

# Value of Captopril Renal Scintigraphy in Hypertensive Patients with Renal Failure

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The aims of this study were to show the value of captopril renal scintigraphy for detecting a renovascular cause in hypertensive patients with renal failure and to assess the ability to predict the beneficial effect of revascularization on renal function. **Methods:** Thirty-eight patients with renal failure (mean glomerular filtration rate = 35 mL/min) underwent renal scintigraphy after injection of  $^{99m}\text{Tc}$ -mercaptoacetyltriglycine. Baseline scintigraphy was performed, and the test was repeated 24 h later after oral administration of 50 mg captopril given 60 min before the test. **Results:** In 5 of 6 patients with a renovascular cause for renal failure, and 2 of 3 patients with a probable arterial pathology, scintigraphy had a high probability. The result was indeterminate in the other 2 patients. In 5 of 11 patients with negative arteriography and 14 of 18 patients with probable absence of renovascular pathology, we found a low probability of functional renal artery stenosis. Six revascularization procedures were performed and were predictive of a beneficial effect in 5 patients. Time of peak activity was an effective predictor in each case. **Conclusion:** In hypertensive patients with renal failure, captopril renal scintigraphy can detect hemodynamic dysfunction downstream from a renal artery stenosis and can predict the beneficial effect of revascularization in some cases.

**Key Words:** captopril renal scintigraphy; renal failure

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**T**he association of renal failure with hypertension (HT) raises diagnostic difficulties considering the numerous potential causes (arteriopathy, diabetes mellitus, long-standing HT, nephropathy). Renovascular hypertension (RVHT) is the most common form of secondary arterial HT, with a low prevalence (0.5%–1%) in a nonselected hypertensive population (1); however, it can induce renal function deterioration. RVHT is mainly due to stimulation of the renin angiotensin system secondary to renal ischemia downstream from a stenosing lesion. Renin secretion by the juxtaglomerular vessels of the ischemic kidney and the subsequent increase in angiotensin II production cause efferent glomerular arteriolar vasoconstriction that tends to maintain a normal glomerular filtration rate (GFR). On the other hand, angiotensin II induces systemic HT secondary to peripheral

resistance increase, tubular sodium reabsorption and hemodynamic changes in the contralateral kidney (2). Other factors such as thromboxan  $A_2$  and endothelium-derived constrictor factor add harmful vasoconstrictor effects (3,4). In a subsequent renin-independent stage, sodium retention and intrarenal angiotensin II production have been thought to maintain HT (2). Progressively, the arterial walls are modified and thickened in the ischemic and contralateral kidneys. Angiotensin-converting enzyme inhibitors (ACEIs) may worsen renal function by reducing the GFR (5,6). Captopril-induced acute renal failure is a well-known complication in severe bilateral renal artery stenosis (RAS) or arterial stenosis in a solitary kidney. Therefore, ACEIs may be used to unmask RAS (7–9).

Making a positive diagnosis may be difficult in a patient presenting with arterial HT and renal failure. Renal arteriography is the gold standard; unfortunately, it is potentially harmful, because it punctures an atherosclerotic artery wall and, above all, because of the renal toxicity of iodinated contrast media (10). The value of alternative tests for detecting RAS in patients with HT has been debated (11,12), but it is uncertain whether these data can be transposed to the diagnosis of RAS as a cause of renal failure (13). Doppler ultrasonography is often limited by investigational difficulties (14); whereas, MRI appears promising with no risk to renal function (15). Nevertheless, despite a good sensitivity for the detection of proximal RAS, MRI's lack of sensitivity for the diagnosis of distal, segmental or fibrodysplastic RAS is a limitation of the technique, not to mention its cost and availability. Moreover, the presence of a stenosing lesion does not imply its hemodynamic significance and role in causing HT and renal failure (16). The evaluation of the hemodynamic effects on renal function downstream from a stenosis is essential. ACEI-sensitized renal scintigraphy is a simple renal-safe method that can detect hemodynamically significant RAS. The aim of this study was to clarify the role of captopril-enhanced renal scintigraphy in the diagnosis of RAS in patients with renal failure and in evaluating the functional prognosis after revascularization.

## MATERIALS AND METHODS

### Patients

Thirty-eight patients with renal failure (25 men, 13 women, age range 29–83 y) were evaluated retrospectively for the presence of RAS. The patients were referred to our institution on the basis of

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suggestive signs, including renal failure, HT and arteriopathy (arteritis, angina).

## Methods

The presence or absence of RAS was confirmed, ruled out or presumed in the patients, depending on clinical and radiomorphological criteria, without the help of captopril renal scintigraphy. The patients were classified into four groups according to the diagnosis of RAS: present, probably present, probably absent and absent. Then, these data were compared with the probability of RAS from the results of captopril scintigraphy.

### Glomerular Filtration Rate Evaluation

GFR was calculated with the classic Cockcroft and Gault method (17) according to sex, age, weight and serum creatinine level. The mean GFR was  $35 \pm 17$  mL/min.

### Renal Artery Imaging

Eighteen patients underwent arteriography. Intravenous digital subtraction angiography (IDSA) was performed in 2 patients with moderate renal failure. Five patients underwent MR angiography and 6 others underwent Doppler ultrasonography. For ultrasonography, the following criteria were used: (a) proximal criteria: renal-to-aortic ratio  $>3.5$  and peak systolic velocity  $>180$  cm/s are suggestive of more than 60% stenosis and (b) distal criteria: early systolic acceleration  $<3$  m/s<sup>2</sup>, ascension time of systolic peak  $>0.07$  s, absence of the early systolic peak and lowering of the resistivity index  $<0.56$  are present for stenoses reducing diameter by more than 75% (18). Seven patients had no renal artery imaging.

### Diagnosis of Renal Artery Stenosis

The distribution of patients according to diagnosis established without the help of captopril renal scintigraphy is shown in Table 1.

**TABLE 1**  
Distribution of Patients According to Diagnosis

| No. of patients (n = 38) | Diagnosis                                      | Arguments of diagnosis  |
|--------------------------|--|---|
| 6                        | Functionally significant renal artery stenosis | Improved or stabilized BP or GFR after percutaneous angioplasty (n = 5) or bypass (n = 1)   |
| 3                        | Probable renovascular pathology                | Clinical and biological arguments with stenosis on arteriography (n = 1), US (n = 1) or MRI (n = 1)   |
| 18                       | Probable absence of renovascular pathology     | No stenosis on:<br>MRI (n = 4)<br>IDSA (n = 2)<br>US (n = 5)<br>Renal biopsy (n = 2)<br>Absence of GFR deterioration with long-term ACEI or ARA treatment (n = 5) |
| 11                       | Absence of renovascular pathology              | No stenosis on arteriography  |

BP = blood pressure; GFR = glomerular filtration rate; US = ultrasonography; IDSA = intravenous digital subtraction angiography; ACEI = angiotensin-converting enzyme inhibitor; ARA = angiotensin receptor antagonist.

A renovascular pathology was confirmed in 6 patients because of the association of HT, renal failure, radiologically confirmed RAS and also, normalized blood pressure (BP) in 1 patient, improvement of BP in 5 others, improvement of GFR in 3 patients and stabilized GFR in 2 others after revascularization.

In 3 patients, significant renal artery stenosis was considered highly probable on clinical, biologic and radiologic evidence, but revascularization was not attempted for clinical or technical reasons. Nevertheless, BP improved or stabilized with appropriate treatment in the 3 patients.

RAS was ruled out in 11 patients because of arteriographic results.

In 18 patients, the cause of renal failure was probably not renovascular because of the absence of RAS on radiologic investigations, or no worsening of GFR after long-term treatment with ACEI or angiotensin receptor antagonist. Two patients underwent renal biopsy, the results of which showed the absence of microangiopathy in 1 diabetic patient and the presence of glomerulosclerosis in the other.

### Angiotensin-Converting Enzyme Inhibitor-Enhanced Renal Scintigraphy

Each patient underwent dynamic renal scintigraphy before and 60 min after oral administration of 50 mg captopril (Squibb Laboratories, Paris, France), an ACEI, with cautious venous hydration (7 mL/kg for 1 h before the test with a 5% glucose solution [PERFUFLEX; Fresenius France Pharma, Louviers, France]) and cessation of ACEIs and diuretics 3–5 d before scintigraphy. After administration of captopril, the BP was monitored every 15 min. The two scintigraphic tests were performed at 24-h intervals, under the same conditions of hydration for both tests, after the injection of <sup>99m</sup>Tc-mercaptoacetyltriglycine (MAG3) (Mallinckrodt Medical BV, Petten, Holland) at a dose of 37 MBq (1 mCi)/10 kg body weight, which was increased according to GFR. Renal images were obtained with a wide-field-of-view gamma camera fitted with a general-purpose, gamma ray, low-energy collimator (DSX or DST gamma camera; SMV International, Buc, France). The acquisition protocol was 60 1-s images, then 24 10-s images and, finally, 45 20-s images. A region of interest (ROI) was drawn around each kidney, with a background ROI situated around the lower half of each kidney. If radiotracer stagnates in renal pelvis or calyces, only a cortical nephrogram was generated. Sequential images were obtained. Background-corrected renograms were generated to calculate functional parameters: split renal function (SRF) defined as the rate of uptake of each kidney versus total renal uptake calculated between the second and the third minute after injection; time of peak activity ( $T_{max}$ ); and 20 min over peak value (ratio of 20 min activity versus  $T_{max}$ ). A parametric image of time to maximum counts was also produced and displayed in a continuous color scale to visualize prolonged tracer transit. Scintigraphic interpretation was done by comparing baseline and postcaptopril tests of each patient with thresholds established by the Santa Fe consensus. Results are expressed as probability, and significance was considered to be the following: (a) low probability of presence of functional RAS ( $<10\%$ ): normal baseline test (SRF  $\geq 45\%$ ,  $T_{max} \leq 5$  min and residual cortical activity (RCA)  $> 45\%$ ) unchanged with captopril or abnormal baseline test improved after ACEI; (b) indeterminate probability: abnormal baseline test (SRF  $< 45\%$  for one kidney,  $T_{max} > 5$  min or RCA  $> 45\%$ ) and no change after captopril; and (c) high probability ( $>90\%$ ): significant deterioration of renogram

after ACEI compared with baseline test, using the Santa Fe thresholds. In each patient, BP and renal function were monitored for at least 6 mo after radionuclide test.

## RESULTS

### Captopril Renal Scintigraphy

Table 2 shows the results of captopril scintigraphy according to the presence or absence of RAS. Table 3 summarizes the scintigraphic results of patients with a high probability of functional RAS with  $T_{max}$  ( $\Delta T_{max}$ ) and RCA ( $\Delta RCA$ ) variations and HT diagnosis. Of 9 patients with a high probability, 6 presented with unilateral artery stenosis with subsequent improvement of BP and improvement or stabilization of GFR after revascularization (angioplasty:  $n = 3$ , bypass:  $n = 1$ ) or appropriate medical treatment ( $n = 2$ ) and 1 patient had unilateral thrombosis with contralateral artery stenosis. In the last patient, percutaneous angioplasty showed slow GFR deterioration. Two false-positive scans showed unilateral change after captopril and were of a patient with a predialysis diabetic nephropathy and another patient with left kidney atrophy and no RAS on arteriography.

Ten patients (26%) were classified as having indeterminate probability of RAS. Table 4 shows the captopril scintigraphic studies of those patients with curve aspects and renal artery imaging results. Two had RAS that was confirmed in 1 by subsequent improvement in BP and GFR stabilization after angioplasty and visualized by MRI in the second patient. In the other 8 patients, renal stenosis was ruled out on arteriography in 4. Among 4 other patients, MRI showed no stenosis in 1 patient, 2 patients underwent ultrasonography that had negative results and the fourth patient had negative IDSA results.

Finally, in 19 patients with a low probability of RAS on captopril scintigraphy, 5 had no RAS on arteriography. Fourteen patients probably did not have a renovascular pathology.

Combining high and indeterminate probability results, captopril renal scintigraphy yielded 100% sensitivity, 66% specificity, 47% positive predictive value (PPV) and 100% negative predictive value (NPV).

Among patients with certain or probable RAS, mean GFR was  $40 \pm 15$  mL/min for high-probability scintigraphy and

**TABLE 2**  
Analysis of Results of Captopril Renal Scintigraphy  
According to Diagnosis of Renal Artery Stenosis

| Diagnosis on<br>captopril scintigraphy | Renal artery stenosis |                     |                    |        | Total |
|--|-----------------------|---------------------|--------------------|--------|-------|
|  | Pres-<br>ent          | Probably<br>present | Probably<br>absent | Absent |       |
| High probability                       | 5                     | 2                   | 0                  | 2      | 9     |
| Indeterminate probability              | 1                     | 1                   | 4                  | 4      | 10    |
| Low probability                        | 0                     | 0                   | 14                 | 5      | 19    |
| Total                                  | 6                     | 3                   | 18                 | 11     | 38    |

Results are numbers of patients.

**TABLE 3**  
Patients with High Probability of Renal Artery Stenosis

| Patient no.<br>(n = 9) | Captopril scintigraphy |                  | Presence<br>of RAS |
|------------------------|------------------------|------------------|--------------------|
|                        | $\Delta T_{max}$ (min) | $\Delta RCA$ (%) |                    |
| 1                      | 8                      | 16               | +                  |
| 2                      | Left RG                | Left RG          | +                  |
| 3                      | 2.5                    | 11               | +                  |
| 4                      | 3                      | 5                | +                  |
| 5                      | 15                     | 26               | +                  |
| 6                      | 17                     | 50               | Probably +         |
| 7                      | 4                      | 10               | +                  |
| 8                      | Right RG               | Right RG         | -                  |
| 9                      | Right RG               | Right RG         | -                  |

$\Delta RCA$  = residual cortical activity variation; RAS = renal artery stenosis; RG = rising graph.

21 mL/min for indeterminate-probability scintigraphy. Among patients with renal insufficiency of another cause, mean GFR was  $42$ ,  $31 \pm 13$  and  $40 \pm 18$  mL/min for high (false-positive), indeterminate and low probability, respectively.

Regarding quantitative criteria, SRF was not discriminant, with no significant change before or after captopril administration in any patient. Twenty minutes over peak values were increased in six of nine high-probability scintigraphies (mean increase variation before and after captopril was  $33\% \pm 12\%$ ). Among patients with high-probability scintigraphies,  $T_{max}$  variation before and after ACEI was always superior to 2 min (mean  $T_{max}$  delay was 10.5 min).

**TABLE 4**  
Patients with Indeterminate Probability  
of Renal Artery Stenosis

| Patient no.<br>(n = 10) | Captopril scintigraphy  | Renal artery imaging                        |
|-------------------------|---|---|
| 10                      | Baseline $T_{max}$ = 8 min,<br>RCA = 15% unchanged<br>after captopril | RRAS (A)                                    |
| 11                      | PG with small right kidney  | RRAS (MRI)                                  |
| 12                      | PG on left side with small<br>kidney                                  | Subrenal aorta throm-<br>bosis; no LRAS (A) |
| 13                      | Bilateral PG  | No LRAS (A)                                 |
| 14                      | Bilateral PG  | No RAS (A)                                  |
| 15                      | PG on right side with small<br>kidney                                 | No RAS (MRI)                                |
| 16                      | Asymetric bilateral PG  | No RAS (US)                                 |
| 17                      | Bilateral PG  | No RAS (A)                                  |
| 18                      | Bilateral PG  | No RAS (US)                                 |
| 19                      | Delayed baseline $T_{max}$ un-<br>changed after ACEI on<br>left side  | No RAS (US)                                 |

RRAS = right renal artery stenosis; A = arteriography; RCA = residual cortical activity; PG = plateaueing graph; LRAS = left renal artery stenosis; US = ultrasonography.

## DISCUSSION

In 1983, Majd et al. (19) first described the harmful effect of ACEI on renal scintigraphy findings in four children with RAS. Since then, many authors have shown the benefit of captopril-enhanced renal scintigraphy in detecting hemodynamically active stenosis of the renal artery using  $^{99m}\text{Tc}$ -diethylenetriamine pentaacetic acid and/or  $^{131}\text{I}$ - or  $^{123}\text{I}$ -hippuran. The results of various series demonstrate a wide variability, with a sensitivity of 48%–96% and a specificity of 41%–100% (7,18–28). Studies with  $^{99m}\text{Tc}$ -MAG3 are less numerous but give comparable results in diagnosing stenosis (29–31). These discrepancies reflect the heterogeneity of the series, due to patient selection involving variable prevalence and the diverse parameters used for scintigraphy interpretation. Similarly, the criteria for the positive diagnosis of RVHT have evolved because they are no longer based on arteriography but now involve BP outcome after revascularization. Here again, various series differ in their results (20,30,32). Among the numerous published studies, few underline the value of captopril-sensitized renal scintigraphy in renal failure because of the absence of a gold standard examination due to the danger of contrast medium administration (21,33,34). In a previous study, Datsersis et al. (34) demonstrated that captopril renography could detect angiotensin II-dependent renal dysfunction in hypertensive patients with impaired renal function and predict the beneficial effect of ACEI therapy. With renal insufficiency in hypertensive patients, the nephrologist must look for a renovascular cause to propose revascularization as often as possible to preserve renal function. As long as the stenosis persists, ACEIs are proscribed to avoid worsening of renal function. In this study, unlike others, most of the patients (82%) underwent a morphological examination to visualize their renal arteries. Nevertheless, only 18 arteriographies (47%) were performed, thereby ruling out a positive diagnosis of renovascular pathology in 11 patients and confirming diagnosis after results of revascularization in 6. Therefore, the diagnosis was certain in only 45% of the patients, which represents the limitation of this type of study.

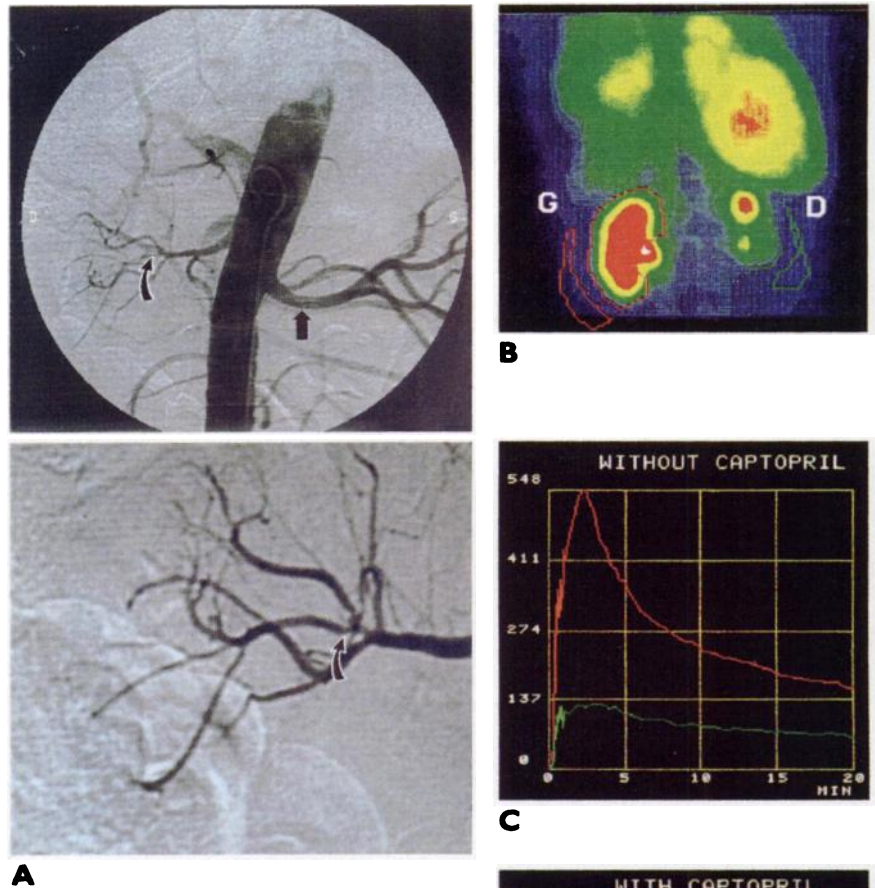
Concerning patients with positive scintigraphies and negative arteriogram, small vessel disease could be an explanation in 1 patient with an atrophic kidney but a more difficult one in a second patient with a unilateral positive test because microangiopathy is usually bilateral. Moreover, revascularization of a damaged kidney downstream from an arterial stenosis will not definitely improve renal function either because of the long-term effect of HT on the contralateral kidney. Therefore, in this instance, a renovascular pathology cannot be ruled out because of the absence of improvement in BP or GFR after revascularization. Considering these limitations, captopril renal scintigraphy has 100% sensitivity for the diagnosis of functional RAS and 66% specificity. However, patients with renal failure often have an altered baseline scintigram with, in absence of ACEI effect, a subsequent indeterminate probability result. If we modify criteria of interpretation as the following: (a) if the

findings are unilateral, the graphs are rising, with a smaller kidney, before and after captopril, the study is considered as a high probability for RVHT; (b) if the findings are bilateral, the graphs are plateauing or rising, unchanged after captopril, the test is of low probability, we obtain other results, improving specificity. As shown in the Table 4, we can differentiate among those 10 patients: Five patients had a low-probability test (bilateral plateauing curves before and after captopril) with absence of RAS in 3 patients and probably absent RAS in 2 others, 3 patients with high-probability test (false-positive) and subrenal aortic thrombosis in 1 patient, and probably absent RAS in 2 others. Finally, 2 patients with high-probability results had a right RAS on arteriography in the first patient and probably unilateral stenosis on MRI in the second one. Therefore, captopril renal scintigraphy has 100% sensitivity for the diagnosis of functional RAS, 83% specificity, 64% PPV and 100% NPV. For predicting revascularization results, captopril-enhanced renal scintigraphy also has 100% sensitivity; however, the number of patients was very small ( $n = 6$ ).

From the quantitative point of view, SRF did not seem to be a discriminant parameter, but  $T_{\text{max}}$  and 20 min residual activity were of value, because, in each high probability,  $T_{\text{max}}$  was delayed and RCA was increased in 6 of 9 patients. Unfortunately, mean parenchymal transit time (MPTT) is not a routine parameter in our institution. In effect, because the activity curves can exhibit a prolonged upslope, thus making  $T_{\text{max}}$  difficult to determine, few authors have shown the value of MPTT calculated by the deconvolution method (34,35). In indeterminate-probability scans, MPTT can indicate significant prolonged transit times and, therefore, classify them as high probability. In most cases,  $T_{\text{max}}$  and 20 min over peak values are sufficient for interpretation. Even with an atrophic renal parenchyma, captopril scintigraphy can help greatly in understanding the mechanism of HT and renal failure. Figure 1 shows the results in a patient with HT and moderate impaired renal function. Scintigraphy reveals superior polar parenchyma uptake in the right kidney, with altered right curve on baseline nephrogram and delayed  $T_{\text{max}}$  after captopril administration. Because of low right kidney uptake with regard to the contralateral kidney, we drew an ROI over the entire kidney, but if we had included only the functioning upper right pole, the generated nephrogram would have been more altered. This result was classified as high probability of functional right RAS. Arteriography showed the absence of a main right renal artery but showed a segmental superior right accessory artery with multiple stenoses.

## CONCLUSION

In hypertensive patients with impaired renal function, captopril renal scintigraphy is of great value for identifying a curable renovascular cause and for identifying when revascularization can be suggested to such patients. Few studies essentially on RVHT have been published because there is no gold standard in the presence of renal failure, but with the



**FIGURE 1.** 56-y-old patient with HT and moderate impaired renal function (GFR = 40 mL/min). (A) Arteriographic results: normal left renal artery; right renal artery not visualized (thrombosis suspected), segmental superior right accessory artery with multiple distal stenoses. (B) Uptake image with only right superior polar parenchymal uptake. (C) Baseline scintigram with altered right curve (<20% uptake, >3 min  $T_{max}$ ). (D) Nephrogram after captopril administration shows delayed  $T_{max}$ .

new developments in MRI and Doppler ultrasonography techniques, we believe that the captopril radionuclide test in patients with impaired renal function will progressively be better evaluated.

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