To evaluate the utility of renal duplex scanning and the captopril test in the detection and functional assessment of renovascular disease, by comparing their results with those of angiography and captopril isotopic renography (CIR).

Sixty hypertensive patients with aortoiliac disease and 16 with clinically suspected renovascular hypertension (RVH) were included. All the patients underwent renal duplex scanning prior to angiography. In addition, isotopic renograms and a determination of peripheral plasma renin activity (PRA) at baseline and 60 min after oral intake of 50 mg of captopril were both performed. A postcaptopril PRA > 5.7 ng/mL/h was considered as diagnostic of a positive captopril test. On the basis of the results of the angiography and isotopic renograms, all the patients were classified into three groups: group I (n = 33), essential hypertension (EHT); group II (n = 20), hypertension and angiographic RAS > 60% but negative CIR; and group III (n = 24), RAS > 60% and positive CIR. This last condition was considered as highly suspicious for RVH.

Renal duplex scanning showed greater accuracy than captopril PRA or CIR for detecting RAS > 60% (groups II and III) with 87.3% versus 52.4% and 45.3% sensitivity (S), and 91.5% versus 84.4% and 92.8% specificity (Sp), respectively. The captopril test correctly identified 44 of 51 EHT patients (groups I and II) and 20 of 23 highly suspected of RVH (group III) with 87% S, 86.5% Sp, 74.1% PPV, and 93.6% NPV. Accuracy was further increased when a combined approach (renal duplex scanning and captopril test) was followed (82.6% S, 93.7% Sp, 86.4 PPV, and 91.8 NPV).

In our study, renal duplex scanning was a useful screening method for detecting anatomical RAS. A combination of both renal duplex scanning and captopril test may be an appropriate approach to the primary screening for RVH, thereby permitting the selection of those patients indicated for angiography. Am J Hypertens 1997;10:1290–1296 © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Renovascular, ultrasonography, isotopic renography, captopril, renin.
Most of the diagnostic methods used for the assessment of renovascular disease actually evaluate only selected features of the disease. Angiography allows for the morphological detection of renal artery stenosis (RAS). Evaluation of renal perfusion has usually relied on urography or isotopic renography. Otherwise, assessment of the renin-angiotensin system has been made possible by means of functional tests, such as the use of dynamic changes in plasma renin activity or renal scans after captopril administration. Indeed, development of angiotensin converting enzyme (ACE) inhibitors has brought about not only a major improvement in blood pressure control, but also a new diagnostic approach to renovascular hypertension (RVH). ACE inhibition acts as a pharmacologic probe to investigate the role of angiotensin II in the pathophysiology of RVH. Patients with RVH have a marked hyperreninemic response to captopril stimulation compared with that in patients with essential hypertension (EHT). This pathophysiology forms the basis of the captopril plasma renin activity test. On the other hand, decreased angiotensin II levels resulting from ACE inhibition also affect intrarenal hemodynamics, an effect that forms the basis of the captopril-stimulated renography studies. More recently, duplex scanning has proven to be accurate enough for detecting RAS based on hemodynamical parameters. However, to date no diagnostic method permits the simultaneous detection of RAS and the functional assessment of renal perfusion. On the other hand, the choice of the ideal screening method is complicated by the lack of absolute accuracy. For that reason, strategies based on a combination of tests may be a more reliable approach.

The aim of this study was to evaluate the utility of renal duplex scanning and captopril testing for the detection and functional assessment of renovascular disease, by comparing their results with those of angiography and captopril isotopic renography.

PATIENTS AND METHOD

The study population consisted of 78 consecutive patients: 60 hypertensive patients with aortoiliac disease and 18 submitted for clinical suspicion of renovascular hypertension (RVH). Patients were considered for inclusion when blood pressure was \( \geq 160/90 \) mm Hg without treatment or while on a one-drug regimen, and when their hypertension needed two or more drugs to be controlled. Those cases with plasma creatinine levels \( > 1.5 \) mg/dL and those with a solitary or transplanted kidney were excluded, as these conditions decrease sensitivity and increase the risk of acute renal failure in response to captopril administration, respectively.

Angiography, renal duplex scanning, isotopic renography, and captopril test were performed in all the patients. Indication for angiography was established on the basis of aortoiliac occlusive disease or clinical suspicion of RVH. Their results were used as the gold standard for anatomical RAS. Captopril test and renal duplex scanning were performed simultaneously, prior to captopril isotopic renography (CIR). On the basis of the results of the angiography and isotopic renograms, all the patients were classified into three groups: group I, essential hypertension (EHT); group II, EHT and RAS \( \geq 60\% \) with negative CIR (EHT + RAS); and group III, RAS \( > 60\% \) with positive CIR. This last condition was considered as highly suspicious of RVH and used as gold standard for comparative analysis.

The duplex examination was carried out using a 2.25 MHz phased array transducer (ATL Ultramark 9 DP, Seattle, WA). An anterior approach with different cross-sectional images was used to identify the origin of both main renal arteries. Once the Doppler signal was obtained, the renal arteries were scanned all along their length, trying to keep the incident angle as close to \( 60^\circ \) as possible. Finally, the length and cortical thickness of both kidneys were measured, recording the Doppler signals in the renal parenchyma (interlobar arteries). On the basis of previously published validation studies, we used a peak systolic velocity (PSV) greater than 200 cm/sec in the main renal artery as the diagnostic criterion for detecting RAS \( > 60\% \). Renal arteries were considered occluded when kidney length was \( < 8.5 \) cm, cortical thickness \( < 1 \) cm, and no Doppler signal could be registered in the renal parenchyma. Aortography or selective renal intra-arterial digital subtraction angiography was performed in all the patients. The percentage of diameter reduction (\% RAS) was calculated after measurement of the diameter of the renal artery immediately adjacent to the stenosis (D) and at the level of maximum stenosis (d):

\[
\text{% RAS} = \left( \frac{(D-d)}{D} \right) \times 100.
\]

Three grades of stenosis were established for both diagnostic methods: \(< 60\%; \geq 60\%; \) and occlusion.

\( \beta \)-Blockers, diuretics, and ACE inhibitors were discontinued for at least 7 days, and any antihypertensive treatment for 24 h, before performing CIR or determination of PRA. Peripheral blood was extracted from an antecubital vein after decubitus resting for 30 min. Arterial pressure was recorded every 15 min during the test. A new blood sample was obtained 60 min after oral intake of 50 mg of captopril. For PRA determinations, a commercial radioimmunoassay (RIA) kit was used, and the results expressed as ng/mL/h of angiotensin I generated “in vitro.” RIA sensitivity was 0.17 ng/mL and intra- and interassay variabilities were 4.6% and 7.6%, respectively. The baseline normal value was 1.4 ± 0.46 ng/mL/h. Following Frederick-
TABLE 1. OPERATIVE CHARACTERISTICS OF RENAL DUPLEX SCANNING, CAPTOPRIL ISOTOPIC RENOGRAPHY, AND CAPTOPRIL PLASMA RENIN ACTIVITY (PRA) FOR DETECTING RAS > 60%

<table>
<thead>
<tr>
<th>Method</th>
<th>S</th>
<th>E</th>
<th>VPP</th>
<th>VPN</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duplex</td>
<td>87.3</td>
<td>91.5</td>
<td>86.0</td>
<td>93.5</td>
<td>90.6</td>
</tr>
<tr>
<td>Isotopic renography</td>
<td>45.3</td>
<td>92.8</td>
<td>77.4</td>
<td>75.6</td>
<td>76.0</td>
</tr>
<tr>
<td>PRA</td>
<td>52.4</td>
<td>84.4</td>
<td>81.5</td>
<td>57.4</td>
<td>66.2</td>
</tr>
</tbody>
</table>

All values are given as percentages.

son criteria, a positive captopril test was considered when PRA > 5.7 ng/mL/h.

Baseline and postcaptopril Tc99m-DTPA scintigraphies were performed in all the patients. Standard gamma camera views were obtained and recorded both on film and by a microcomputer system, with reference to hand-drawn limits of the renal parenchyma. Isotopic renograms were classified according to the suggestions of the Working Party on Diagnostic Criteria of Renovascular Hypertension with Captopril Renography. A scan was considered abnormal when delay in upslope maximal activity > 6 min or difference in uptake > 6% at 2 to 3 min between both kidneys were detected.

Statistical analysis (SPSS-PC+) included accuracy of the different techniques in terms of sensitivity (S), specificity (Sp), and predictive values, considering the results of angiography and CIR as gold standards of RAS and RVH, respectively. Captopril effect on arterial pressure and PRA was assessed by means of multivariate ANOVA (MANOVA) with intra- and intergroups contrasts. Statistically significant difference was considered at P < .05 for bilateral comparisons.

RESULTS

Sixty-three patients (80.8%) were men and 15 (19.2%) women, with a mean age of 63.9 ± 11 years (range 18 to 81 years). Sixteen patients (20.5%) were hypertensive (blood pressure > 160/90 mm Hg) under dietcontrol and 41 (52.6%) were treated with one drug. Twenty-one (26.9%) needed two or more drugs to control their hypertension. Regarding atherogenic risk factors, 48 patients (61.5%) smoked > 10 packs–year, 14 (17.9%) had diabetes mellitus, and 23 (29.5%) had dislipidemia. Eighteen (23.0%) had a past history of coronary disease, 54 (69.2%) peripheral arterial occlusive disease, and 6 (7.7%) aortic aneurysm.

Agreement of Duplex Scanning versus Angiography

Angiographic findings revealed no lesions or mild stenosis of the renal artery in 34 patients. A total of 44 patients had RAS > 60%, unilateral in 30 and bilateral in 14, which included seven cases with complete occlusion of the renal artery.

Renal duplex scanning allowed us to identify 142 of 149 patent renal arteries. Even though the Doppler signal was detected in the interlobar arteries, one of the two renal arteries could not be identified at its origin in seven patients (three on the right and four on the left). Based on the aforementioned criteria (PSV > 200 cm/sec to differentiate RAS > 60% and a kidney length < 8.5 cm with absence of flow to identify renal artery occlusion), renal duplex scanning correctly identified 86 of 94 RAS < 60%; 41 of 48 with RAS > 60%; and six out of seven occlusions. Overall agreement showed a κ value of 0.8. Renal duplex scanning accuracy showed 87% S and 91% Sp for detecting RAS > 60% (Table 1). Accuracy for detecting renal artery occlusion was: S = 85.7%; Sp = 100%; PPV = 100%; and NPV 99.3%.

Captopril Isotopic Renography

Isotopic renography results were assessed in all except one patient, in whom activity–time curves were considered technically inadequate.

Activity–time curves revealed no change in 51 patients. Twenty-four patients showed captopril-induced modifications suggestive of RVH (unilateral in 18 and bilateral in six). Another two patients had positive CIR, but no lesion was detected in the angiography and they were considered as false positives.

On the basis of angiographic findings and CIR, all the patients were classified into three groups. Thirty-three patients had no or minimal lesions in their renal arteries and they were classified as EHT (group I). Twenty patients with RAS > 60% (unilateral in 16 and bilateral in four), but a negative result in captopril renograms, were included in the group of EHT associated with RAS (group II). Finally, the 24 patients with RAS > 60% and positive CIR were considered as highly suspect for RVH (group III).

On the other hand, when stenosis grading was considered as the gold standard for the diagnosis of re-

TABLE 2. MEAN VALUES ± SD OF BASELINE AND POSTCAPTOPRIL MEAN ARTERIAL BLOOD PRESSURE IN THE DIFFERENT GROUPS: EHT (GROUP I); EHT + RAS > 60% (GROUP II); AND HIGHLY SUSPECT FOR RVH (GROUP III)

<table>
<thead>
<tr>
<th></th>
<th>Baseline, mm Hg</th>
<th>Captopril, mm Hg</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>112 (12.1)</td>
<td>103.3 (14.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Group II</td>
<td>117.9 (14.7)</td>
<td>108.0 (12.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Group III</td>
<td>118.4 (13.1)</td>
<td>104.4 (15.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total</td>
<td>115.4 (13.3)</td>
<td>104.8 (14.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values given are means, with standard deviations (SD) in parentheses.

* MANOVA (intragroup variability).
novascular disease, captopril isotopic renography correctly identified 90 of 96 RAS < 60% and 27 of 58 RAS > 60%. Therefore, accuracy for detecting RAS > 60% was 45.3% S and 92.8% Sp (Table 1).

Captopril Hypotensive Response  Mean blood pressure (MBP) values were calculated from systolic (SBP) and diastolic (DBP) measurements:

$$\text{MBP} = \frac{(\text{SBP} + 2\text{DBP})}{3}.$$  

Multivariate analysis of the variance of captopril-induced response showed a significant decrease in all groups (Table 2). However, no significant difference was registered between groups I and II ($P = .735$), nor between both those groups considered together and group III ($P = .144$). On the contrary, this last contrast
showed a statistically significant difference when only the variation of SBP was considered ($P = .032$).

**PRA Captopril Test** Baseline and postcaptopril PRA were assessed in 74 patients. Technical problems during the extraction or processing of the samples precluded getting adequate data in the other four cases. Captopril-induced changes in PRA are shown in Figure 1.

Multivariate analysis of the variance did not show a statistically significant difference in baseline values between groups I and II ($P < .612$), but it did between both of those groups considered together and group III ($P < .001$). Intragroup analysis revealed a statistically significant difference only in group III (Table 3). The PRA captopril test correctly identified 44 of 51 EHT patients (groups I and II), with a 86.3% Sp, and 20 of 23 RVH patients (group III) with a 87% S (Table 4).

**Renal Revascularization** Twenty patients underwent renal revascularization (angioplasty in 12 and renal bypass in seven) or primary nephrectomy (one patient). Two patients died in the first 30 days after the procedure: one because of a myocardial infarction and the other because of a stroke. Clinical results of renal revascularization were assessed in the remaining 18 patients following the suggestions of the Cooperative Study on Renovascular Hypertension. Eight of 11 patients from group III showed a cure or improvement of their hypertension, as compared to one of seven patients from group II ($P < .05$).

**DISCUSSION** Renal duplex scanning has recently been demonstrated to be accurate enough to detect RAS with a diameter reduction $> 60\%$. A PSV in the main renal artery ranging from 100 cm/sec to 300 cm/sec $^6$–$^9$ and a RAR $> 3.5^{10}$–$^{12}$ have been used as diagnostic criteria with different accuracy rates. In the present study, a threshold value of PSV $> 200$ cm/sec allowed us to detect RAS $> 60\%$ with 87% S and 91% Sp.

Clinical utility of the PRA captopril test and isotopic renography have frequently been correlated with their ability to noninvasively identify renovascular disease. Nevertheless, confusing data exists on the review of the recent methods used to assess the accuracy of these tests: detection of RAS based on comparisons with angiographic findings, or RVH based on the prediction of the clinical results of renal revascularization.

Moreover, there are few studies comparing the results of the different screening methods. Svetkey et al.,$^{13}$ in their series on 77 patients with a 16.7% prevalence of RVH, found that captopril isotopic renography showed maximum sensitivity (91% S) followed by captopril PRA test in peripheral blood (73% S) and in renal veins (64% S). In the study by Elliot et al.$^{14}$ on 100 patients, 59 with RAS $> 75\%$, captopril isotopic renography proved to be more accurate (92% S and 80% Sp) than the captopril challenge test (76% S and 58% Sp).

### TABLE 3. BASELINE AND POSTCAPTOPRIL PLASMA RENIN ACTIVITY (PRA) IN THE DIFFERENT GROUPS: EHT (GROUP I); EHT + RAS $> 60\%$ (GROUP II); AND HIGHLY SUSPECT FOR RVH (GROUP III)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline (ng/mL/h)</th>
<th>Captopril (ng/mL/h)</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>32</td>
<td>2.06 (2.52)</td>
<td>3.35 (4.20)</td>
<td>.087</td>
</tr>
<tr>
<td>Group II</td>
<td>19</td>
<td>1.27 (0.95)</td>
<td>2.64 (2.14)</td>
<td>.156</td>
</tr>
<tr>
<td>Group III</td>
<td>23</td>
<td>7.67 (9.13)</td>
<td>14.71 (10.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>3.60 (5.97)</td>
<td>6.70 (8.56)</td>
<td></td>
</tr>
</tbody>
</table>

* Missing cases: 4.
* MANOVA (intragroup variability).

### TABLE 4. OPERATIVE CHARACTERISTICS OF CAPTOPRIL PLASMA RENIN ACTIVITY (PRA) AND DUPLEX SCANNING FOLLOWED BY PRA CAPTOPRIL TEST FOR THE DETECTION OF HIGHLY SUSPECT FOR HVR (RAS $> 60\%$ AND POSITIVE CAPTOPRIL ISOTOPI RENOGRAPHY)

<table>
<thead>
<tr>
<th>Method</th>
<th>S</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA</td>
<td>87.0</td>
<td>86.3</td>
<td>74.1</td>
<td>93.6</td>
<td>86.5</td>
</tr>
<tr>
<td>Duplex</td>
<td>82.6</td>
<td>93.7</td>
<td>86.4</td>
<td>91.8</td>
<td>90.1</td>
</tr>
</tbody>
</table>

* All values are given as percentages.
In their review of recent literature, Davidson and Wilcox\textsuperscript{15} suggest that magnetic resonance imaging and duplex scanning should be the preferred methods for the screening of anatomical RAS; the PRA captopril test for primary screening in high-risk populations; and CIR for predicting blood pressure response subsequent to revascularization procedures.

In this study, duplex scanning and the PRA captopril test results were compared with isotopic renography results, for detection of both RAS and RVH. As less than half of the patients underwent renal revascularization, and due to the difficulties in assessing the clinical results of the procedure (especially in chronic stages of the disease), patients were considered as highly suspect for RVH on the basis of angiographic RAS > 60\% and a positive CIR (group III).

Captopril-induced hypotensive response has been proposed with diagnostic purpose.\textsuperscript{16,17} Postma et al\textsuperscript{18} observed a decrease in systolic blood pressure among HVR patients significantly higher than in EHT individuals. These changes were correlated with baseline PRA. However, other investigators have not found differences in captopril-induced hypotensive response between EHT and RVH patients.\textsuperscript{19} In the present series, variations in MBP after captopril administration showed no significant difference between the different groups. Neither was there any relationship to baseline or postcaptopril PRA. These results suggest that, although the decrease in systolic pressure is significantly higher in HVR than in EHT, this effect is insufficient to accurately differentiate either group of patients.

In this study, a captopril-induced PRA increase over the threshold value was statistically significant only among those cases highly suspect for RVH (group III). A lower accuracy of the PRA captopril test has been reported in the presence of bilateral RAS.\textsuperscript{20,21} However, all six patients with bilateral lesions and positive captopril isotopic renograms were correctly identified by the captopril test in this series.

A comparison of the different methods revealed that duplex scanning was more accurate than was the PRA captopril test or CIR for detecting RAS > 60\%. Nevertheless, caution is advisable in the analysis of these results. Firstly, the PRA captopril test does not allow for identifying the stenosed renal artery. Therefore, its results are expressed in terms of patients, not renal arteries. Secondly, in order to follow the same criteria as those used in renal duplex scanning, a cutoff point of > 60\% reduction of the vessel diameter was used for the consideration of a hemodynamically significant RAS. Most of the patients with positive results from captopril isotopic renograms and PRA showed more severe lesions in their renal arteries. Therefore, a greater diameter reduction as a threshold diagnostic criterion should probably have increased the sensitivity of these tests. In any case, these results demonstrate that duplex scanning allows for an earlier detection of RAS than do other noninvasive diagnostic methods.

Similar results have been referred to by Dondi et al\textsuperscript{22} in their study on 63 patients examined by means of isotopic renography and duplex scanning. Accuracy of isotopic renography was greater for detecting severe stenosis (RAS > 50\% in the authors' measurement method). However, duplex scanning was more accurate for detecting any grade of stenosis.

Captopril PRA showed a notable agreement with captopril renography for detecting those patients highly suspect for RVH (86.3\% S and 87\% Sp). Accuracy was further increased when a combined approach consisting of duplex scanning followed by captopril PRA was used (82.6\% S and 93.7 Sp). This permits raising specificity while decreasing the false positive rate, as duplex scanning permits discounting RAS in most of these patients. However a mild de-
crease in sensitivity is observed due to technically inadequate duplex examinations or duplex errors, as it occurred with two patients in our series.

On the basis of these results we have designed the algorithm shown in Figure 2. Renal duplex scanning and plasma renin activity should be the first screening methods for clinically suspected renovascular disease. A negative result in both tests practically rules out RVH. Angiography should be reserved for those cases with positive results in both tests. Isotopic renography should be limited to those patients with positive results in only one of them. However, further studies will be needed in order to assess the clinical utility of this strategy.

CONCLUSIONS

These results suggest that renal duplex scanning is a useful elective screening method for noninvasively detecting anatomical RAS. A combination of both renal duplex scanning and PRA captopril test may be an appropriate approach for the primary screening of RVH, permitting the selection of those patients indicated for angiography.

REFERENCES