Simplified Captopril Renography in Diagnosis and Treatment of Renal Artery Stenosis


To improve the diagnosis and forecast the response to surgery or renal angioplasty in patients with hypertension and renal artery stenosis, we employed a simplified captopril renography protocol in conjunction with renal arteriography in 94 clinically selected patients. Fifty hypertensive patients (group 1) with a high clinical likelihood of renovascular hypertension were evaluated using a simplified captopril renography protocol and renal angiography on the arterial side. Criteria for normal captopril renal scintigrams were established based on this original cohort and validated in an additional 44 clinically comparable patients (group 2). Renal revascularization or nephrectomy was performed in 39 patients, and success of the procedure was determined in the 34 patients for whom 3-month follow-up was available. In the 94 patients, 44 (47%) had renal artery stenosis. Simplified captopril renography was 91% sensitive and 94% specific in identifying or excluding renal artery stenosis in the combined group, with no difference in the diagnostic utility between groups 1 and 2, or in those with renal insufficiency (n=38) or those with bilateral disease (n=17). Scintigraphic abnormalities induced by captopril were strongly associated with cure or improvement in blood pressure control following revascularization or nephrectomy (15 of 18), while the lack of captopril-induced changes was associated with failure of such intervention (13 of 16) (p=0.0004). We conclude that simplified captopril renography is highly sensitive and specific in the diagnosis of renal artery stenosis in a clinically selected high-risk population and that the test accurately predicts the success or failure of therapeutic intervention. (Hypertension 1991; 18:289–298)

Though unusual, renovascular hypertension is the most common curable form of hypertension. The clinical presentation is often typical, yet no single clinical characteristic or cluster of characteristics is sufficiently sensitive or specific to identify patients who are likely to have the disorder and therefore require renal arteriography.1 Screening of all hypertensives for renovascular hypertension has long been abandoned, and even in patients at high risk, most noninvasive tests are no longer routinely recommended.2 The diagnostic approach is further complicated in that typical lesions of renal artery stenosis may be observed in normotensive individuals, and technically successful revascularization of an ischemic kidney may not cure or even improve the patient's hypertension.

An ideal noninvasive test to evaluate clinically appropriate patients for renovascular hypertension must not only be safe but also should accomplish three purposes. First, the test must be highly sensitive and identify nearly all patients with anatomic renal artery lesions. Second, it should be reasonably specific and exclude those patients in whom arteriography is likely to show normal or only minimally diseased renal arteries. This is especially important since many patients in whom this diagnosis is suspected, such as those with renal insufficiency or severe generalized atherosclerosis, may be at significant risk from arteriography. Third, the ideal test should also demonstrate the hemodynamic significance of the lesion and predict whether percutaneous transluminal angioplasty, nephrectomy, or surgical renal revascularization will cure or improve the patient's hypertension.

The experience with currently available methods to diagnose renal artery stenosis, including the recently introduced captopril test, has not been satisfactory.3 Though the comparison of renal vein renin
activity in each kidney is quite sensitive, especially in patients with unilateral renal artery stenosis and normal renal function, it is not sufficiently accurate in patients with bilateral disease or renal insufficiency. \(^\text{3,4}\) Therefore, we and others have advocated proceeding directly to arteriography as the sole diagnostic procedure in patients believed, on clinical grounds, to have a high likelihood of renal artery stenosis. \(^\text{2,5}\)

Currently available tests also fail to predict the outcome of revascularization or nephrectomy. While there is ample evidence that a lateralizing renal vein renin ratio identifies patients who will be cured or improved with greater than 90% positive predictive value, such a ratio does not identify those patients in whom revascularization will fail. \(^\text{4,5,6}\) Therefore, we have also proceeded with surgery or angioplasty if anatomically appropriate lesions were present and there were no contraindications to the procedure.

During the latter part of the 1980s, the diagnostic utility of renal scintigraphy was improved substantially by comparing the results of the test before and after (or simply after) the administration of a single dose of the angiotensin converting enzyme inhibitor captopril. The protocols suggested for captopril renography have recently been summarized by Saddler and Black. \(^\text{8}\) We believe that many of these protocols were hazardous in that they required stopping therapy with some or all antihypertensive agents, often for lengthy periods, or inconvenient in that certain protocols that employed both technetium-99m-labeled diethyleneetriamine pentaacetic acid (Tc-99m DTPA) and \(^{[131]}\)Iodohippurate required multiple scans, which had to be done on separate days. \(^\text{5,6,10}\) Moreover, it was not clear that these studies could distinguish hemodynamically significant lesions for which revascularization would cure or improve the patient’s hypertension (functional renal artery stenosis or true renovascular hypertension) from those lesions for which revascularization would not be beneficial (anatomic renal artery stenosis in the patient with essential hypertension or irreversible renal ischemic disease).

Accordingly, we employed a simplified protocol that does not require stopping medication, except for angiotensin converting enzyme inhibitors the day prior to the scintigrams, and has both scans performed on the same day on an outpatient basis. We report the results of simplified captopril renography in 94 patients judged on clinical grounds to have a high likelihood of renal artery stenosis and to require arteriography to confirm or exclude the diagnosis. We derived our criteria for a positive or negative simplified captopril renogram by evaluating retrospectively 23 patients with essential hypertension among the original 50 patients (group 1) and then validating these criteria prospectively in a second cohort (group 2) of patients who were similarly selected. \(^\text{19}\) We found the simplified captopril renogram to be more than 90% sensitive and specific in diagnosing renal artery stenosis in both groups, and the presence or absence of captopril-induced changes properly predicted the outcome of intervention with greater than 80% accuracy.

**Methods**

**Patient Population**

In late 1987, simplified captopril renography became available at our institution. Between December 27, 1987, and June 30, 1990, during the course of clinical evaluation, we studied all adult patients referred to the Yale University Hypertension and Preventive Cardiology Service whom we strongly suspected by clinical criteria of having renal artery stenosis and who agreed to and were able to tolerate renal scintigraphy and renal arteriography. The patients we evaluated were those with acceleration of hypertension that previously had been easily controlled; a history of heavy tobacco use along with other evidence suggesting renovascular hypertension, such as abdominal or flank bruit or other signs of occlusive vascular disease; or hypertension with an elevated serum creatinine level not explicable by another etiology. We did not evaluate patients primarily because of renal insufficiency. Nor did we study patients simply because of the age at which their hypertension was first diagnosed, if none of the other typical features of renal artery disease were present. We also studied patients with resistant hypertension, which we defined as diastolic blood pressure of greater than 90 mm Hg despite two or more appropriate antihypertensive drugs administered in optimal doses (Table 1).

**Study Protocol**

A full description of our simplified captopril renography protocol and method of analysis has been published recently. \(^\text{19}\) In brief, all antihypertensive medications, except for angiotensin converting enzyme inhibitors, were continued up to and including the day of the test. Captopril was withheld for 12 hours, enalapril for 24 hours, and lisinopril, the longest-acting angiotensin converting enzyme inhibitor currently available in the United States, was withheld for 48 hours. After oral hydration at home (2–3 glasses of tap water), a standard renal scintigram was performed using 12 mCi of Tc-99m DTPA. Using a large-field-of-view gamma camera and a minicomputer system, a sequence of dynamic images were acquired in the posterior view at a rate of 20 seconds per frame with the patient lying supine over the collimator. To control for residual activity after the first dose, images were acquired prior to the second injection and then subtracted from each frame of the postcaptopril scan. Regions of interest were determined for the kidneys and held constant and used for both the precaptopril and postcaptopril studies. Urinary losses were replaced with tap water to ensure adequate hydration for the second scintigram. After 3 hours, 50 mg captopril was administered orally. Blood pressure was measured for safety.
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 50)</th>
<th>Group 2 (n = 44)</th>
<th>Groups 1 and 2 (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>57.0 ± 15.1</td>
<td></td>
<td>56.8 ± 14.0</td>
</tr>
<tr>
<td>Range</td>
<td>18-83</td>
<td></td>
<td>18-77</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>8</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>White</td>
<td>42</td>
<td>84</td>
<td>37</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(highest recorded, mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>197 ± 27</td>
<td></td>
<td>183 ± 30*</td>
</tr>
<tr>
<td>Range</td>
<td>140-260</td>
<td></td>
<td>136-270</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(highest recorded, mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>108 ± 15</td>
<td></td>
<td>104 ± 21</td>
</tr>
<tr>
<td>Range</td>
<td>72-140</td>
<td></td>
<td>62-164</td>
</tr>
<tr>
<td>Cigarette smokers (&gt;25 pack-years)</td>
<td>35</td>
<td>70</td>
<td>27</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.7 ± 1.6</td>
<td></td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td>Range</td>
<td>0.6-11.7</td>
<td></td>
<td>0.6-3.6</td>
</tr>
<tr>
<td>Renal insufficiency (serum creatinine ≥ 1.5 mg/dl)</td>
<td>20</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>Resistant hypertension (see text)</td>
<td>35</td>
<td>70</td>
<td>19</td>
</tr>
</tbody>
</table>

*p = 0.02 different from group 1 by t test.
†p = 0.01 different from group 1 by χ² test.

Therapeutic interventions included renal artery bypass in 15, nephrectomy in two, and percutaneous renal artery angioplasty in 22 patients. All patients undergoing angioplasty had immediate repeat arteriography to assess vessel patency. Repeat arteriography after surgery was not routinely performed.

Study Criteria

We defined a positive simplified captopril renogram as one that is abnormal either prior to or following the administration of captopril (Table 2). Based on the findings in the patients without renal artery stenosis in group 1, a scan was considered abnormal if the time to peak activity was greater than or equal to 11 minutes on either the precaptopril or the postcaptopril scan or if the glomerular filtration rate ratio between kidneys (higher/lower glomerular filtration rate) was greater than 1.5 on the postcaptopril scan.19 If the only abnormality on either scan was a glomerular filtration rate ratio of greater than 1.5 on the precaptopril scan that became less than 1.5 on the postcaptopril scan, the simplified captopril renogram was read as normal. We also examined whether captopril induced changes in the scintigram.12 A scan with captopril-induced changes was one in which a normal time to peak activity and/or purposes, but values were not systematically analyzed. One hour later, a repeat scintigram was done with the patient in the same position as in the first scan, with the same regions of interest employed. Renogram curves were plotted after subtracting the activity in the renal pelvis from that in the renal parenchyma. Time to peak activity was then derived from the renogram curves. Glomerular filtration rate was calculated for each kidney using the algorithm of Gates.20 Other studies, such as renal scintigraphy with [131I]iodohippurate or plasma or renal vein renin activity either with or without captopril, were not performed routinely.

All patients underwent transfemoral intra-arterial digital subtraction renal angiography, typically within 1 week, but invariably within 1 month, after the simplified captopril renogram. Arteriograms were reviewed independently by a vascular radiologist without knowledge of the results of scintigraphy. The simplified captopril renograms were interpreted by a senior nuclear medicine specialist and two associates unacquainted with the clinical details or the results of the arteriograms. Intraobserver and interobserver concordance for the scans of patients in group 1 was greater than 93%.19 Such data were not obtained for the patients in group 2.
TABLE 2. Diagnostic Criteria

<table>
<thead>
<tr>
<th>Test</th>
<th>Groups 1 and 2 (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive simplified captopril renogram: time to peak activity ≥11 minutes on either precaptopril or postcaptopril scan and/or glomerular filtration rate ratio between kidneys &gt;1.5 on postcaptopril scan.</td>
<td>39 30</td>
</tr>
<tr>
<td>Captopril-induced change on simplified captopril renogram: normal precaptopril time to peak activity and/or glomerular filtration rate ratio that becomes abnormal on postcaptopril study.</td>
<td>24 21</td>
</tr>
<tr>
<td>Positive angiogram (atherosclerosis): stenosis &gt;75% luminal diameter or stenosis &gt;50% with poststenotic dilatation, or branch renal artery stenosis.</td>
<td>43 37</td>
</tr>
<tr>
<td>Positive angiogram (fibromuscular dysplasia): lesions characterized as mild, moderate, or severe, without percentage stenosis assigned. Only moderate or severe lesions considered positive.</td>
<td>37 31</td>
</tr>
<tr>
<td>Cure following intervention: diastolic blood pressure ≤90 mm Hg 3 months following intervention.</td>
<td>21 18</td>
</tr>
<tr>
<td>Improvement following intervention: diastolic blood pressure reduced by 15% on same or fewer agents, or to normal (≤90 mm Hg) on fewer agents, 3 months following intervention.</td>
<td>24 21</td>
</tr>
</tbody>
</table>

statistical analysis

Groups were compared using $\chi^2$ and t tests for categorical and continuous variables, respectively. Data are expressed as mean ± SD.

results

In all, 94 patients (50 in group 1 and 44 in group 2) were included in the study. Nine of these patients were not evaluated by our service yet are reported because they had similar clinical characteristics, had undergone simplified captopril renography, and by arteriography had a prevalence of renal artery stenosis (four of nine) similar to that of our 85 patients. All of the 94 patients were evaluated because of hypertension and none primarily because of renal insufficiency. The prestudy medical regimen was identified in 90 of the 94 patients. We evaluated another 10 patients in the Hypertension Clinic who underwent simplified captopril renography but did not have arteriography because of subsequent refusal or inability to tolerate the procedure. Since arteriography was not done, we did not include these patients in the study. Fifty-two other patients had simplified captopril renography done without subsequent arteriography. The test was ordered by other physicians, and these patients were also not included in the present report because we could not be certain of the indications for testing or the renal artery anatomy.

Of the 94 patients included, 44 (47%) had renal artery stenosis. Of those with significant renal artery stenosis, 41 had atherosclerotic disease, two had fibromuscular dysplasia of the main renal artery, and one had fibromuscular dysplasia of an intrarenal branch. Two additional patients had mild fibromuscular dysplasia of the main renal artery, and one patient demonstrated both fibromuscular dysplasia and atherosclerosis. She is included in the latter category because atherosclerosis was the predominant lesion. There were no serious complications from simplified captopril renography, and no patient developed clinically significant hypotension. Following arteriography one patient experienced transient renal dysfunction and a second developed mild congestive heart failure. Therapeutic interventions were conducted in 39 patients, for whom 3-month follow-up data were available in 34 at the time of submission of this manuscript. One patient was lost to follow-up, and four are awaiting a 3-month postprocedure evaluation. The remaining five patients with renal artery stenosis are awaiting interventions. Table 1 illustrates the clinical characteristics of the overall cohort of study patients and confirms that groups 1 and 2 were clinically comparable. Table 3
lists the drugs that patients were receiving when the simplified captopril renogram was performed. Table 4 compares the demographic and clinical characteristics of patients found to have renal artery stenosis and patients with normal or minimally affected renal arteries and, presumably, essential hypertension. One patient with unilateral renal dysplasia who did not undergo nephrectomy is included in the group without renal artery stenosis. Patients with renal artery stenosis were older, more likely to have an abdominal bruit, and had a significantly lower diastolic blood pressure and wider pulse pressure than those with negative arteriograms. Of the 15 black patients studied, five had renal artery stenosis.

The diagnostic utility of simplified captopril renography is shown in Table 5. The test was more than 90% sensitive and specific in both groups and had comparable diagnostic value in the 38 patients with renal insufficiency (serum creatinine concentration of greater than or equal to 1.5 mg/dl). Eight of these patients (five with renal artery stenosis, three without) had serum creatinine values greater than or equal to 3.0 mg/dl. Simplified captopril renography agreed with the findings at arteriography in all of these patients. Seventeen patients (39%) had bilateral renal artery stenosis. Simplified captopril renography was positive (though not necessarily for both kidneys) in 15, with a sensitivity of 88%.

We examined the effect of drug therapy at the time of simplified captopril renography on the diagnostic utility of the test (Table 6). In general, specificity was maintained regardless of previous treatment. Though the number of patients receiving angiotensin converting enzyme inhibitors was small, use of these agents reduced the sensitivity of simplified captopril renography to 70%. Diuretic therapy did not affect the accuracy of the examination.

In seven patients (8% of the study cohort), simplified captopril renography did not coincide with the arteriographic findings. Three patients had false-positive studies; one patient had congenital renal dysplasia, the second had a renal cyst, and in the third there was no explanation for the false-positive study. False-negative studies were found in four
patients, including the patient with fibromuscular dysplasia of a branch renal artery. Two patients with false-negative studies had bilateral 50% stenosis with poststenotic dilatation. Though both patients underwent renal artery angioplasty of both lesions, neither patient was improved. In one patient the reason for the false-negative study was not clear.

Table 7 shows the blood pressure response after 3 months in 34 of the 39 patients with renal artery stenosis who underwent interventions. Fifteen patients were improved and three, two with fibromuscular dysplasia and one with atherosclerosis, were cured. Twenty-five of the 44 patients with renal artery stenosis (57%) had captopril-induced changes in their second scintigram. Eighteen of these had a procedure with adequate follow-up. Captopril-induced scintigraphic changes were strongly associated with improvement or cure following intervention \( (p = 0.0004) \). Lack of such changes was strongly predictive of failure to improve blood pressure control. The patients without captopril-induced changes who did not improve following intervention (13 of 16) had either normal studies that remained normal after captopril (five patients) or abnormal initial scans (eight patients). In either case, intervention was undertaken on the basis of arteriographic evidence, as has been our practice up to the present. Three patients died of complications following revascularization. None had exhibited captopril-induced changes, and none demonstrated even transiently improved blood pressure control after revascularization. Eight patients with failed interventions later had repeat renal scintigraphy to exclude technical failure as a cause for the lack of blood pressure control. In no case was restenosis at a dilated site or closure of a bypass graft suggested by decreased renal perfusion, thus pointing to essential hypertension or irreversible renal parenchymal damage as the cause for chronically refractory hypertension. Repeat arteriography was not performed routinely.

### Table 5. Diagnostic Value of Simplified Captopril Renography

<table>
<thead>
<tr>
<th>Group</th>
<th>Renal artery stenosis present</th>
<th>Renal artery stenosis absent</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive SCR</td>
<td>Negative SCR</td>
<td>Positive SCR</td>
<td>Negative SCR</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Group 1</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>25</td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td>Group 2</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>22</td>
<td>90%</td>
<td>96%</td>
</tr>
<tr>
<td>Groups 1 and 2</td>
<td>40</td>
<td>4</td>
<td>3</td>
<td>47</td>
<td>91%</td>
<td>94%</td>
</tr>
<tr>
<td>Renal insufficiency (serum creatinine ≥1.5 mg/dl) (n=38)</td>
<td>20</td>
<td>3</td>
<td>1</td>
<td>14</td>
<td>87%</td>
<td>93%</td>
</tr>
</tbody>
</table>

SCR, simplified captopril renogram.

### Table 6. Influence of Prestudy Medical Regimen

<table>
<thead>
<tr>
<th>Drug therapy</th>
<th>Renal artery stenosis present</th>
<th>Renal artery stenosis absent</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors (alone or in combination)</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>15</td>
<td>70%</td>
<td>94%</td>
</tr>
<tr>
<td>No angiotensin converting enzyme inhibitors</td>
<td>31</td>
<td>1</td>
<td>2</td>
<td>30</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>26</td>
<td>4</td>
<td>1</td>
<td>24</td>
<td>87%</td>
<td>96%</td>
</tr>
</tbody>
</table>

Accurate data on type of drug therapy at time of study were available in 90 of 94 patients. SCR, simplified captopril renogram.

### Discussion

We have demonstrated that simplified captopril renography is a safe and highly sensitive and specific noninvasive test for the diagnosis of anatomic renal artery stenosis in a population at high risk for this disorder. Of equal importance, the presence or absence of captopril-induced changes accurately predicted the success or failure of intervention. We have shown the diagnostic usefulness of the test even in patients with abnormal kidney function or bilateral disease, two patient groups in which other diagnostic methods have not been sufficiently sensitive or specific.\(^3,^4\) There were no significant test-related adverse reactions and patients were able to remain on their antihypertensive medications, avoiding any danger of acceleration of hypertension during the pretest period. Our data suggest that it may be necessary to stop angiotensin converting enzyme inhibitors for longer than we have done.

During the past decade it has become especially important to identify patients with this potentially curable form of secondary hypertension. Not only have surgical techniques and results improved, but also percutaneous transluminal renal angioplasty has enabled patients who could not tolerate major sur-
Numerous approaches to the diagnosis of renovascular hypertension have been advocated enthusiastically over the last 30 years.3 10 22 23 The tests can be divided into three types: 1) imaging, 2) biochemical measurements with and without pharmacological enhancement or hemodynamic analysis, and 3) morphological studies (renal biopsy). Virtually none has fulfilled its initial promise. It is not clear whether the failure of the tests can be ascribed to technical problems, to an incomplete understanding of the pathophysiology of renovascular hypertension, or simply to the use of a test in an inappropriate population (namely, one with a low prevalence of the disease).26

The imaging studies formerly recommended include rapid-sequence intravenous pyelography and renal scintigraphy, which have largely been abandoned because of unacceptably low accuracy. Preliminary reports have suggested a role for renal Doppler ultrasound,25 though definitive data concerning the value of this modality are not yet available. Biochemical assays with or without hemodynamic measurements presume that the kidney, in response to reduced perfusion, will augment renin production and that consequently the renal vein renin level or systemic plasma renin activity will rise.27 28 Though this is the case in acute animal models, it is less clearly so in humans and animals with chronic renal artery lesions.29 31 Many of the biochemical or hemodynamic tests used to diagnose renal artery stenosis and predict cure are based on this pathophysiological construct.4 32

In humans, however, the measurement of peripheral plasma renin activity with or without enhancement by volume depletion has proven unreliable and not even as useful as intravenous pyelography.1 4 Renal vein renin sampling may be highly sensitive (greater than 90%), but it requires an invasive procedure and sufficient laboratory proficiency.4 6 22 The lack of specificity of the test, however, implies that an arteriogram will still be required in many patients and contribute little to what is learned from simply performing an arteriogram and proceeding to revascularization.

Pharmacological agents that influence the renin-angiotensin system have long been used to enhance the value of diagnostic tests for renal artery stenosis. The angiotensin II blocker saralasin was studied and abandoned because neither the degree or direction of blood pressure change nor the response of plasma renin activity was sufficiently sensitive or specific to justify the use of this agent as a diagnostic tool.1 24 25 More recently, Muller and associates3 measured plasma renin activity after oral captopril administration in the so-called captopril test. They derived diagnostic criteria based on the drug's effect on plasma renin activity and then applied these retrospectively in 246 patients, claiming excellent sensitivity and specificity. No validation of the criteria was undertaken by the authors. The test was not accurate in patients with renal insufficiency and required a normal sodium intake as well as the stopping of all antihypertensive agents. Also, the criteria were based on assays performed by those with vast experience and expertise in measuring plasma renin activity, raising the possibility that other laboratories may not be able to duplicate the results.3 24 26

Two groups recently have attempted a prospective confirmation of the value of the captopril test.35 36 Their results diverged widely. Frederickson and associates35 used the captopril test in 100 patients, 29 of whom had renal artery stenosis, and reported it to be sufficiently sensitive and specific. All medications, including diuretics, were withheld for 7 days, and not all patients termed essential hypertensives had angiograms to prove that renal artery stenosis was not present. In a better-designed study, Postma and associates36 performed the captopril test in 149 unselected patients and found it far too insensitive (39%) to be useful. This group of investigators discontinued sodium restriction as well as all antihypertensive medication for 2 weeks. Postma and associates36 were also unable to confirm the value of each of the biochemical criteria recommended by Muller and associates.3

Our approach to the evaluation of a diagnostic test for renal artery stenosis was to use well-described clinical criteria to select an enriched population in which the pretest probability of disease is high and therefore in which a diagnostic test is most useful.26 We then sought to define the parameters for a positive or negative test employing those patients.

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We then sought to define the parameters for a positive or negative test employing those patients. We excluded patients who did not have adequate and interpretable angiograms on the arterial side. To distinguish anatomic from functional renal artery stenosis, the results of revascularization were evaluated after at least 3 months.
We used clinical criteria similar to those employed by Svetkey and associates in their prospective study of diagnostic methods for renal artery disease. This group identified a population with a lower prevalence of structural renal artery lesions (24%) than we found, perhaps because they used age alone as a criterion (all hypertensives less than 25 or more than 45 years of age at first presentation were considered eligible) and excluded those patients with a serum creatinine concentration of greater than 2.0 mg/dl and those with recent coronary or cerebrovascular events. We did not exclude any patient who could tolerate the study and did not evaluate patients simply on the basis of age at the initial diagnosis of hypertension. In addition, unlike Svetkey and associates, we considered patients with atherosclerotic disease in other vascular beds to be at high risk for renal artery stenosis. Using our criteria, we found a population with a 47% prevalence of renal artery stenosis.

We did not compare prospectively the usefulness of simplified captopril renography with other noninvasive methods because of our doubts about the captopril test as originally described and our disinclination to rely on assays of plasma renin activity to find cases of renal artery stenosis. These doubts were supported by the results of Svetkey and associates. They showed that neither captopril-stimulated peripheral renin activity nor renal vein renin determinations were sufficiently sensitive in their selected high-risk patients, nor did such studies predict the failure of therapeutic interventions. Though we measured the blood pressure response to angiotensin converting enzyme inhibition is not diagnostically meaningful. Moreover, as Nally and associates found in their captopril renography study, a decrease in blood pressure after drug administration did not differentiate patients with renal artery stenosis from those with essential hypertension.

The results reported here extend our preliminary observations and those of Geyskes and associates that the presence of captopril-induced changes effectively differentiates functional from anatomic renal artery stenosis. We hypothesized that a normal precaptopril scan that remains normal after captopril administration suggests essential hypertension, perhaps in the setting of coincident but subcritical renal artery obstruction, and that an abnormal (using our criteria) precaptopril scan that does not change after drug administration indicates a fixed or irreversible renal ischemic lesion. In either situation, intervention would not be expected to reduce blood pressure. However, an abnormality induced by the drug suggests a functional or reversible renal ischemic lesion and predicts a good outcome after renal artery revascularization. Our results support this hypothesis, though the sample size is still small and further validation by others is warranted.

Despite promising results, 8% of the studies performed did not coincide with the angiographic findings. We have carefully analyzed each of these cases. Two of the three patients with false-positive simplified captopril renograms had unilateral renal abnormalities (cyst and dysplasia), and the other patient may have been dehydrated. It is noteworthy that two of the four patients with false-negative studies had bilateral 50% stenosis with poststenotic dilatation but were not improved following bilateral angioplasty, suggesting that they may have been essential hypertensives with anatomic renal artery stenosis and that simplified captopril renography correctly predicted the failure of angioplasty. Only renal arteriography would have provided the diagnosis in the one patient with fibromuscular dysplasia of a branch renal artery.

We wish to emphasize that the data presented here pertain only to hypertensive patients suspected of having renal artery stenosis and not to the general hypertensive population or to patients for whom the search for renal artery stenosis may be indicated for other reasons, such as renal insufficiency. We do not contend that simplified captopril renography should be used as a screening test for a general population of hypertensives. The diagnostic utility of the test remains to be determined for such a population. However, it is likely that unless testing is confined to a high-risk group, more false-positive results will be obtained.

In our view, there are four classes of patients with renal arterial lesions. The first class comprises patients with clinically silent subcritical lesions who have normal blood pressure and renal function. The second is a well-described group of patients who also have normal blood pressures but exhibit renal insufficiency on the basis of progressive renal ischemia and may benefit from revascularization. The diagnostic utility of simplified captopril renography was not evaluated in patients of either of these first two classes.

The third class comprises patients with functional renovascular hypertension with or without renal insufficiency. These patients are hypertensive, and they will have positive captopril scintigrams with captopril-induced changes and should respond well to therapeutic interventions. The last class comprises patients with anatomic renal artery stenosis. They have hypertension, though not necessarily because of renal artery disease. Or, they may have been functional renovascular hypertensives whose lesions have progressed to the point of irreversible ischemic renal injury. In support of this idea is work by Hughes and associates, who showed that patients with longer durations of hypertension experienced poorer outcomes following surgery. Our data strongly suggest that the lack of captopril-induced changes on the postcaptopril scintigram will distinguish such patients with anatomic renal artery stenosis from those with functional renal artery stenosis and thus permit the
former group to avoid revascularization procedures that are highly likely to fail.

In conclusion, we found that a simplified captopril renography protocol holds major promise in the diagnosis of renovascular hypertension. The high specificity and negative predictive value permit even slightly longer than has been our practice. The utility of simplified captopril renography in high-risk hypertensive patients may need to be withheld for highly suspected patients to avoid arteriography. The safety of simplified captopril renography is an important advantage in that antihypertensive therapy can be continued without significantly influencing the accuracy of the test, though angiotensin converting enzyme inhibitors may need to be withheld for slightly longer than has been our practice. The utility of simplified captopril renography is high sensitivity and positive predictive value implying that the test should be used only in such a cohort and not as a general screening maneuver in the hypertensive population at large. Once the diagnosis of renal artery stenosis is established anatomically, the success of intervention may be anticipated on the basis of captopril-induced changes, confirming that the observed lesion was of hemodynamic significance and suggesting that relief of the arterial obstruction will improve blood pressure control.

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