Evaluation of Hypertensive Patients by Means of Captopril Enhanced Renal Scintigraphy with Technetium-99m DTPA

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One-hundred five hypertensive patients underwent conventional renal scintigraphy followed 2 or 3 days later by Captopril-enhanced renal scintigraphy, performed 1 hr after premedication with 50 mg of Captopril per os. All patients were then submitted to renal arteriography, performed within 15–30 days. Fifty-five patients had no renal artery stenosis, 29 had unilateral disease, and 21 bilateral. Overall, 34/37 patients were diagnosed by the provocative test as having at least one renal artery affected by a stenosis >50%. Of those with no stenosis (n = 55) or stenosis <50% (n = 13) only two cases were falsely positive. Thus sensitivity was 92% and specificity 97%. For single kidney identification with stenosis >50%, sensitivity of renal scintigraphy after Captopril administration was 94% and specificity 98%. Captopril enhanced renal scintigraphy is thus suggested as the first test to be performed in hypertensive patients referred for renal scintigraphic studies. Only those cases with equivocal results require a baseline study for better assessment.


Renal artery stenosis (RAS) is the most common cause of secondary hypertension, potentially remediable by surgery or angioplasty (1). Efforts have therefore been made to find a safe and reliable technique for detecting renovascular disease (RVD).

Although renal scintigraphy in the past has seemed to offer great potential, it has been applied with differing results from group to group (2,3). It has not achieved widespread application because of the high incidence of false-positive results, unacceptable in a low-prevalence disease such as renovascular hypertension (RVH) (4). In order to improve its diagnostic accuracy, some authors (5–8) have recently proposed provocative tests with angiotensin converting enzyme (ACE) inhibitors that pharmacologically block intrarenal autoregulation modulated by the renin-angiotensin system (9). To date however, only studies on limited groups of selected patients, mostly with unilateral RAS have been carried out (5–8).

The aim of this study was to investigate prospectively the potential of renal scintigraphy after ACE inhibition in detecting RAS in a population of mild to severe hypertensives referred to the nuclear medicine department during their diagnostic workup, and compare the results to those obtained for conventional renal scintigraphy.

MATERIALS AND METHODS

From October 86 through May 88, a baseline scintigraphic study followed 2 to 3 days later by a second study after ACEI was performed on 105 hypertensive patients (67 males, 38 females) referred for renal scintigraphy and falling under at least one of the following criteria: (a) rapid onset of severe hypertension, or worsening of preexisting high blood pressure levels, (b) no response to a well-balanced antihypertensive drug regimen, and (c) age less than 30 yr. Antihypertensive therapy was not necessarily suspended, except for diuretics (for at least 48 hr) and ACE inhibitor drugs (for at least 1 wk). Within 15–30 days all patients were further submitted to abdominal angiography with selective renal arteriography, performed by femoral route according to Seldinger’s technique. Where femoral arteries were obstructed, the brachial artery was chosen. Baseline renal scintigraphy (BA-RS) was
carried out by means of a large field-of-view gamma camera equipped with a LEAP collimator, linked to a minicomputer (Elscint APEX 415). Scintigraphic data were acquired after rapid injection of 220 MBq of technetium-99m diethylene-triaminepentaacetic acid ([TmTc]DTPA), in a frame mode, matrix format of 64 × 64, with a time per frame of 10 sec, for a total time of 1,120 sec. The same procedure was followed for the Captopril-enhanced renal scintigraphy (CE-RS) when patients, after a 4-hr fasting, were given 50 mg of Captopril orally 1-hr prior to the examination. To avoid possible side effects, patients were kept in supine position and their blood pressure monitored every 15 min until tracer injection. To ensure a good state of hydration, patients were asked to drink 300 ml of water 1 hr before each scintigraphic study.

Computer processing of scintigraphic studies was performed to produce time-activity curves after selection of a region of interest (ROI) around each kidney and a semilunar background ROI for each kidney, from the lower pole to the middle of the lateral contour. Split renal function (SRF) was calculated from background-corrected renograms as the relative uptake of each kidney from 90 to 150 sec in relation to the activity recorded over both kidneys in the same time interval (LK or RK/LK + RK*100). In some instances, after the software had become available, parenchymal transit time (PTT) was also calculated by applying a deconvolution procedure to each renogram (10,11).

Scintigraphic data were analyzed with regard to split renal function (SRF) and renogram upslope. BA-RS was considered positive when SRF exceeded the normal limits of 44%-56% (i.e., the difference between the percentages of each kidney was more than 12) and/or renogram shape was apparently abnormal. This latter criterion was the only way to evaluate patients with a solitary kidney or with bilateral disease.

To evaluate CE-RS a third parameter was introduced: delay of time to maximum counts, as compared to BA-RS. Furthermore, renogram upslope changes were graded from 0 to 3 (0 = virtually no change; 1 = mild changes; 2 = apparent changes; 3 = flattening of the curve). The CE-RS was considered positive when either a severe decrease in split renal function (Fig. 1) or a delay of time to peaking activity of more than 5 min (Fig. 2) and/or a grade 2 or 3 change of renogram shape was observed. This combined criterion proved to be very useful in evaluating bilateral stenosis (Fig. 3).

Statistic analysis of SRF and PTT was accomplished by means of the paired Student's t-test, nonparametric analysis of variance, and goodness of the fit test for normality.

RESULTS

On the basis of renal angiography the population studied was divided into three groups: Group 1 with no RAS, Group 2 with unilateral RAS, and Group 3 with bilateral RAS (main clinical parameters are summa-

![Figure 1](image1.png)

FIGURE 1
Stenosis of right renal artery (60%). Mean arterial blood pressure was 110 mmHg before and 106.67 after Captopril. Plasma creatinine was 176 μmol/l. Baseline study (upper row), left kidney: split renal function 51% and parenchymal transit time 270 sec. Right kidney 49% and 320 sec. Captopril-enhanced renal scintigraphy (lower row) showed a sharp decrease of right kidney function (39%) and an increase in transit parameters (420 sec) from the side affected.

![Figure 2](image2.png)

FIGURE 2
66-yr-old female, right RAS of 60%. BA-RS shows symmetric kidney uptake (2A). CE-RS demonstrates a mild decrease of tracer uptake from the affected side, without, however, any visualization of the pelvi-calyceal system (2B) (each scintigram collects 1 min of acquisition).
rized in Table 1). Group 1 (negatives) consisted of 55 patients. This group, in turn, was subdivided into two subgroups; Subgroup a including 42 cases without clinical or laboratory signs of other nephropathies and Subgroup b including 13 patients, nine of whom had angiographic findings that suggested nephrosclerosis (six bilaterally, three unilaterally) diagnosed from the presence of small cortical scarring, vascular tree rarification, and “pruning” of smaller arterioles. One was affected by sequelae of previous obstructive uropathy and one had a hypoplastic kidney. Two other patients were found to be affected by Berger’s nephropathy and papillary necrosis, respectively. In all 13 cases BA-RS turned out positive, whereas CE-RS showed no variation suggestive of RAS. Of the 42 cases in Subgroup a, CE-RS was falsely positive in only two, one bilaterally (Fig. 4) and one monolaterally.

Group 2 (unilateral disease) consisted of 29 patients, two of whom had the contralateral kidney removed for reasons unrelated to hypertension. RAS was >50% in 20 cases and <50% in nine. Of the 20 patients with a stenosis >50%, CE-RS demonstrated a decrease of at least 5% of SRF in 12 cases and a delay of time to maximum counts of at least 5 min in 11. Both changes occurred simultaneously in seven instances. Two other patients did not show any change because of a markedly compromised renal function, already detected at BA-RS. The last patient turned out falsely negative.

Group 3 (bilateral disease) consisted of 21 patients. In this group, RAS was found to be bilaterally >50% in 12 patients, unilaterally >50% in five, and bilaterally <50% in four. The first subgroup showed, on CE-RS, a characteristic bilateral decrease of renogram upslope associated with a marked delay of time to peak (Fig. 3). Captopril administration almost always (Table 1, right-end column) resulted in a significant reduction in mean arterial blood pressure (MAP), but important side effects were never observed.

**TABLE 1**

Population Studied (n = 105)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean age (yr)</th>
<th>Creat (µmol/l)</th>
<th>Baseline MAP (mmHg)</th>
<th>Captopril MAP† (mmHg)</th>
<th>Confidence level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RAS</td>
<td>55</td>
<td>50.9</td>
<td>104.4 (26.5 sd)</td>
<td>116.5 (12.9 sd)</td>
<td>102.0 (14.8 sd)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>(a) no nephropathy</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) with nephropathy</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral RAS</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) &gt;50%</td>
<td>20</td>
<td>52.3</td>
<td>146.5 (84.3 sd)</td>
<td>119.7 (14.7 sd)</td>
<td>107.5 (15.4 sd)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>(b) &lt;50%</td>
<td>9</td>
<td>54.1</td>
<td>98.4 (16.6 sd)</td>
<td>112.2 (7.9 sd)</td>
<td>102.9 (9.6 sd)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Bilateral RAS</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) bilaterally &gt;50%</td>
<td>11</td>
<td>60.4</td>
<td>155.5 (74.1 sd)</td>
<td>122.1 (11.4 sd)</td>
<td>115.0 (11.9 sd)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>(b) unilaterally &gt;50%</td>
<td>6</td>
<td>55.1</td>
<td>95.2 (20.5 sd)</td>
<td>120.0 (13.3 sd)</td>
<td>108.1 (12.8 sd)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>(c) bilaterally &lt;50%</td>
<td>4</td>
<td>44.2</td>
<td>83.2 (20.9 sd)</td>
<td>126.6 (17.3 sd)</td>
<td>112.9 (7.5 sd)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Statistical significance of MAP variations after Captopril (paired Student’s t-test).
† RAS = renal artery stenosis.
‡ MAP = mean arterial blood pressure.
FIGURE 4
50-yr-old man with peripheral vascular disease. Mean arterial blood pressure was 116.67 mmHg before and 71.67 after Captopril. Plasma creatinine was 140 μmol/l. Baseline study (upper row) is within normal limits. Captopril study performed after a period of very low sodium intake shows a bilaterally positive response (central row). After sodium repletion, a second test turned out (lower row) absolutely negative.

From the whole population studied, 208 kidneys were evaluated, two patients having a solitary kidney. Forty-nine kidneys were found to have a renal artery affected by a RAS >50%. Twenty-two kidneys supplied by a renal artery with RAS <50% (nine from Group 2 and 13 from Group 3) were grouped together with the 137 kidneys with no RAS (110, 18, and nine from Groups 1, 2, and 3, respectively), for a total of 160 kidneys. Overall results are reported in Tables 2 and 3. Sensitivity and specificity were calculated for the identification of kidneys with a renal artery affected by a stenosis >50%. This limit was not taken as a proof of RVH but rather as a limit below which RAS is very unlikely to be the cause of high blood pressure levels, whereas RAS >50% is very often associated with RVH (12–18).

### TABLE 2
Correlation Between Renal Angiography and Renal Scintigraphy

<table>
<thead>
<tr>
<th></th>
<th>BA-RS&lt;sup&gt;+&lt;/sup&gt;</th>
<th>CE-RS&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP&lt;sup&gt;+&lt;/sup&gt;</td>
<td>S&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nonischemic kidneys</td>
<td>n = 160</td>
<td>83%</td>
</tr>
<tr>
<td>Ischemic kidneys</td>
<td>n = 48</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>+</sup> Baseline renal scintigraphy.
<sup>+</sup> Captopril enhanced renal scintigraphy.
<sup>+</sup> Specificity.
<sup>+</sup> Sensitivity.

Note: Total number of kidneys is 208, being two patients with a solitary kidney.

### TABLE 3
Identification of Patients with RAS >50%

<table>
<thead>
<tr>
<th></th>
<th>BA-RS&lt;sup&gt;+&lt;/sup&gt;</th>
<th>CE-RS&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SP&lt;sup&gt;+&lt;/sup&gt;</td>
<td>S&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>S&lt;sup&gt;+&lt;/sup&gt;</td>
<td>59%</td>
<td>92%</td>
</tr>
<tr>
<td>SP&lt;sup&gt;+&lt;/sup&gt;</td>
<td>80%</td>
<td>97%</td>
</tr>
</tbody>
</table>

<sup>+</sup> Baseline renal scintigraphy.
<sup>+</sup> Captopril-enhanced renal scintigraphy.
<sup>+</sup> Sensitivity.
<sup>+</sup> Specificity.

**Split renal function.** A preliminary statistical analysis on a control group of patients who had neither RAS nor clinical or laboratory signs of other nephropathies, was carried out. The distribution of SRF of a single kidney was not significantly different from a normal Gaussian distribution, with a mean value of 50.6% (s.d. ± 3.4%). In unilateral disease ischemic kidneys were found to have a SRF of 44.7% (± 7.5%), a value which is statistically different (p < 0.05) from normal kidney values. However, Captopril administration did not increase its statistical significance but instead reduced it to a nonsignificant level (p = 0.086), owing to the spread of observed values.

**Parenchymal transit time.** It was not possible to calculate PTT in all cases, but kidneys where the analysis was performed were divided into normals (no RAS, no signs or other nephropathies), nephrosclerotic without RAS and stenotic (Table 4). In normal kidneys (n = 30) PTT on baseline conditions was 313.7 ± 33.6 sec; after Captopril it decreased to a mean value of 270.7 ± 39.5 sec (statistically significant p, < 0.01). In stenotic kidneys (n = 15), baseline PTT had a value of 331.3 ± 59.0 sec, not statistically different from normals (T = 0.93). However, after ACE inhibition it increased to 406.4 ± 47.8 sec that is significant compared to baseline PTT of stenotic kidneys (p < 0.01) and, more especially, that of normal kidneys (p < 0.001). Nephrosclerotic kidneys without RAS (n = 6) showed a mean value of 391.4 ± 28.6 sec that is statistically different.
DISCUSSION

Considering recent advances in the treatment of RVH, a safe, noninvasive technique is needed to reliably detect stenotic lesions that potentially threaten kidney function (19,20). It should, in fact, be remembered that the improvement in blood pressure control by use of the recently available newer classes of antihypertensive drugs, such as ACE inhibitors, may carry with it a deterioration in renal function in the case of RAS (21–23).

After the first reports on the effects of ACEI on renal handling of radiolabeled compounds (24), studies have been carried out to investigate the efficacy of radioisotopic studies after Captopril administration in diagnosing RVH (5–8).

The definition of renal arterial stenosis "potentially threatening kidney function" and/or "hemodynamically significant" is still an unresolved problem.

Many authors have emphasized the importance of renal vein renin ratio (RVRR) that as well as being a relatively invasive procedure also suffers from other shortcomings. It gives no information on bilateral disease (25) and even in unilateral RAS is burdened by false-negative results (26,27); in some studies RVRR failed to predict surgical cure of hypertension (28,29).

Blood pressure behavior after surgery or renal angioplasty is another accepted criterion to define the hemodynamic significance of RAS. We feel, however, that this is not always the case. It is known that RVH may be superimposed on essential hypertension causing "compound hypertension" (30) making revascularization ineffective for the lowering of high blood pressure levels though useful in reversing renal failure (31,32). Moreover, it has been found that response to revascularization in stenotic kidneys might depend on the duration of hypertension and not only the degree of RAS (33).

On the other hand, revascularization performed on patients with RAS, either by surgery or balloon angioplasty, is aimed not only at removing a cause of hypertension, generally controllable by medical therapy, but also at preserving renal function that might be impaired by renovascular disease (RVD).

In many studies on the curability of RVH, the decision whether a patient should be operated upon, was taken on the "anatomic" finding of a renal arterial stenosis of at least 50% (12,13,17,18). Finally, it was found that RAS >50% is very often associated with RVH (12–18).

On this basis, we feel that an arterial lumen reduction of at least 50% could be an acceptable standard for evaluating scintigraphic results in hypertensive patients.

In our experience, unilateral RAS >50% as already outlined in the result section, did not always show a decrease in SRF on the affected side. The evaluation of the delay of time to maximum counts was of great help in identifying four patients with RAS >50%. Though one of these had a solitary kidney and could not have been evaluated in any other way, the other three were the oldest of the group (66, 63, and 76 yr old, respectively). Interestingly, those who showed the most severe decrease of SRF were among the youngest. The different way these two subgroups responded to ACEI might well reflect the different degree of renin-dependence of their intrarenal hemodynamics, that decreases with duration of RVD (29,34). The same answer might also explain the pattern observed in bilateral disease, a condition presumed to be "volume dependent" rather than "renin dependent" (7).

In our patients, 13 kidneys had a RAS greater or equal to 90% and in six cases the corresponding kidney, which showed no arteriographic evidence of collateral circulation, was so poorly visualized on BA-RS that no change could have been detected by CE-RS. We feel, however, that these observations do not necessarily discriminate against the use of DTPA, as others have asserted (8), because the association of hypertension and poorly visualized kidney renders renal angiography necessary. Our study, where a poorly visualized kidney was always associated with a severe RAS, supports our conviction.

<table>
<thead>
<tr>
<th>Renal status</th>
<th>No. of subjects</th>
<th>BA-RS transit time (sec ± s.d.)</th>
<th>CE-RS transit time (sec ± s.d.)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal kidneys</td>
<td>30</td>
<td>313.7 ± 33.6</td>
<td>270.7 ± 39.5</td>
<td>T = 3.56 (p &lt; 0.01)</td>
</tr>
<tr>
<td>Nephrosclerotic kidneys</td>
<td>6</td>
<td>391.4 ± 28.6</td>
<td>354.4 ± 46.6</td>
<td>T = 2.26 (p = 0.05)</td>
</tr>
<tr>
<td>Stenotic kidneys</td>
<td>15</td>
<td>331.3 ± 59</td>
<td>406.4 ± 47.8</td>
<td>T = 3.72 (p &lt; 0.01)</td>
</tr>
</tbody>
</table>
Moreover, with DTPA, the superior physical qualities of its label $^{99m}$Tc allow for the acquisition of better images (35). In many of our cases the visual inspection of scintigraphic sequences was of great help for diagnosis, especially for bilateral disease.

The specificity of the test was assessed in 55 patients who had no angiographic evidence of RAS. In 13 cases abnormalities such as nephroangiosclerosis, hypoplasia, and obstructive uropathy, which are usually associated with many false positives in conventional renal scintigraphy, were present and in all instances CE-RS was of great help in ruling out RVH, while BA-RS was falsely positive. Two normal BA-RS studies met our positiveness criteria for RAS $>$50% on CE-RS, one bilaterally and one unilaterally. The former patient, however, experienced a profound drop in blood pressure with values below 90/60 mmHg and was found to have a very low urinary sodium excretion rate, an expression of a low sodium diet (20–30 mEq/day). An activation of the renin-angiotensin system as a result of sodium depletion was probably responsible for the false positivity of the first provocative test. The same study, repeated after normalization of sodium balance, turned out absolutely negative (Fig. 4). Finally CE-RS proved to be negative in 13 out of 13 patients with RAS $<$50%.

PTT analysis was of great interest. In patients with essential hypertension PTT decreased significantly after ACEI, which might be explained by the increased renal blood flow due to peripheral as well as intrarenal vasoconstriction (36), while in stenotic kidneys it increased most significantly. This agrees with the theory of deconvolution analysis where PTT depends on water and salt reabsorption, that increases when peritubular capillary pressure is less than intratubular luminal pressure. DTPA is thus concentrated in a smaller volume of fluid and takes longer to move down the nephrons, thus increasing PTT (37).

In summary, CE-RS with $^{99m}$TcDTPA proved to be a very accurate tool for the screening of RAS $>$50%, in both unilateral and bilateral disease. This technique is moreover highly specific, a condition of the utmost importance for tests to screen out a disease of fairly low prevalence such as RVH (38,39).

CE-RS could therefore be applied as a screening procedure for RVH after a moderate preselection of patients. If the test is negative, it could be reasonable to rule out angiotensinogenic hypertension. In our experience, monolateral RAS often though not always appears in a very typical pattern (i.e., severe reduction of tracer uptake by the affected kidney). In bilateral stenosis changes are more subtle and comparison with a baseline study could be of great help in identifying RAS $>$50%.

Finally our study provides statistical evidence for the usefulness of PTT analysis in the identification of stenotic kidneys. Unfortunately this evaluation was not carried out on all patients and further studies are needed to better assess PTT role in evaluating RVH.

REFERENCES


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