140/90 mm Hg or less without antihypertensive medication. "Significant improvement" was inferred if systolic or diastolic blood pressure decreased by at least 15% without change in antihypertensive regimen, or if less medication was required to maintain normal blood pressure. Patients who showed no improvement in blood pressure after percutaneous transluminal angioplasty or revascularization underwent repeat arteriography to document patency of the treated renal artery. If the treated renal artery was not patent on the repeat examination, further treatment (angioplasty or surgery) was recommended. In patients with renal artery stenosis, renovascular hypertension was ruled out only when there was arteriographic evidence that the stenosis had been successfully relieved without subsequent improvement in blood pressure.

Using response to treatment as the gold standard of diagnosis, we calculated the sensitivity, specificity, and predictive values of each diagnostic test by standard methods.33 Confidence intervals for proportions were calculated by Miettinen's exact method.34

Results

Between November 1984 and December 1986, 74 hypertensive adults were evaluated. Eight subjects were excluded from analysis. Four of these refused conventional renal arteriography. In four other patients who had renal artery stenosis on conventional arteriography, the presence or absence of RVH could not be definitively established because intercurrent cardiovascular disease precluded treatment with percutaneous transluminal angioplasty or surgery. The remaining 66 patients had conventional renal arteriography and at least one other diagnostic test.

Major complications occurred in four patients, all of whom underwent percutaneous transluminal angioplasty. In two patients, thrombus caused acute renal artery occlusion, which resolved with thrombolytic therapy in both cases. A femoral pseudoaneurysm requiring surgical repair developed in two patients who underwent percutaneous transluminal angioplasty. Minor complications occurred in 13 individuals and included superficial infection at catheter insertion site (one patient), groin hematoma after arteriography or angioplasty (six patients), subintimal hematoma after angioplasty (one patient), mild allergic reaction to contrast material (two patients), transient increase in serum creatinine (one patient), and transient hypotension (two patients).

Of the 66 patients available for analysis, 11 had renovascular hypertension, as defined above. Therefore, our clinical criteria identified a subpopulation with 16.7% prevalence of RVH. Table 1 demonstrates that patients with and without RVH were comparable with respect to age and sex. Table 1 also shows prevalence rates by race. Forty of the total group evaluated were white; eight of these (20%) experienced a decrease in blood pressure after angioplasty or surgery. Twenty-six of the total group evaluated were black; three of these (11.5%) had RVH. Therefore, in our clinically selected patients, the prevalence of RVH was similar in both black and white subjects. Of the 11 patients with RVH, nine had atherosclerotic disease and two had fibromuscular dysplasia. Bilateral renal artery stenosis was present in eight patients, six of whom ultimately were found to have RVH. In five patients, blood pressure decreased after unilateral intervention on the side of the more severe stenosis. The sixth subject with RVH and bilateral renal artery stenosis had no blood pressure response to angioplasty of the more severe stenosis but had a dramatic decrease in blood pressure after angioplasty of the contralateral stenosis.

All patients met one or more of our entry criteria, and many subjects met multiple criteria. As seen in Table 2, most subjects qualified for the study because of severe, progressive, or difficult to control hypertension. Nine of the 11 (82%) patients with RVH and 46 of 55 (84%) without RVH met at least one of these three criteria. Of 15 patients who had abdominal, renal, or flank bruits, seven (47%) had RVH. All bruits were systolic, except for one patient with RVH who had a diastolic bruit.

**Table 1. Demographic Characteristics of Patients With and Without Renovascular Hypertension**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RVH</th>
<th>No RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>Age ± SD (range)</td>
<td>49±12 (28–65)</td>
<td>48±13 (20–77)</td>
</tr>
<tr>
<td>% male</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>Prevalence by race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (20%)</td>
<td>32 (80%)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (11.5%)</td>
<td>23 (88.5%)</td>
</tr>
</tbody>
</table>

RVH, renovascular hypertension; n, number of patients.
Table 2. Entry Criteria Met by Total Study Population and by Those Patients With Renovascular Hypertension

<table>
<thead>
<tr>
<th>Criterion</th>
<th>n with RVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe hypertension</td>
<td>41</td>
</tr>
<tr>
<td>Progressive hypertension</td>
<td>21</td>
</tr>
<tr>
<td>Difficult to control hypertension</td>
<td>31</td>
</tr>
<tr>
<td>Bruit</td>
<td>15</td>
</tr>
<tr>
<td>Recent onset of hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Early onset of hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Late onset of hypertension</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal IVP</td>
<td>7</td>
</tr>
</tbody>
</table>

Many patients met more than one criterion. n, number of patients; RVH, renovascular hypertension; IVP, intravenous pyelogram.

Six of the 11 patients with renovascular hypertension were treated with percutaneous transluminal angioplasty, three with nephrectomy and two with renal artery bypass surgery. Five of these subjects had normal blood pressure without antihypertensive medication at least 1 month after treatment (angioplasty in two, nephrectomy in two, and revascularization surgery in one subject). Six subjects had significant improvement in blood pressure, as defined above, after treatment (angioplasty in four, nephrectomy in one, and revascularization surgery in one subject).

Table 3 summarizes the sensitivity, specificity, and predictive values of each of the diagnostic tests evaluated. Each individual had arteriography and at least one other test, but all patients did not have all tests. The number of patients in each diagnostic category who underwent each test are listed in the first column of the table. Captopril-stimulated peripheral renin activity was greater than 4 ng/ml/hr in eight of the 11 patients with RVH (sensitivity 73%). Captopril-stimulated peripheral renin was 4 ng/ml/hr or less in 33 of 46 patients without RVH (specificity 72%). In our clinically selected, high prevalence population, an elevated captopril-stimulated peripheral renin level raised the likelihood of RVH to 38% (positive predictive value). A low captopril-stimulated peripheral renin value excluded the diagnosis of RVH with 92% assurance (negative predictive value).

Table 3 also demonstrates that the captopril-stimulated renal vein renin ratio, by standard calculations (higher/lower), was 1.5 or greater in seven of 11 patients with RVH (sensitivity 64%), and in 24 of 48 without RVH (specificity 50%). These test characteristics improved somewhat if the renal vein renin ratio was considered elevated only if the ratio was 1.5 or greater and both right and left renal vein renins were greater than 1.0 ng/ml/hr. With this modification, the sensitivity of the captopril-stimulated renal vein renin ratio remained 64% and the specificity increased to 73%. In our patients, a nonlateralizing test (ratio less than 1.5 or both renal vein renin values less than 1.0 ng/ml/hr) excluded RVH with 90% assurance (negative predictive value), and a lateralizing test selected patients with a 35% likelihood of having RVH (positive predictive value). Alternatively, calculation of the Vaughan

<table>
<thead>
<tr>
<th>Test</th>
<th>n with/without RVH</th>
<th>Sens (%) (95% CI)</th>
<th>Spec (%) (95% CI)</th>
<th>PV+ (%) (95% CI)</th>
<th>PV- (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril-stimulated peripheral renin activity &gt;4</td>
<td>11/46</td>
<td>73 (42–93)</td>
<td>72 (57–83)</td>
<td>38 (19–69)</td>
<td>92 (79–98)</td>
</tr>
<tr>
<td>Captopril-stimulated RVR ratio ≥1.5</td>
<td>11/48</td>
<td>64 (34–87)</td>
<td>50 (36–64)</td>
<td>22 (8–40)</td>
<td>86 (69–95)</td>
</tr>
<tr>
<td>Captopril-stimulated RVR ratio ≥1.5 and both RVR’s ≥1</td>
<td>11/48</td>
<td>64 (34–87)</td>
<td>73 (59–84)</td>
<td>35 (17–57)</td>
<td>90 (77–97)</td>
</tr>
<tr>
<td>Captopril-stimulated Vaughan ratio</td>
<td>11/48</td>
<td>64 (34–87)</td>
<td>73 (59–84)</td>
<td>35 (17–57)</td>
<td>90 (77–97)</td>
</tr>
<tr>
<td>Postcaptopril differential GFR ratio</td>
<td>11/50</td>
<td>91 (63–99)</td>
<td>50 (36–64)</td>
<td>28 (15–45)</td>
<td>96 (82–99)</td>
</tr>
<tr>
<td>Postcaptopril differential ERPF ratio</td>
<td>10/46</td>
<td>80 (48–100)</td>
<td>42 (28–56)</td>
<td>23 (3–39)</td>
<td>90 (72–98)</td>
</tr>
<tr>
<td>IV-DSRA</td>
<td>11/48</td>
<td>100 (57–82)</td>
<td>71 (26–64)</td>
<td>44 (26–64)</td>
<td>100 (76–100)</td>
</tr>
</tbody>
</table>

Prevalence of renovascular hypertension, 16.7%; n, number of patients; RVH, renovascular hypertension; Sens, sensitivity; CI, confidence interval; Spec, specificity; PV+, positive predictive value; PV−, negative predictive value; RVR, renal vein renin; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; IV-DSRA, intravenous digital subtraction renal angiography.
ratio did not significantly improve the sensitivity, specificity, or predictive value of captopril-stimulated selective renal vein renin activity.

Renal function was considered asymmetric if there was more than a 6% difference between the two kidneys (i.e., if one kidney contributed less than 47% total renal function), as assessed by differential GFR renography after captopril. This test identified patients with RVH with 91% sensitivity and 50% specificity. In our 16.7% prevalence population, lateralization by GFR renography raised the likelihood of having RVH to 28% (positive predictive value). A nonlateralizing GFR renogram ruled out RVH with 96% assurance (negative predictive value). Using the same criterion for lateralization of renal perfusion, we found that postcaptopril ERPF renography had lower sensitivity (80%) as well as lower specificity (42%).

Intravenous digital subtraction renal angiography was abnormal in all 11 patients with RVH (sensitivity 100%). In eight of these patients, IV-DSRA clearly demonstrated renal artery stenosis. In the remaining three patients, IV-DSRA was inconclusive or technically inadequate. As mentioned above, we assumed that both inconclusive and inadequate studies would lead to arteriography. Therefore, since the diagnosis of RVH would not have been missed in these patients, inconclusive and technically inadequate studies were considered true-positive studies.

Of the 55 patients without renovascular hypertension, 48 had IV-DSRA performed. Thirty-four of these patients had a normal study (specificity 71%), and the remaining 14 had false-positive intravenous digital subtraction renal angiograms. Of these 14 patients with false-positive studies, nine had technically inadequate or inconclusive studies. These studies were considered false positives since they would fail to exclude a true-negative patient from further evaluation. Three patients had false-positive studies because a renal artery stenosis on IV-DSRA was not confirmed on conventional arteriography. In two additional patients, both IV-DSRA and conventional renal arteriography demonstrated renal artery stenosis, but the studies were considered false positives because the diagnosis of RVH was excluded when technically successful percutaneous transluminal angioplasty did not result in a decrease in blood pressure.

Therefore, in our study population a normal IV-DSRA ruled out RVH with 100% assurance (negative predictive value), and an abnormal or inconclusive intravenous digital subtraction angiogram was associated with a 44% likelihood of the patient having RVH (positive predictive value).

The sensitivity, specificity, and predictive value data presented in Table 3 apply to a high prevalence, clinically selected population. Table 4 provides hypothetical data on the potential of each of these tests to screen for RVH in an unselected population, assuming that the sensitivities and specificities observed in our patient population also apply to a population with lower prevalence of RVH. Since previously published reports suggest that the prevalence of renovascular hypertension is less than 5% in unselected hypertensive patients, we calculated the positive and negative predictive values for each diagnostic test applied to a population with 5% prevalence of RVH. As seen in Table 4, when the observed sensitivity and specificity are applied to a low prevalence population, negative predictive values are high for each test simply because the presumed pretest probability was so low (5%). Positive predictive values vary somewhat more widely. A captopril-stimulated peripheral renin level greater than 4 ng/ml/hr increased the likelihood of RVH to 12% (positive predictive value). Positive predictive values were lower in the other tests evaluated, except for IV-DSRA, which had a positive predictive value of 15%. We do not consider IV-DSRA a potential screening test in unselected hypertensive patients because it is invasive and expensive. Therefore, the hypothetical data in Table 4 suggest that captopril-stimulated peripheral renin activity is the best available screening test for RVH.

We also evaluated the ability of functional tests (renal vein renin ratio and differential renography) to predict blood pressure response to intervention in patients with renal artery stenosis. Stenosis of a main renal artery was found in 16 patients. Correction of the stenosis resulted in cure or improvement in high blood pressure in 11 of these patients. In the remaining five patients, blood pressure did not

<table>
<thead>
<tr>
<th>Test</th>
<th>Predictive value + (%)</th>
<th>Predictive value - (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril-stimulated peripheral renin activity &gt;4</td>
<td>12</td>
<td>98</td>
</tr>
<tr>
<td>Captopril-stimulated RVR ratio</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>Captopril-stimulated RVR ratio &amp; both RVR's ≥1</td>
<td>11</td>
<td>97</td>
</tr>
<tr>
<td>Captopril-stimulated Vaughan ratio</td>
<td>11</td>
<td>97</td>
</tr>
<tr>
<td>Postcaptopril differential GFR ratio</td>
<td>9</td>
<td>99</td>
</tr>
<tr>
<td>Postcaptopril differential ERPF ratio</td>
<td>7</td>
<td>97</td>
</tr>
<tr>
<td>IV-DSRA</td>
<td>15</td>
<td>100</td>
</tr>
</tbody>
</table>

Predictive values are based on an estimated 5% prevalence of renovascular hypertension in unselected hypertensive patients. Calculations are based on the assumption that the sensitivities and specificities observed in our patient population are applicable to a population with 5% prevalence of RVH. RVR, renal vein renin; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; IV-DSRA, intravenous digital subtraction renal angiography.
change after correction of renal artery stenosis. Therefore, 11 patients had renovascular hypertension, and five had essential hypertension with coincidental renal artery stenosis. Table 5 summarizes the ability of functional tests to predict reversibility of hypertension in these 16 patients. Postcaptopril selective renal vein renin ratio was elevated in seven of the 11 patients with RVH (sensitivity 64%), but was also elevated in four of five patients with essential hypertension (specificity 20%). Sensitivity and specificity of the Vaughan ratio were identical. Postcaptopril differential renography, both GFR and ERPF, was asymmetric in most patients with RVH (sensitivity 91% and 80%, respectively) but was also asymmetric in 80% of patients with essential hypertension (specificity 20%).

### Table 5. Characteristics of Functional Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril-stimulated RVR ratio</td>
<td>64</td>
<td>20</td>
</tr>
<tr>
<td>Captopril-stimulated Vaughan ratio</td>
<td>64</td>
<td>20</td>
</tr>
<tr>
<td>Postcaptopril differential GFR ratio</td>
<td>91</td>
<td>20</td>
</tr>
<tr>
<td>Postcaptopril differential ERPF ratio</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

Values are from 16 patients with known renal artery stenosis. 11 of whom had renovascular hypertension. RVR, renal vein renin; GFR, glomerular filtration rate; ERPF, effective renal plasma flow.

Discussion

Renovascular hypertension is a potentially curable form of high blood pressure. Therefore, in ideal circumstances all cases would be detected and definitively treated. Clinical selection criteria can be used to identify hypertensive patients likely to have RVH. For instance, renovascular disease is present in 30% of patients with grade 3 or 4 hypertensive retinopathy and in 39% of patients with abdominal or flank bruits. Other clinical features reported to be predictive of renovascular disease include recent onset of hypertension, severe or difficult to control hypertension, onset early or late in life, and recent progression in the severity of chronic hypertension. These earlier studies primarily reported associations between clinical features and anatomic evidence of renal artery stenosis. Our data provide evidence that these clinical criteria can also identify a group of patients with renal artery stenosis that is hemodynamically significant: 16.7% of our clinically selected patients had renovascular hypertension, as documented by blood pressure response to correction of the stenosis or removal of the involved kidney. In addition to meeting our selection criteria, many of our patients were referred for evaluation of severe, refractory, or otherwise atypical hypertension. Therefore, this study population may not be representative of all hypertensive patients who meet our selection criteria. Similar surveys in primary care settings are needed. Nonetheless, the group reported here is likely to be similar to other patients referred to tertiary care centers.

In our 16.7% prevalence population, we evaluated the ability of various diagnostic tests to detect RVH. None of the relatively noninvasive tests had sufficiently high sensitivity and specificity to be useful in a high prevalence population. Captopril-stimulated peripheral renin activity had a sensitivity of 73%. Thus, if captopril-stimulated peripheral renin activity were used first in a high prevalence population, 27% of patients with potentially curable hypertension would not be evaluated further, and RVH would go undiagnosed. Twenty-eight percent of our patients without RVH had a falsely elevated captopril-stimulated peripheral renin activity. This false-positive rate might be reduced by studying patients who have been off diuretics for more than 48 hours, the minimum diuretic-free period in this study. Eighty-six percent of our study subjects had discontinued diuretics for more than 48 hours, but only 36% had discontinued diuretics for more than 2 weeks. In addition, subjects with high renin essential hypertension would be likely to have a captopril-stimulated peripheral renin activity greater than 4 ng/ml/hr, potentially reducing the discriminatory power of this test.

Differential GFR and ERPF renography were also insufficiently accurate in a high prevalence population. These noninvasive techniques provide data concerning function and perfusion of each individual kidney. Differential GFR renography documents decreased function of one kidney, presumably due to stenosis of the artery supplying that kidney. Captopril further decreases GFR in a stenosed kidney and increases function in the contralateral kidney, which should accentuate the difference in GFR between the two kidneys. Our data confirm small reports that postcaptopril differential GFR renography detects renal artery stenosis with 92% sensitivity. But our data do not confirm previously reported specificities of 74–90%. Our data suggest that this test has a substantially higher false-positive rate (1 – specificity) than captopril-stimulated peripheral renin activity. Both sensitivity and specificity were lower for measurements of precaptopril and postcaptopril renography may be more useful than a postcaptopril study alone; these data need to be confirmed in larger numbers of patients.

In each of these tests (captopril-stimulated peripheral renin activity, differential GFR, and differential ERPF), the outcome is a continuous variable, and the threshold between normal and abnormal is arbitrary. In each case, the sensitivity of the test can be increased by lowering this threshold but at the expense of a higher false-positive rate. For instance,
when we set the threshold between normal and elevated captopril-stimulated plasma renin at 4 ng/ml/hr, this test had a sensitivity of 73% and a specificity of 72%. Had we set the threshold at 1 ng/ml/hr, the sensitivity would have increased to 82%, but the specificity would have fallen to 48%. The relation between sensitivity and specificity at different thresholds between a normal and an abnormal test can be graphically displayed in receiver operating characteristic (ROC) curves, which are constructed by plotting true-positive rate (sensitivity) against false-positive rate (1-specificity) at different thresholds. An ideal test would have a high true-positive rate and a low false-positive rate. The choice of threshold for a given test is influenced by the pretest probability of disease but in general is the point at which true-positive rate is maximal and false-positive rate is minimal. To determine the optimal threshold between normal and abnormal for captopril-stimulated peripheral renin, differential GFR, and differential ERPF, we constructed ROC curves (Figure 1A-1C). The points on these curves represent the true-positive and false-positive rates at five different thresholds, chosen by division of the observed results into quintiles (Table 6). The points corresponding to the thresholds used in this analysis (captopril-stimulated renin activity greater than 4 ng/ml/hr, Figure 1A; a differential in GFR of 6%, Figure 1B; and a differential in ERPF of 6%, Figure 1C) are marked with an asterisk and indicate that in each case our choice of a threshold between normal and abnormal tests provides an optimal trade off between true- and false-positive rates for a 16.7% prevalence population.

Despite optimizing the sensitivity and specificity of peripheral renin, differential GFR, and differential ERPF, each of these diagnostic tests is inferior to IV-DSRA. In our clinically selected study population, IV-DSRA was abnormal or inconclusive in all patients with reversible hypertension. Only 29% had a false-negative test. Therefore, if IV-DSRA was the first and only test used in a 16.7% prevalence group, less than three in 10 subjects without RVH would go on to further evaluation or treatment, and virtually all patients with RVH would be detected. These conclusions rely on the assumption that technically inadequate or inconclusive intravenous studies are considered abnormal and lead to further evaluation with conventional arteriography. In our study population, technically poor IV-DSRA occurred in three of 11 patients with RVH. Renovascular hypertension would not have been detected in these three individuals (4.5% of 66 patients evaluated) if arteriography had not also been performed.

Our data suggest that in clinically selected patients, IV-DSRA is justified as the initial diagnostic test. Furthermore, previously published comparisons as well as our data suggest that IV-DSRA is a reasonable alternative to conventional renal arteriography. Other authors have reported that IV-DSRA detects RVH with a sensitivity of 83–87% and specificity of 79–100%. Our data confirm the high sensitivity and specificity of IV-DSRA. Although based on a
small number of patients with RVH, our data also suggest that the absence of renal artery stenosis on a technically adequate IV-DSRA would convincingly exclude the diagnosis of renovascular hypertension (negative predictive value of 100%). Therefore, in a clinically selected population, IV-DSRA is a reasonable first diagnostic step, which can be used as a safer and less expensive alternative to conventional renal arteriography.

These conclusions about IV-DSRA apply only to patients with clinical features suggestive of RVH. However, the vast majority of hypertensive patients do not have clinical features suggestive of RVH. In this unselected population, the prevalence of RVH is estimated to be less than 5%,19-22 and therefore neither IV-DSRA nor conventional arteriography can be justified. In unselected hypertensive patients, a screening test is needed to rule out RVH and to select those who should be evaluated further. While any potential screening test must be evaluated in a screening (i.e., low prevalence) population to confirm that the sensitivity and specificity are the same as found in a high prevalence population, our data support the suggestion of Muller and others6,7 that captopril-stimulated peripheral renin activity may be a useful screening test for RVH. However, it is far from ideal. An ideal screening test has a low false-negative rate (1 - sensitivity), so that very few patients with RVH fail to be evaluated further. If our data are confirmed in a low prevalence population, 27% with RVH will have a false-negative test and therefore will not be detected by this screening procedure. While this may seem like an unacceptably high false-negative rate, it is better than the other potential screening tests evaluated. Retrospective data from Muller’s study6 suggest that the change in peripheral renin activity with captopril (the "captopril test") may be more sensitive (i.e., lower false-negative rate) than the absolute value after captopril. We chose to measure a single post-captopril peripheral renin in an attempt to design the simplest, least expensive potential screening test. However, larger studies are needed to prospectively compare the captopril test with a single measurement of captopril-stimulated renin activity.

An ideal screening test will also have a low false-positive rate (1 - specificity) so that few patients without RVH are subjected to expensive and invasive testing. Our false-positive rate of 28% suggests that a large number of patients without RVH will undergo arteriography. We hypothesize that this rate will be approximately the same in a low prevalence population. Although a high false-positive rate might conceivably be justified in a high prevalence population, it is unclear whether it would be cost effective to use such a screening test in a low prevalence population, which in this case would result in 28% of a very large target population going on to further evaluation unnecessarily.

Despite these limitations, when our data are hypothetically applied to a low prevalence population (5%), a captopril-stimulated peripheral renin level of 4 ng/ml/hr or less excluded the diagnosis of RVH with 98% certainty (negative predictive value), and a value greater than 4 ng/ml/hr increased the likelihood of renovascular hypertension to 12% (positive predictive value). The negative predictive value does not help us evaluate potential screening tests. In the setting of low likelihood of RVH, negative predictive value is uniformly high. However, positive predictive value was higher for captopril-stimulated peripheral renin than for the other potential screening tests evaluated. Only IV-DSRA had higher predictive values than the stimulated peripheral renin, and this procedure cannot be considered a potential screening test in low prevalence populations because of its expense and invasive nature. If the test characteristics we observed in a 16% prevalence population are truly applicable to a lower prevalence group, our data suggest that an elevated stimulated renin alone may be an adequate (though not ideal) screening test, allowing us to detect the majority of patients requiring further evaluation and to confidently rule out RVH when the stimulated renin is not elevated.

Once patients with high probability of renovascular hypertension are identified by either clinical criteria or a screening test, the next step in the diagnosis of RVH is documentation of renal artery stenosis. As discussed above, renal artery stenosis is detected by either IV-DSRA or conventional renal arteriography. However, the presence of renal artery stenosis does not ensure that RVH is present. Indeed, renal artery stenosis is frequently found at autopsy in both hypertensive and normotensive patients.23 Therefore, once a renal artery stenosis is detected, functional tests are generally employed to assess its hemodynamic significance and to predict blood pressure response to correction of the stenosis. The functional test most frequently used is measurement of the renal vein renin ratio. Differential renal vein renin activity is expected to provide evidence of hypersecretion of renin from a kidney distal to a hemodynamically significant main

TABLE 6. Thresholds Between Normal and Abnormal Test

<table>
<thead>
<tr>
<th>Quintile</th>
<th>PRA (ng/ml/hr)</th>
<th>GFR (%)</th>
<th>ERPF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;0.05</td>
<td>&gt;2</td>
<td>&gt;2</td>
</tr>
<tr>
<td>2</td>
<td>&gt;1.1</td>
<td>&gt;6*</td>
<td>&gt;6*</td>
</tr>
<tr>
<td>3</td>
<td>&gt;4.0*</td>
<td>&gt;14</td>
<td>&gt;10</td>
</tr>
<tr>
<td>4</td>
<td>&gt;17</td>
<td>&gt;26</td>
<td>&gt;22</td>
</tr>
<tr>
<td>5</td>
<td>&gt;109</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Captopril-stimulated peripheral renin activity (PRA), postcaptopril differential GFR (GFR), and postcaptopril differential ERPF (ERPF) were determined by dividing observed values in the study population into quintiles.

*Indicates the threshold used to determine sensitivity and specificity in Table 3.
renal artery stenosis and suppression of renin secretion from the contralateral kidney. Previous surveys of patients with known renal artery stenosis suggest that an elevated renal vein renin ratio is an unreliable predictor of blood pressure response to surgical correction of the stenosis (sensitivity 50–93%, specificity 33–63%). Stimulation with angiotensin converting enzyme inhibitor would be expected to preferentially increase renin release from a kidney with a hemodynamically significant stenosis and thereby increase the renal vein renin ratio. In support of this expectation, captopril markedly improved the test characteristics of renal vein renin ratio (sensitivity 85–100%, specificity 100%) in two small series (n=16 and n=14). Unfortunately, these findings are not confirmed in our study population, in which only seven of 11 patients with RVH had a high renal vein renin ratio. In addition, in four of the five patients in our study with essential hypertension and coincidental renal artery stenosis, both the captopril-stimulated renal vein renin ratio and the Vaughan ratio were elevated (specificity 20%). Therefore, if this functional test were used to guide decisions about whether to correct a renal artery stenosis, 36% of patients with reversible hypertension would be denied the opportunity for cure, and many patients would be treated unnecessarily. Despite the small number of patients evaluated by us and other investigators, these data suggest that the captopril-stimulated renal vein renin ratio does not accurately predict which patients with renal artery stenosis will have a reduction in blood pressure after correction of the stenosis.

An alternative functional test used to determine the hemodynamic significance of a known renal artery stenosis is postcaptopril renography. Geysskes et al report that in 21 patients with renal artery stenosis, postcaptopril renography predicted blood pressure response to surgical correction of the stenosis with sensitivity of 87% but with specificity of only 33%. Data in our 16 patients with renal artery stenosis are similar (sensitivity 91% and specificity 20% for GFR, sensitivity 80% and specificity 20% for ERPF). The very low specificities of these tests mean that most patients with renal artery stenosis, regardless of the hemodynamic significance of the stenosis, will have both postcaptopril renography and captopril-stimulated renal vein renin ratios that suggest lateralization. Therefore, these functional tests do not predict when blood pressure is likely to respond to correction of a renal artery stenosis. At this time, the only way to reliably determine whether a renal artery stenosis is causing hypertension is to correct the stenosis and observe the effect of this intervention on blood pressure.

These data concerning functional tests when renal artery stenosis is known to be present (Table 5) can also be used to demonstrate that the usefulness of these diagnostic tests varies considerably depending on the pretest probability that renovascular hypertension is present. In the 16 patients with renal artery stenosis, 11 of whom had a decrease in blood pressure after correction of a renal artery stenosis, the prevalence of renovascular hypertension is 69%. Using the renal vein renin ratio as an example, if the sensitivity and specificity found in our 16% prevalence population also apply to a 69% prevalence population, we deduce that an elevated ratio would give no information because the positive predictive value (64%) would actually be lower than the pretest probability. This means that renovascular hypertension would be less likely in a patient with a positive test than it would be in a patient with a negative test. These calculations emphasize the need to consider prevalence when diagnostic tests are designed or evaluated as well as the need to define sensitivity and specificity in a broad range of prevalences. It is clear that these functional tests are unable to accurately predict blood pressure response to correction of a renal artery stenosis.

In summary, although based on a relatively small number of patients, our data suggest that clinical criteria can be used to identify a subpopulation of hypertensive adults with 16.7% prevalence of renovascular hypertension. In a clinically selected high prevalence group, IV-DSRA or conventional renal arteriography should be performed. IV-DSRA will be abnormal or inconclusive in virtually all patients with RVH, and a normal study will be sufficient to exclude this diagnosis. In clinically selected populations, less invasive tests are not necessary and may provide false reassurance that renovascular hypertension is absent. On the other hand, neither IV-DSRA nor conventional arteriography can be justified in unselected hypertensive populations. In a low prevalence population, screening with captopril-stimulated peripheral renin activity may be the most useful and efficient procedure. When our observed sensitivities and specificities are used to calculate predictive values in a 5% prevalence group, our data suggest that a normal captopril-stimulated plasma renin activity rules out renovascular hypertension with 98% assurance. In this group, an elevated captopril-stimulated peripheral renin level identifies patients with a 12% chance of having RVH. In our opinion, a 10% or greater chance of renovascular hypertension is sufficient justification for angiographic evaluation. Therefore, patients who have clinical features suggestive of renovascular hypertension or an elevated peripheral renin level should be evaluated further with IV-DSRA or conventional renal arteriography. Once renal artery stenosis is identified in a hypertensive patient, none of the currently available functional tests accurately predict the hemodynamic significance of a stenosis. Therefore, the only way to distinguish renovascular hypertension from essential hypertension with coincidental renal artery stenosis is to correct the anatomic lesion and observe the subsequent effect on blood pressure.
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